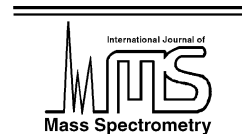




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## Review

# Gas phase nucleophilic substitution

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### Abstract

The literature on gas phase nucleophilic substitution reactions at aliphatic carbon has been reviewed. The emphasis has been on journal articles published in the period 1990–2001. The present review outlines our current understanding of concepts such as potential energy surfaces, structure–energy relationships, microsolvation, and dynamical and mechanistic details based on both experimental and theoretical evidence. The accuracy of various theoretical schemes for calculating potential energy surfaces has been assessed. A critical account on mechanistic concepts used in the literature is given. (Int J Mass Spectrom 214 (2002) 277–314) © 2002 Elsevier Science B.V. All rights reserved.

*Keywords:*  $S_N2$ ;  $S_N1$ ; Mass spectrometry; Ab initio quantum chemistry; Reaction mechanisms; Physical organic chemistry

### 1. Introduction

The purpose of this review is to consolidate the literature in the area of gas phase nucleophilic substitution with emphasis on mechanism. This cornerstone reaction of organic chemistry has been investigated intensely, and it is appropriate to the readership of the *International Journal of Mass Spectrometry* that gas phase studies provide the deepest insight into the mechanistic details of a reaction normally conducted in solution. Experimental and theoretical approaches will be covered in this review, since both have elucidated the kinetics of the gas phase reaction. The 1992 monograph of Shaik, Schlegel and Wolfe [1] covers most of the ideas and facts on the bimolecular nucleophilic substitution reaction up to that time. After 9 years, and also because there is growing con-

cern about the division of these substitution reaction mechanisms into two distinct classes— $S_N1$  and  $S_N2$  (vide infra)—we think it is due time to cover more recent development and material not included in the book. The goal is to give a broadminded, although not comprehensive literature coverage, and also provide our own interpretation of the key characters on this lively mechanistic scene.

### 2. Background and scope

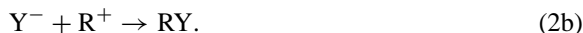
The mechanism of nucleophilic substitutions at aliphatic carbon has been studied for more than 100 years [2], but immense progress was made during the 20th century in unveiling how these reactions occur. The influence of Hughes and Ingold on the way we understand these reactions—especially through Ingold's textbook [3]—has been formidable. They

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introduced the concept of two clearly distinct mechanisms for nucleophilic substitution,  $S_N2$  and  $S_N1$ . The  $S_N2$  mechanism (in the anionic form)



is characterised by being kinetically of second order (first order in each of the reactants; the nucleophile Y and the substrate RX). It was postulated that the observed second order kinetics is the result of passage through the well-known Walden inversion transition state where the nucleophile displaces the nucleofuge (leaving group) from the backside in a single concerted reaction step. Hughes and Ingold's other mechanistic alternative,  $S_N1$ , takes place via two discrete steps

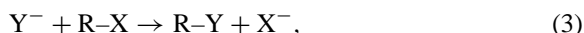


In this picture the unimolecular dissociation step is rate determining. Normally, this initial bond scission is heterolytic, and  $R^+$  is a carbocation. The product is eventually formed upon combination between the carbocation and the nucleophile.

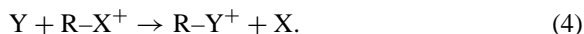
These ideas and much of the rest of the physical organic chemistry heritage, comes mainly from experiments conducted in solution. This is logical, since practical synthesis usually is performed in a solvent. However, effects of the solvent medium may lead to an ambiguous or erroneous mechanistic interpretation, since transport phenomena (diffusion) and solvation effects may prevail. For principal reasons, it would therefore be an advantage to study simplified models of these reactions. The ideal would be to dissect the solution reaction into its components, both with regards to the interaction with solvent molecules and the identification of the sequence of elementary steps.

In many respects, the gas phase provides an ideal environment for studying elementary chemical reactions. Both unimolecular and bimolecular reactions may be studied without interference from surrounding molecules. In this fashion, the intrinsic behaviour may be studied and the role of the solvent exposed. Fortunately, most nucleophilic substitution reactions

are ionic, either anionic



or cationic



For this reason they are well suited for mass spectrometric investigation. After the pioneering work of Bohme and co-workers [4–7] and by the group of Brauman and co-workers [8–10] in the early 1970s, a large number of reactions have been studied using techniques like flowing afterglow [11,12], Fourier transform-ion cyclotron resonance (FT-ICR) [13–15], static high-pressure cells [16–18] and drift cells [19]. In these studies, the amount of ionic reactant and product is monitored as a function of time while varying temperature, relative kinetic energy and other reaction parameters. One great advantage of studying gas phase reactions is that they can be modelled reliably and accurately using computer based theoretical methods. Both *ab initio* quantum chemical and semiempirical methods for the study of the potential energy surfaces and kinetic and dynamic details, have proved very fruitful for our understanding in this area of chemistry. The large proportion of theoretical papers in this review reflects this.

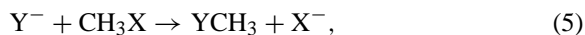
Despite all the detailed and relevant information that may be obtained from gas phase studies, we need to be careful when applying the knowledge to solution phase. Great caution should be exercised since ion–molecule reactions, like those of Eqs. (3) and (4), are greatly enhanced in *vacuo* due to the long-range ion–dipole potential. This interaction is effectively screened in solution, and consequently the dynamics and molecular orientation of ion–molecule collisions in the two media will be different. It is also important to realise that reactivity is greatly influenced by the medium in the sense that relative energies of reactants, products, and transition structures may be drastically altered upon solvation.

In the following section, we discuss the current understanding of the potential energy surface for gas phase bimolecular nucleophilic substitution reactions. In particular we deal with important topics such as the

barrier heights for reaction that are decisive for the reaction rates and pathways, the fundamentally important Marcus relation, and trends and correlations that have been revealed in the literature. We will leave the discussion of the dynamical details that have been elucidated in a number of articles the last decade to Section 4. In Section 5, a brief overview is given of gas phase studies on the effect of solvation and the transition to solution. Finally, we review and criticise the current view on the separation of these reactions into two distinct reaction types, the  $S_N1$  and  $S_N2$  reaction, in Sections 6 and 7.

### 3. The nucleophilic substitution potential energy surface

The most extensively studied gas phase  $S_N2$  reactions are the thermoneutral and exothermic reactions of halide ions with halomethanes



where X and Y are halogens. In particular, the identity reaction (X = Y = Cl) and the exothermic reaction (X = Br and Y = Cl) have been the subject of a large number of experimental and theoretical studies (see Tables 1 and 2). The model of a double-well shape for the potential energy surfaces for these and other  $S_N2$  reactions was developed in the classic 1977 paper of Olmstead and Brauman [20,21]. The important thermoneutral identity reaction is illustrated in Fig. 1a, while the exothermic and the barrier-free exothermic reactions are illustrated in Fig. 1b and c, respectively.

Upon collision of the reactants  $Y^-$  and  $RX = CH_3X$  of Eq. (5) on a double-well potential energy surface (with reaction rate constant  $k_1$ , see Fig. 1), an intermediate pre-reaction ion–dipole complex,  $Y^- \cdots CH_3X$ , is formed which is stabilised relative to the reactants by  $\Delta H_{Rcpl}$  ( $=\Delta H_{cpl}$  for the identity reaction). The complex generating step may be described by methods such as classical Langevin–Gioumousis–Stevenson ion–molecule collision theory [22,23], average dipole orientation (ADO)

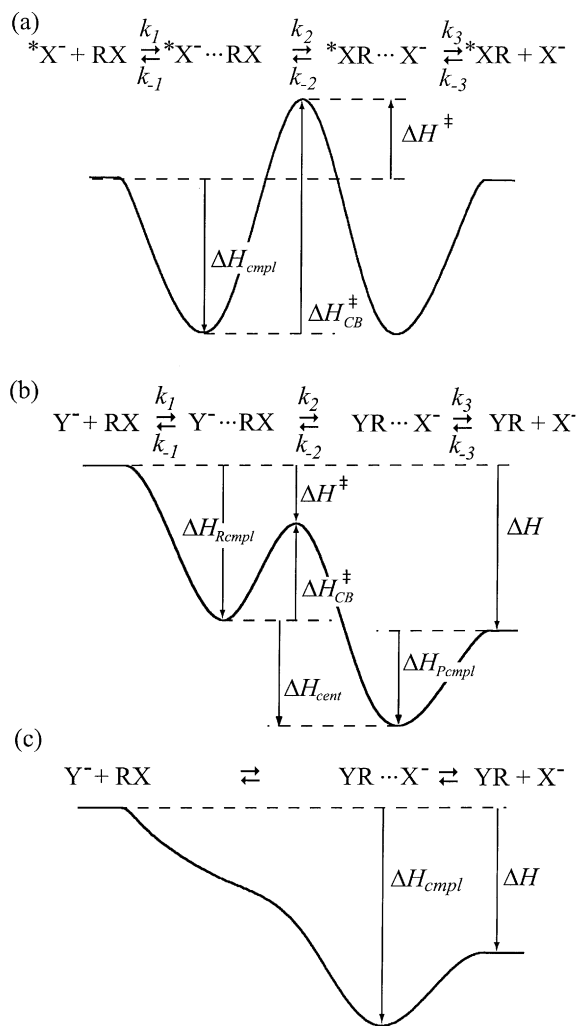


Fig. 1. Potential energy profiles for (a) a thermoneutral identity double-well  $S_N2$  reaction, (b) an exothermic double-well  $S_N2$  reaction with a significant central barrier, and (c) an exothermic  $S_N2$  reaction without a central barrier, with corresponding energy differences. Unless otherwise stated in the text, the energy differences refer to enthalpy differences at 0 K (i.e., including vibrational zero point energies).

theory [24], the trajectory calculation-parameterised method of Su and co-workers [25–28], or the statistical adiabatic channel model of Troe [29]. If the reactant complex does not dissociate back to regenerate the reactants ( $k_{-1}$ ), it may overcome the central reaction barrier ( $k_2$ ),  $\Delta H_{CB}^\ddagger$ , to reach the transition state (structure **1** in Scheme 1) which then breaks down

Table 1

Experimental and theoretical work including values for the rate constants ( $k$ ), reaction efficiencies ( $\phi$ ), and relative enthalpies for the critical points of the potential energy surface (Fig. 1a) for identity  $S_N2$  reactions of halide ions with halomethanes<sup>a,b</sup>

	$\Delta H_{\text{cpl}}^{\ddagger}$ (kJ/mol)	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta H_{\text{CB}}^{\ddagger}$ (kJ/mol)
<b>F<sup>-</sup> + CH<sub>3</sub>F → FCH<sub>3</sub> + F<sup>-</sup></b>			
PdOM (W1') <sup>c</sup>	{57.15}	{-1.55}	{55.61}
PdOM (W2h) <sup>c</sup>	{57.40}	{-1.42}	{55.98}
Wladkowski et al. <sup>d</sup>	56.9 ± 2	-3.3 ± 6	53.6 ± 6
Glukhovtsev et al. <sup>e</sup>	56.5 (57.1) {57.8}	-8.0 (-11.0) {-7.8}	48.5 (46.1) {50.0}
<b>Other theoretical work</b>			
	Benchmark ab initio calculations and assessment of compound thermochemistry and density functional methods by Parthiban et al. [34].		
	Ab initio and RRKM study ( $k = 1.5 \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$ at 300 K) by Wladkowski et al. [75].		
	Calculated G2(+) barrier height by Hoz et al. [72] (also for X = Cl, Br, and I).		
	Density functional and ab initio calculations by Ziegler and co-workers [156] (also for X = Cl, Br, and I).		
	Ab initio study of $\alpha$ -secondary kinetic isotope effects by Glad and Jensen [149] (also for X = Cl, Br, and I).		
	An assessment of the density functional generalised gradient approximations (GGAs) by Baerends and co-workers [158].		
	Quantum dynamical calculations of Basilevsky and Ryaboy [265].		
<b>Cl<sup>-</sup> + CH<sub>3</sub>Cl → ClCH<sub>3</sub> + Cl<sup>-</sup></b>			
PdOM (W1') <sup>c</sup>	{44.10}	{12.84}	{56.94}
PdOM (W2h) <sup>c</sup>	{45.77}	{11.17}	{56.94}
Botschwina <sup>f</sup>		{11.5 ± 1.0}	
Schmatz <sup>g</sup>	{44.0}	{11.0}	{55.0}
Glukhovtsev et al. <sup>e</sup>	44.0 (43.7) {44.8}	11.5 (9.8) {12.6}	55.5 (53.5) {57.4}
Li et al. [88]	43.5		
<b>Other experimental work</b>			
	Experimental determination of reaction rate as a function of kinetic energy by Bierbaum and co-workers [35,67,74]; $k = 3.5 \pm 1.8 \times 10^{-14} \text{ cm}^3 \text{ s}^{-1}$ at 300 K [67]. Estimated barrier height, $\Delta H^{\ddagger} = 4 \pm 4 \text{ kJ/mol}$ [67].		
	Examination of the promotion of the reaction by kinetic energy including kinetic isotope effects [68] and comparison with a collision theory model [275] by Ervin. [68] also contains a review of earlier work on this reaction.		
<b>Other theoretical work</b>			
	Extensive theoretical investigations by Hase and co-workers [80,247–251,254,260,263,264], including several complete potential energy surfaces [80,260], classical trajectory studies [248,250,251,254,260], and direct dynamics trajectory studies [263,264]. For reviews, see [252,262].		
	Benchmark ab initio calculations and assessment of compound thermochemistry and density functional methods by Parthiban et al. [34].		
	Reaction efficiency ( $\phi = 8 \times 10^{-6}$ ) and RRKM barrier ( $\Delta H^{\ddagger} = 10.5 \text{ kJ/mol}$ ) by Wladkowski and Brauman [69].		
	Statistical phase space prediction for the barrier, $\Delta H^{\ddagger} = 12 \text{ kJ/mol}$ , by Graul and Bowers [106].		
	Ab initio and transition state theory study including the construction of full potential energy surfaces by Tucker and Truhlar [81,82].		
	Test of the performance of the B3-LYP density functional by Glukhovtsev et al. [155].		
	Car-Parrinello molecular dynamics study by Baerends and co-workers [60].		
	Hybrid ab initio molecular orbital and Monte Carlo study for ion-dipole complex at 300 K by Asada et al. [316].		
	Reaction path Hamiltonian study by Okuno [351].		
	Potential energy surface and reaction path Hamiltonian study by Billing [84].		
	Density functional study of Adamo and Barone [157].		
	Quantum dynamical calculations by Clary, Schmatz and co-workers [85,87,266–268,281], including a study of scattering resonances [268] and use of a state-of-the-art CCSD(T) potential energy surface [85,87,281].		
	Quantum scattering study of Yu and Nyman [280].		

Table 1 (Continued)

	$\Delta H_{\text{cpl}}$ (kJ/mol)	$\Delta H^\ddagger$ (kJ/mol)	$\Delta H_{\text{CB}}^\ddagger$ (kJ/mol)
$\text{Br}^- + \text{CH}_3\text{Br} \rightarrow \text{BrCH}_3 + \text{Br}^-$			
PdOM (W1') <sup>c</sup>	{41.96}	{4.27}	{46.23}
PdOM (W2h) <sup>c</sup>		{3.22}	
Glukhovtsev et al. <sup>e</sup>	41.1 (40.5) {42.6}	5.8 (4.5) {6.2}	46.9 (45.0) {48.7}
Li et al. [88]	46.9		
Other theoretical studies	Benchmark ab initio calculations and assessment of compound thermochemistry and density functional methods by Parthiban et al. [34].		
$\text{I}^- + \text{CH}_3\text{I} \rightarrow \text{ICH}_3 + \text{I}^-$			
Glukhovtsev et al. <sup>e</sup>	36.0 (35.3)	6.5 (5.5)	42.5 (40.8)
Experimental studies	A number of spectroscopic studies on the $\text{I}^- \cdots \text{CH}_3\text{I}$ ion-dipole complex ( $\Delta H_{\text{cpl}} = 37 \pm 2$ kJ/mol [93]) with particular focus on detection and characterisation of charge-transfer excited states by Johnson and co-workers [93,95–98].		
Other theoretical studies	Ab initio study of $\text{I}^- \cdots \text{CH}_3\text{I}$ energy and geometric parameters taking into account basis set superposition errors, by Hu and Truhlar [94].		

<sup>a</sup> Only the most recent and accurate data are included. The reader is referred to the articles cited for earlier studies.

<sup>b</sup> Enthalpies are given at 0 K. Enthalpies at 298 K are given in parentheses, while values at 0 K uncorrected for the small zero point vibrational energies are given in braces.

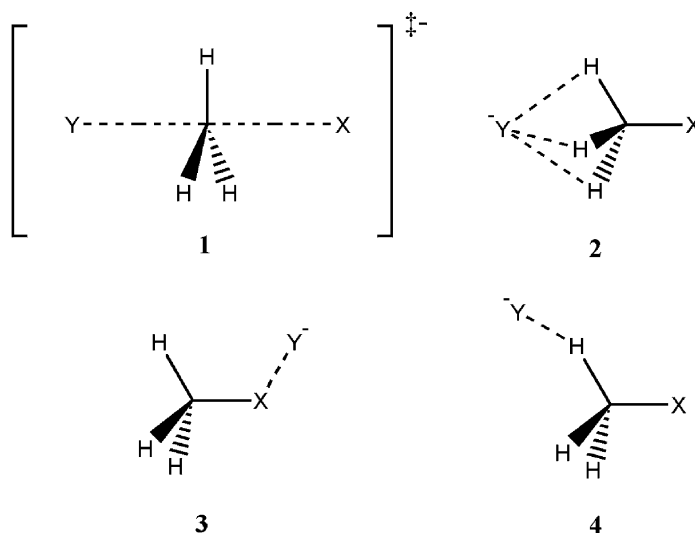
<sup>c</sup> W1' and W2h benchmark ab initio results of Parthiban et al. [34].

<sup>d</sup> Ab initio predictions by Wladkowski et al. [75].

<sup>e</sup> G2(+) calculations of Glukhovtsev et al. [32]. Data in braces from [34].

<sup>f</sup> CCSD(T) benchmark prediction of Botschwina [86].

<sup>g</sup> CCSD(T) predictions of Schmatz [87].



Scheme 1.

Table 2

Experimental and theoretical work including values for the rate constants ( $k$ ), reaction efficiencies ( $\phi$ ), and relative enthalpies for the critical points of the potential energy surface (Fig. 1b) for non-identity  $S_N2$  reactions of halide ions with halomethanes<sup>a,b</sup>

	$\Delta H_{R_{\text{cpl}}}$ (kJ/mol)	$\Delta H^\ddagger$ (kJ/mol)	$\Delta H_{\text{CB}}^\ddagger$ (kJ/mol)	$\Delta H_{\text{Pcpl}}$ (kJ/mol)	$\Delta H$ (kJ/mol)
<b><math>F^- + CH_3Cl \rightarrow CH_3F + Cl^-</math></b>					
PdOM <sup>c</sup>	{64.6}	{-52.5}	{12.1}	{39.8}	{136.6}
BHSO <sup>d</sup>	{66 ± 1}	{-52} -52 <sup>e</sup>	{14 ± 1}	{40 ± 1}	-132 (-132) {-136}
Glukhovtsev et al. <sup>f</sup>	64.4 (64.6)	-52.5 (-54.7) {-52.8}	11.9 (9.9)	39.3 (39.3)	-127.5 (-127.8)
Experimental studies					
Reaction rate constant (O'Hair et al. [49]): $k = 14 \pm 3 \times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$ ( $\phi = 0.61$ ; 0.68 for $CD_3Cl$ ).					
Reaction rate constant as a function of temperature and average kinetic energy by Su et al. [274].					
Guided ion beam tandem mass spectrometric and ab initio theoretical study of $S_N2$ and competing reactions by Angel and Ervin [61].					
Kinetic energy release study of VanOrden et al. [352].					
Other theoretical studies					
Detailed potential energy surface [257], high level classical trajectory calculations [261] and rate constants calculated applying statistical theories [257] by Hase and co-workers.					
Direct ab initio dynamics studies of Tachikawa and Igarashi [353,354].					
<b><math>F^- + CH_3Br \rightarrow CH_3F + Br^-</math></b>					
PdOM <sup>c</sup>	{71.2}	{-68.5}	{2.7}	{35.6}	{173.3}
Glukhovtsev et al. <sup>f</sup>	68.9 (68.9)	-65.8 (-67.7) {-66.1}	3.1 (1.2)	34.6 (34.5)	-159.6 (-160.1)
Experimental studies					
Reaction rate constant (O'Hair et al. [49]): $k = 19 \pm 5 \times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$ ( $\phi = 0.84$ ; 0.86 for $CD_3Br$ ).					
Reaction rate constant as a function of temperature and average kinetic energy by Su et al. [274].					
<b><math>F^- + CH_3I \rightarrow CH_3F + I^-</math></b>					
Glukhovtsev et al. <sup>f</sup>	69.6 (69.6)	-68.9 (-70.9) {-69.2}	0.8 (-1.3) <sup>g</sup>	30.7 (30.4)	-177.5 (-178.1)
Experimental studies					
Reaction rate constant (O'Hair et al. [49]): $k = 19 \pm 5 \times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$ ( $\phi = 0.87$ ; 0.89 for $CD_3I$ ).					
Reaction rate constant as a function of temperature and average kinetic energy by Su et al. [274].					
<b><math>Cl^- + CH_3Br \rightarrow CH_3Cl + Br^-</math></b>					
PdOM <sup>c</sup>	{49.8}	{-13.8} <sup>h</sup>	{36.0}	{43.2}	{-35.8}
SBS <sup>i</sup>	{46.9}	{-9.2 ± 0.4} -9.5 <sup>e</sup>	{38.1}	{40.5}	-34.3 (-34.1) {-35.7}
Schmatz <sup>j</sup>	{47.2}	{-8.9} -9.2 <sup>e</sup>	{38.3}	{41.3}	{-31.8}
Glukhovtsev et al. <sup>f</sup>	46.3 (45.9)	-6.8 (-8.4) {-6.5}	39.5 (37.5)	39.0 (38.6)	-32.1 (-32.3)
Li et al. <sup>k</sup>	52.3	-7.5	44.8	45.6	-31.4
Other experimental work					
Variable-temperature selected ion flow drift tube determination of rate constant as a function of kinetic energy and temperature including isotope effects [114,115]. At 300 K, $k = 2.4 \pm 0.6 \times 10^{-11}$ and $2.7 \pm 0.7 \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$ for $CH_3Br$ and $CD_3Br$ , respectively [115].					
FT-ICR mass spectrometry kinetic energy dependence of reaction rate study by Craig and Brauman [111]. At 350 K, $k = 2.8 \pm 0.8 \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$ .					
Reaction rate constant (Bierbaum and co-workers [35,37]): $k = 2.7 \pm 0.5 \times 10^{-11}$ ( $\phi = 0.015$ ) and $3.4 \pm 0.7 \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$ for $CH_3Br$ and $CD_3Br$ , respectively.					
Relative kinetic energy distribution studies from dissociation of metastable reactant and product complexes by Graul and Bowers [105,106], including phase space modelling of $\Delta H^\ddagger = -8.2 \pm 1.5 \text{ kJ/mol}$ (300 K).					
Isolation and activation of reactant and product complexes by Johnson and co-workers [107].					
Atmospheric pressure determination of rate constant ( $k = 3.4 \pm 0.7 \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$ at 398 K and 640 Torr [19]) as a function of temperature, and estimated reaction barrier, $\Delta H^\ddagger = -9.2 \text{ kJ/mol}$ , by Grimsrud and co-workers [19,55], as well as rate constants at higher than atmospheric pressure [112].					
Study of formation of $ClBr^-$ at superthermal collision energies by Cyr et al. [356].					

Table 2 (Continued)

	$\Delta H_{\text{Rcpl}}$	$\Delta H^\ddagger$ (kJ/mol)	$\Delta H_{\text{CB}}^\ddagger$	$\Delta H_{\text{Pcpl}}$	$\Delta H$ (kJ/mol)
Measurements of rate constants down to 23 K by Le Garrec et al. [113]. Thermal dissociation rate study by Seeley et al. [108], giving an effective RRKM barrier, $\Delta H_{\text{CB}}^\ddagger = 22.5 \pm 2.5$ kJ/mol at 298 K. Dissociation of reactant channel ion-dipole complex by preferential excitation of intra- and intermolecular modes by Tønner and McMahon [109]. Infrared spectroscopic study of entrance and exit channel ion-dipole complexes by Ayotte et al. [110].					
Other theoretical studies					
Extensive theoretical investigations by Hase and co-workers, including several complete potential energy surfaces derived from ab initio [102,103] and semi-empirical calculations [255] employed in statistical rate theory [103], classical trajectory studies [253,255], a quantum dynamical study [259], as well as an analysis based on the reaction path Hamiltonian [256] and Lyapunov exponents [258]. For a review, see [262]. Quantum dynamical studies of Clary, Schmatz and co-workers [87,113,269]. Car–Parrinello molecular dynamics calculations by Raugei et al. [283]. Ab initio energies for stationary points on the potential energy surface and statistical theory calculations of rate constants and kinetic isotope effects by Hu and Truhlar [169].					
$\text{Cl}^- + \text{CH}_3\text{I} \rightarrow \text{CH}_3\text{Cl} + \text{I}^-$ Glukhovtsev et al. <sup>f</sup>	45.8 (45.3)	−13.8 (−15.3) {−14.2}	32.0 (30.0)	34.4 (33.9)	−49.9 (−50.4)
Experimental studies					
Reaction rate constant (Gronert et al. [37]): $k = 1.7 \pm 0.3 \times 10^{-10}$ ( $\phi = 0.095$ [106]) and $2.0 \pm 0.4 \times 10^{-10}$ $\text{cm}^3 \text{s}^{-1}$ for $\text{CH}_3\text{I}$ and $\text{CD}_3\text{I}$ , respectively. Kinetic energy release distributions (KERDs) from dissociation of metastable ion-dipole complexes by Graul and Bowers [106], including phase space modelling of $\Delta H^\ddagger = -19 \pm 2$ kJ/mol (300 K). Study of formation of $\text{ICl}^-$ at superthermal collision energies by Cyr et al. [356].					
Other theoretical work					
Ab initio calculations and statistical theory calculations of rate constants and kinetic isotope effects by Hu and Truhlar [169].					
$\text{Br}^- + \text{CH}_3\text{I} \rightarrow \text{CH}_3\text{Br} + \text{I}^-$ Glukhovtsev et al. <sup>f</sup>	40.7 (40.0)	−2.3 (−3.5) {−2.0}	38.4 (36.5)	36.3 (35.7)	−17.9 (−18.0)
Experimental studies					
Reaction rate constant (Gronert et al. [37]): $k = 2.9 \pm 0.6 \times 10^{-11}$ ( $\phi = 0.022$ [106]) and $3.8 \pm 0.8 \times 10^{-11}$ $\text{cm}^3 \text{s}^{-1}$ for $\text{CH}_3\text{I}$ and $\text{CD}_3\text{I}$ , respectively. KERDs from dissociation of metastable ion-dipole complexes by Graul and Bowers [106], including phase space modelling of $\Delta H^\ddagger = -11 \pm 2$ kJ/mol (300 K). Photoelectron spectroscopic study of ion-dipole complex [95].					
Other theoretical work					
Ab initio calculations and statistical theory calculations of rate constants and kinetic isotope effects by Hu and Truhlar [169].					

<sup>a</sup> Only the most recent and accurate data are included. The reader is referred to the articles cited for earlier studies.

<sup>b</sup> Enthalpies are given at 0 K. Enthalpies at 298 K are given in parentheses, while values at 0 K uncorrected for the small zero point vibrational energies are given in braces.

<sup>c</sup> W1' ab initio results of Parthiban et al. [34].

<sup>d</sup> CCSD(T) study of Botschwina and co-workers [100].

<sup>e</sup> Estimated employing zero point vibrational energy corrections from Glukhovtsev et al. [33].

<sup>f</sup> G2(+) calculations of Glukhovtsev et al. [33].

<sup>g</sup> The reaction  $\text{F}^- + \text{CH}_3\text{I} \rightarrow \text{CH}_3\text{F} + \text{I}^-$  has little or no barrier for reaction depending upon the level of theory [33].

<sup>h</sup> The value in ref. [34], Table 6 is in error [355].

<sup>i</sup> CCSD(T) study of Schmatz et al. [101].

<sup>j</sup> CCSD(T) study of Schmatz [87].

<sup>k</sup> High-pressure mass spectrometric investigation by McMahon and co-workers [88,109].

into the product ion–dipole complex,  $YCH_3 \cdots X^-$ . This is stabilised relative to the products by  $\Delta H_{\text{pcmpl}} (= \Delta H_{\text{cmpl}}$  for the identity reaction). This ion–dipole complex may again re-isomerise across the central barrier ( $k_{-2}$ ) or it dissociates and forms the products ( $k_3$ ). Within this model, the kinetics has been described by unimolecular reaction rate theory once the pre-reaction complex has been generated. Assuming steady state conditions, the reaction rate constant may be approximated by [30,31]

$$k_{\text{obs}} = \frac{k_1 k_2 k_3}{k_{-1} k_{-2} + k_{-1} k_3 + k_2 k_3} = k_{\text{coll}} \phi, \quad (6)$$

where the rate constants are defined in Fig. 1,  $k_1 = k_{\text{coll}}$ , and  $\phi$  is the reaction efficiency. For the thermoneutral identity reaction, the simplified expression reads

$$k_{\text{obs}} = \frac{k_{\text{coll}} k_{\text{isom}}}{k_{\text{diss}} + 2k_{\text{isom}}} = k_{\text{coll}} \phi, \quad (7)$$

where  $k_{-1} = k_3 = k_{\text{diss}}$ , and  $k_{-2} = k_2 = k_{\text{isom}}$ . The rate determining overall activation barrier illustrated in the figure has been termed  $\Delta H^\ddagger$ , while the enthalpy difference between the entrance and exit channel complexes is  $\Delta H_{\text{cent}}$  (i.e., the enthalpy change for the elementary step over the central energy barrier). The total reaction exothermicity is  $\Delta H$ .

This model is now widely believed to be the correct description of the potential energy surface for most gas phase  $S_N2$  reactions, with reaction rates and efficiencies being determined mainly by the height of the central barrier. Strong support for this also comes from a large number of theoretical ab initio calculations (see e.g., [32–34]), which currently is the most efficient way of obtaining detailed information about the potential energy surfaces. For a large number of  $S_N2$  reactions, the reactants are fairly strongly attracted to one another and the result is a long-lived reactant complex (see also Section 4), but for exothermic reactions with an insignificant barrier (Fig. 1c) transformation may occur at nearly every encounter. Importantly, the re-dissociation of the reactant ion–dipole complex into the reactants is entropically favoured over the highly structured  $S_N2$  displacement step for reactions with a central barrier. Consequently, even reactions with a

negative overall energy barrier,  $\Delta H^\ddagger$ , occur with low efficiency, and only displacements with barriers below or slightly above the energy of the reactants occur at a measurable rate. There are thus a relatively narrow “window” of reactions that have measurable reaction rates below the collision rate and which reveal the most interesting information about the potential energy surfaces [35]. Theoretical calculations do not suffer from this limitation.

Another complication that is encountered in the experimental work on  $S_N2$  reactions, is due to competing reactions such as bimolecular elimination (E2) (see e.g., [35–42]), bimolecular substitution involving allylic rearrangement ( $S_N2'$ ) [43], proton or electron transfer (e.g., [44–48]), and association. In particular, discriminating between  $S_N2$  and E2 reactions is problematic, since in many cases the ionic products are of identical elemental composition. Experimental procedures for distinguishing between the two reaction pathways for anionic systems have involved investigating deuterium kinetic isotope effects (KIEs) (see e.g., [37,49]). Also the recent technique of Gronert and co-workers is very promising, focusing on employing dianions as nucleophiles, making direct discrimination between E2 and  $S_N2$  products possible [50–53]. A comprehensive overview of processes that may be competing with  $S_N2$  reactions in various experiments has recently been given by Gronert [52].

The double-well potential energy surface of Fig. 1 also explains the negative temperature dependence for reactions with a negative overall energy barrier [54–56] and why the reactions are fairly insensitive to temperature changes. Most of the energy that is needed to pass the reaction barrier comes from the attractive dipole–ion potential [57]. It is emphasised that the double-well model also is applicable for the substitution reaction in condensed phases. However, for reactions in solution, the ion–dipole complexes may be absent or at least are destabilised relative to the separate reactants (see e.g., [58–60]). This will be discussed further in Section 5.

The “backside” ion–molecule complex **2** (Scheme 1) is at the entrance channel for the Walden inversion passage over the central barrier with the corresponding



transition state **1**. The “frontside” (**3** or a related structure) complex and substitution mechanism will be discussed in detail in Section 6. The structure **2** has generally been believed to be the global energy minimum at the pre-reaction side of the potential energy surface for the X and Y halogen system of Eq. (5) (e.g., [32] and references therein). However, this was questioned in a recent study by Angel and Ervin [61], where it was found that the hydrogen-bonded complex  $F^- \cdots H-CH_2Cl$  (**4**) was lower in energy than structure **2**. While the stability of **4** may be limited to systems with strongly directed  $H \cdots F$  hydrogen bonds, this example illustrates the importance of detailed studies of the potential energy surface. This may also have implications for the reliability of reduced dimensionality methods that do not sample all internal degrees of freedom in the system. For a number of other nucleophilic substitution reactions—especially cationic reactions—**2** is usually not the most stable ion–molecule complex, and more often a “frontside” complex similar to **3** is lower in energy. This situation is particularly prominent when X is capable of forming hydrogen bonds to Y (see e.g., [62]). As we will discuss below, complex **3** may be the direct precursor for front side nucleophilic substitution.

Following the pioneering work of Olmstead and Brauman [20], statistical transition state theory has been applied in the description of gas phase nucleophilic substitution reactions. The assumptions of these theories may not be fully justified in all cases as will be discussed in Section 4, but errors introduced appear to be modest, especially for the larger systems. Before returning to the dynamical features in Section 4, we will review the understanding of the potential energy surfaces for these reactions.

### 3.1. The identity reaction

Valuable insight into the nature of the  $S_N2$  reaction—as for many other elementary reactions—has been obtained by applying Marcus theory [30,63–66]. For the nucleophilic substitution reaction of Fig. 1, Marcus theory describes the activation energy for the *elementary* step over the central bar-

rier,  $\Delta H_{CB}^\ddagger$ , as being equal to an *intrinsic* barrier,  $\Delta H_{CB,0}^\ddagger$ , modified by the barrier lowering *exothermicity*,  $\Delta H_{cent}$ , of the reaction

$$\Delta H_{CB}^\ddagger = \Delta H_{CB,0}^\ddagger + \frac{1}{2} \Delta H_{cent} + \frac{(\Delta H_{cent})^2}{16 \Delta H_{CB,0}^\ddagger}. \quad (8)$$

The intrinsic barrier is the barrier of the reaction under thermoneutral conditions. For the thermoneutral identity reactions with the nucleophile and nucleofuge being identical, there is no thermodynamical driving force for the reaction and thus only an intrinsic barrier. Consequently, the relationships between structure and reactivity for these identity reactions (i.e., underlying *intrinsic* nucleophilicity) are extremely important, since the reactivity is a fundamental property of the nucleophile and can be used to characterise nucleophiles in general. Unfortunately, identity reactions are difficult to study experimentally. They often have barriers close to or higher than the energy of the reactants, and therefore are extremely slow. However, some of these reactions have been studied experimentally, usually by employing pure isotope labelled reactants in order to discriminate between reactants and products (see e.g., [31,62,67–71]). Due to experimental limitations and the approximate nature of the theoretical models applied, early data for identity  $S_N2$  reactions is often of limited value in terms of accuracy. During the last decade, however, a fair amount of nucleophiles and substrates have been studied with sufficient accuracy for real trends to become transparent. A rather comprehensive compilation of rate data as well as experimental and theoretical predictions for the potential energy surfaces from a number of recent studies is given in Tables 1 and 2 (Table 3 of Hoz et al. [72] as well as [73] contain additional barriers for thermoneutral substitution reactions).

All of the identity halide exchange reactions of Table 1 (Eq. (5) with  $X = Y$ ) are expected to be slow, and experimental data is only available for the chloride exchange reaction [35,67,74]



The reaction rate is at the limit of what is measurable and corresponds to reaction for approximately

Table 3

Experimental and theoretical values for the rate constants ( $k$ ), reaction efficiencies ( $\phi$ ), and relative enthalpies for the critical points of the potential energy surface (Fig. 1a) for identity  $S_N2$  reactions<sup>a</sup>

	$k$ ( $\text{cm}^3 \text{s}^{-1}$ )	$\phi$	$\Delta H_{\text{cnp1}}$ (kJ/mol)	$\Delta H^\ddagger$ (kJ/mol)
$^{37}\text{Cl}^- + ^{35}\text{ClCH}_2\text{CN} \rightarrow ^{37}\text{ClCH}_2\text{CN} + ^{35}\text{Cl}^-$ WLAB <sup>b</sup> , WB <sup>c</sup>	$3.3 \pm 0.9 \times 10^{-10}$	0.11	81.2	-25
$^{81}\text{Br}^- + ^{79}\text{BrCH}_2\text{CN} \rightarrow ^{81}\text{BrCH}_2\text{CN} + ^{79}\text{Br}^-$ WB <sup>c</sup>	$2.6 \pm 1.1 \times 10^{-10}$	0.13	–	-31
$^{37}\text{Cl}^- + \text{C}_6\text{H}_5\text{CH}_2^{35}\text{Cl} \rightarrow \text{C}_6\text{H}_5\text{CH}_2^{37}\text{Cl} + ^{35}\text{Cl}^-$ WB <sup>c</sup>	$6.8 \pm 2.3 \times 10^{-13}$	0.0003	–	+1.7
WWB <sup>d</sup>	$6.5 \pm 2.6 \times 10^{-13}$	0.00029	–	+0.8
$^{81}\text{Br}^- + \text{C}_6\text{H}_5\text{CH}_2^{79}\text{Br} \rightarrow \text{C}_6\text{H}_5\text{CH}_2^{81}\text{Br} + ^{79}\text{Br}^-$ WB <sup>c</sup>	$1.3 \pm 0.2 \times 10^{-11}$	0.0076	–	-11
$^{37}\text{Cl}^- + \text{X}-\text{C}_6\text{H}_5\text{CH}_2^{35}\text{Cl} \rightarrow \text{X}-\text{C}_6\text{H}_5\text{CH}_2^{37}\text{Cl} + ^{35}\text{Cl}^-$ , WWB <sup>d</sup>				
X = <i>m</i> -CH <sub>3</sub>	$1.1 \pm 0.5 \times 10^{-12}$	0.00037	–	-0.8
X = <i>m</i> -OCH <sub>3</sub>	$5.3 \pm 2.5 \times 10^{-12}$	0.0017	–	-4.6
X = <i>m</i> -F	$1.8 \pm 0.2 \times 10^{-11}$	0.0079	–	-11
X = <i>m</i> -Cl	$6.2 \pm 1.7 \times 10^{-11}$	0.027	–	-15
X = <i>m</i> -CF <sub>3</sub>	$2.5 \pm 0.4 \times 10^{-10}$	0.081	–	-21
$\text{H}_2^{18}\text{O} + \text{R}-\text{OH}_2^+ \rightarrow \text{R}-^{18}\text{OH}_2^+ + \text{H}_2\text{O}$ , UB-A <sup>e</sup>				
R = CH <sub>3</sub>	$2.2 \pm 0.4 \times 10^{-13}$	(-50)	-13	(-8)
R = CH <sub>3</sub> CH <sub>2</sub>	$6.7 \pm 1.3 \times 10^{-14}$	(-47)	-5	(1)
R = (CH <sub>3</sub> ) <sub>2</sub> CH	$4.6 \pm 0.9 \times 10^{-11}$	(-45)	-18	(-3)
R = (CH <sub>3</sub> ) <sub>3</sub> C	$4.0 \pm 0.8 \times 10^{-10}$	(-44)	-23	(-20)
$\text{Cl}^- + \text{R}-\text{Cl}$ , Li et al. <sup>f</sup> and Jensen <sup>g</sup>				
R = CH <sub>3</sub>		43.5	(44.4)	(9.6)
R = CH <sub>3</sub> CH <sub>2</sub>		51.9	(49.4)	(24)
R = <i>n</i> -propyl			(43.9)	(16)
R = <i>i</i> -propyl		61.5	(54.8)	(36)
R = <i>i</i> -butyl			(54.4)	(25)
R = <i>t</i> -butyl		69.5	(61.5)	(76)
R = neopentyl			(45.2)	(51)

<sup>a</sup> The reader is referred to the articles cited for earlier studies.

<sup>b</sup> FT-ICR and RRKM data of Wladkowski et al. [31].

<sup>c</sup> FT-ICR and RRKM study of Wladkowski and Brauman [69].

<sup>d</sup> FT-ICR and RRKM data of Wladkowski et al. [70].

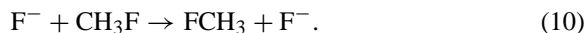
<sup>e</sup> FT-ICR/RRKM and ab initio MP2 (in parentheses) data from Uggerud and Bache-Andreassen [62].

<sup>f</sup> High-pressure MS study of Li et al. [88].

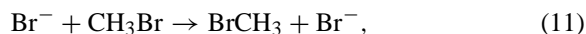
<sup>g</sup> Ab initio MP2 calculations by Jensen [148] in parentheses.

only 1 in every 125,000 collisions [67,69]. Rice–Ramsberger–Kassel–Marcus (RRKM) calculations of Wladkowski and Brauman [69], puts the overall barrier at 10.5 kJ/mol, but it should be noted that these barriers have been calculated applying transition state theory which has been questioned for the present reaction (see Section 4). Since there is only one stable fluorine isotope, there are limited prospects for an experimental study involving the fluoride ion, for

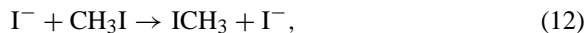
example, for the reaction [75]



However, theoretical calculations predict the overall reaction barrier for the reactions



and



to be lower than for reaction (9) (see Table 1), indicating that they might be accessible for current state-of-the-art experiments. Almost 15 years after the experiments on reaction (9) were performed [67], a reinvestigation of this reaction as well as reactions (11) and (12) might be appropriate.

Experimental results (combined with RRKM calculations) are also available for identity substitution reactions between chloride and bromide ions and a number of  $\alpha$ -substituted methyl chlorides and bromides [31,69–71,76,77] (Table 3). All these reactions have an overall reaction barrier,  $\Delta H^\ddagger$ , below or slightly above the energy of the reactants, the highest barrier being approximately +1 kJ/mol for the reaction between  $\text{Cl}^-$  and  $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$ . Finally, Craig and Brauman have successfully studied the gas phase identity reactions between chloride and primary  $n$ -alkyl chlorides by FT-ICR mass spectrometry. In these systems, introduction of  $\omega$ -substituents (CN, Cl and OH) lead to “intramolecularly solvated” reactions and a lowering of the overall reaction barrier compared with the unsolvated system [78,79]. This is contrary to the usual trend of reduced reaction rates upon full or partial solvation of the reactants (see Section 5).

Recently, the first experimental results for identity cationic gas phase  $\text{S}_{\text{N}}2$  reactions became available [62] (Table 3). This was also the first gas phase study of identity  $\text{S}_{\text{N}}2$  reactions involving nucleophilic attack at secondary and tertiary carbon—the reaction barriers being lower than what has been found earlier in anionic systems involving stronger nucleophiles.

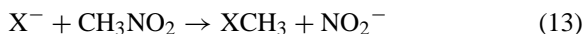
The potential energy surfaces for reactions (9)–(12) have been extensively studied by theoretical methods (Table 1). Full analytical potential energy surfaces for reaction (9) generated from ab initio data are available from the groups of Hase [80], Truhlar [81–83], and Billing [84], while a high quality two-dimensional surface recently was developed by Schmatz et al. [85]. These surfaces confirm the double-well model of Fig. 1a, with a central barrier separating the entrance and exit channel with the corresponding ion–dipole complexes. While the full analytical surfaces and a number of other theoretical studies give values for the energies at the critical points of the potential en-

ergy surfaces for the reactions of Table 1 with some uncertainty, a number of very recent studies have finally pinned down the relevant parameters with high accuracy employing current state-of-the-art electronic structure methods. The complexation energies and barrier heights for these reactions between halide ions and methyl halides are now known within a few kJ/mol from the benchmark calculations of Botschwina [86] and Schmatz [87] for reaction (9), and most recently by the group of Martin and co-workers [34] for reactions (9)–(11) (see Table 1). These results are in good agreement with the few experimental results that are available,  $\Delta H^\ddagger = 4 \pm 4$  kJ/mol [67],  $\Delta H^\ddagger = 10.5$  kJ/mol [69], and  $\Delta H_{\text{cpl}} = 43.5$  kJ/mol [88], for reaction (9) which is to be compared with the highest quality ab initio results,  $\Delta H^\ddagger = 11.2$  kJ/mol [34],  $\Delta H^\ddagger = 11.5$  kJ/mol [86] and  $\Delta H_{\text{cpl}} = 45.8$  kJ/mol [34]. Note that the ab initio data does not include the zero-point vibrational energy which amount to approximately 1 kJ/mol for the enthalpy differences in this system [32]. The experimental estimate for the reaction barrier is based on statistical theory RRKM calculations [69]; possibly of questionable accuracy for reactions (9)–(12) (see Section 4).

The G2-type calculations of Hoz et al. [72] and Glukhovtsev et al. [32] (see Table 1) are in good agreement with the above benchmarks. This is quite promising since the G2 [89] and more recent G3 [90] models may be applied for studies of a much larger number of  $\text{S}_{\text{N}}2$  reactions. In our own experience, the models may currently be used for  $\text{S}_{\text{N}}2$  reaction systems containing at least 6–8 first row atoms in addition to hydrogens [91]. Note that additional G2 data for 12 additional  $\text{S}_{\text{N}}2$  reactions is given in [72], and that G2 data for the identity  $\text{S}_{\text{N}}2$  reactions (9)–(12) with retention of configuration is available from Glukhovtsev et al. [92]. For a discussion of various theoretical approaches for the calculation of gas phase substitution reaction potential energy surfaces, see Section 3.3.

Several studies have concentrated on the properties of the ion–dipole complexes for identity  $\text{S}_{\text{N}}2$  reactions. Li et al. [88] have determined the complexation energies for  $\text{X}^- \cdots \text{RX}$  ( $\text{X} = \text{Cl}, \text{Br}$ ) by high-pressure mass spectrometry and find a steady growth in  $\Delta H_{\text{cpl}}$

with the size and corresponding increase in polarisability of the alkyl group R. Finally, the complex  $I^- \cdots CH_3I$  has been the subject of a number of studies by the Johnson group, including photoelectron spectroscopy [93] (see also [94]), and attempts on characterising charge transfer excited states [95–98]. While the  $I^- \cdots CH_3I$  complex proved to involve experimental difficulties, similar experiments for the photoexcitation of  $X^- \cdots CH_3NO_2$  ( $X = Cl, Br, I$ ) to the  $X \cdots CH_3NO_2^-$  charge transfer complex successfully initialised the non-identity (vide infra)  $S_N2$  reaction

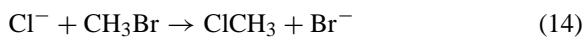


upon decomposition of the charge transfer complex [99]. Experiments of this type represent a significant advance in the possibilities for experimentally characterising the transition states for  $S_N2$  reactions.

### 3.2. Exothermic substitution—the non-identity reaction

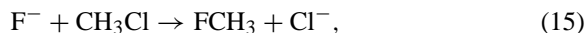
During the last decade, a large number of publications have dealt with non-identity  $S_N2$  reactions in the gas phase. A fairly comprehensive summary for reaction (5) ( $X$  and  $Y$  halogens) is given in Table 2. As for the identity reactions of Table 1, the state-of-the-art benchmark studies of Botschwina et al. [100] ( $X = Cl$  and  $Y = F$ ), Schmatz et al. [101] ( $X = Br$  and  $Y = Cl$ ), and Martin and co-workers [34] ( $X, Y = F, Cl, Br$ ) yield relative enthalpies for the stationary points of the potential energy surface that are accurate to within a few kJ/mol. This is confirmed by the comparison of “bottom-of-the-well” (i.e., energies excluding zero-point energies) theoretical and experimental data ( $X, Y = F, Cl, Br$ ) given in Tables 5 and 6 of ref. [34].

The experimental data is more abundant and accurate than for the identity reactions due to the higher reaction rates for the exothermic non-identity reactions. In particular, the reaction



has been studied in great detail (Table 2). Good agreement between theory and experiment is found both for complexation energies, overall exothermicities and

reaction barriers for reaction (14) and the other substitutions when experimental data are available. The exception is for the reaction barrier for [66]



where more accurate new measurements seem to be in order. As for the identity reactions discussed in Section 3.1 there is good agreement between the benchmark theoretical work discussed above and the G2(+) results of Radom and co-workers [33]. This gives credibility to the G2 method in general for gas phase nucleophilic substitution and in particular to the accuracy of the G2 enthalpies for the reactions of Table 2 involving iodine as the nucleofuge.

Full potential energy surfaces are available for reaction (14) and (15) from Hase and co-workers [102,103] as well as a reduced dimension surface of high quality by Schmatz [87] for reaction (14). The surfaces have been employed for statistical transition state theory based methods as well as both quantum dynamical and classical trajectory calculations (see Section 4).

The above full potential energy surfaces and calculations of energies at critical points by Parthiban et al. [34] and by Glukhovtsev et al. [33] confirm the double-well potential model of Fig. 1. They also demonstrate that as the reaction becomes more exothermic, there is a transition from the situation in Fig. 1a through 1c and a steady decrease of the central barrier height. An example is provided by reaction (5) with  $Y = F$  and  $CH_3X$  ( $X = F, Cl, Br, I$ ) where the reaction exothermicity sequence  $\Delta H = 0, -128, -160, -178$  kJ/mol corresponds to barrier heights of  $\Delta H_{CB}^\ddagger = 49, 12, 3, \sim 0$  kJ/mol (all data from Radom and co-workers [32,33]). For the reaction between  $F^-$  and  $CH_3I$  the potential energy profile is perhaps better illustrated as barrier-free as in Fig. 1c. In any case, this is the situation for the reaction between  $H_2O$  and  $CH_3FH^+$  and between  $NH_3$  and  $CH_3FH^+$  as found in ab initio studies by Uggerud [104].

Impressive experimental work has been performed for all the reactions between halide ions and methyl halides of Table 2, particularly for reaction (14). For this reaction, both the entrance and exit channel

ion–dipole complexes have been prepared [105–109], spectroscopically characterised [110] and activated to obtain reactants and products [105–109]. McMahon and co-workers [88,109] have determined the complete potential energy profile for the reaction (Table 2), which is in reasonable agreement with the benchmark theoretical data considering experimental error bars (see also [34]). The reaction has been studied at a wide range of pressures, from the near vacuum conditions of the FT-ICR mass spectrometer (see e.g., [111]), to higher than atmospheric pressure in a buffer gas in the ion mobility mass spectrometer of Grimsrud and co-workers [19,55,112]. The latter authors worry that the high-pressure limit for the reaction had not been reached [112] and that mechanistic conclusions drawn in [55] should be viewed with some caution. Nevertheless, the experimental overall reaction barrier of  $\Delta H^\ddagger = -9.2$  kJ/mol [55] is in perfect agreement with the benchmark theoretical results of Schmatz et al. [101] including zero-point vibrational energy corrections (from [33]),  $\Delta H^\ddagger = -9.5 \pm 0.4$  kJ/mol.

The reaction has also been studied at a wide range of temperatures, with rate data for temperatures as low as 23 K available from Le Garrec et al. [113]. The temperature dependence is negative for the rate constant, explainable by the activation energy being slightly below the energy of the separated reactants. Several other groups have also studied the reaction rate as a function of temperature and average kinetic energy [111,114,115] in particular in order to study the non-statistical issues that will be discussed in Section 4. In many respects, reaction (14) is probably the best characterised in organic chemistry.

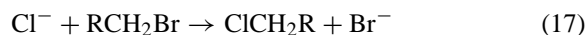
While the unsymmetrical reactions between halide ions and methyl halides of Table 2 are among the best studied gas phase  $S_N2$  reactions, work involving reactions between halide ions and larger primary or branched alkyl halides have also been published (e.g., [37,51,54–56,116–119]), focusing mainly on reactivity changes upon increased alkyl substitution of the reactants and competition with E2 pathways. In addition, substitution and competing reactions at partially and fully halogenated alkanes have been studied [45,48,120–122]. For some of these sys-

tems, there are indications that electron transfer from the anion governs the reactivity [45]. Finally,  $S_N2$  reactions involving a large number of non-halide nucleophiles and nucleofuges have been performed (e.g., [35,37,48,51,99,116,117,119,123–130]), most of which are discussed elsewhere in this review.

The shape of the potential energy surfaces for non-identity reactions is strongly influenced by the thermochemical driving force of the reaction, for example as expressed by the Marcus equation in Eq. (8). For non-identity reactions ( $X \neq Y$ ) the intrinsic barrier to be inserted in Eq. (8) may be obtained by the additivity postulate, in which the barrier is given as the average of the barrier for the two corresponding identity reactions

$$\begin{aligned} \Delta H_{CB,0}^\ddagger(X, Y) \\ = \frac{1}{2}(\Delta H_{CB,0}^\ddagger(X, X) + \Delta H_{CB,0}^\ddagger(Y, Y)). \end{aligned} \quad (16)$$

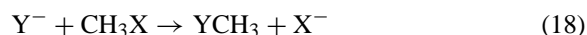
After an early ab initio test of the Marcus relation by Wolfe et al. [131,132], the Marcus treatment has more recently been tested experimentally by Wladkowski and Brauman [69] for the reactions



where  $R = CN$  and  $C_6H_5$ .

Strictly, the Marcus relation is only valid for elementary reactions. However, by assuming that the reactant and product ion–dipole complexation energies are equal [133], the Marcus relation was employed for the full three step  $S_N2$  sequence. Wladkowski and Brauman used RRKM theory (believed to be valid for these reactions [71,76,77]) in order to obtain activation energies for the reactions, and verified the additivity postulate by obtaining  $\Delta H^\ddagger(Br, Cl)$  within 0.8 and 2.1 kJ/mol of the mean for the two corresponding identity reactions for  $R = C_6H_5$  and  $CN$ , respectively [69].

Based on their comprehensive G2(+) ab initio data for the



reaction (X and Y are halogen) [32,33], Radom and co-workers have also tested the Marcus treatment and additivity postulate for the six reactions of Table 2 [33]. For the central unimolecular reaction step, they find excellent agreement between calculated and derived (Eq. (16)) energy barriers (largest and average difference 2.4 and 1.1 kJ/mol, respectively). They find, however, that the extensions of Marcus theory in order to permit a treatment of the full double-well reaction profile that have been suggested by Wolfe et al. [132] and by Dodd and Brauman [133] (as discussed above) do not perform particularly well. These Marcus-type estimates are reasonable for the reactions with a low exothermicity, but overestimates  $\Delta H^\ddagger(X, Y)$  by as much as 20 kJ/mol for the reactions with a large exothermicity. Radom and co-workers also found a linear relationship between the overall barrier,  $\Delta H^\ddagger$ , and the reaction enthalpy,  $\Delta H$  (and between  $\Delta H_{\text{CB}}^\ddagger$  and  $\Delta H_{\text{cent}}$ ) in accordance with the Bell–Evans–Polanyi principle [1,134,135]. Note that no such relationship was found by Wolfe et al. [132] for a larger group of  $S_{\text{N}}2$  reactions, admittedly employing less rigorous ab initio methods. Finally, insight into the relationship between  $\Delta H^\ddagger$  and the thermodynamic reaction driving force has been provided by Shi and Boyd [136] and by the group of Lee and co-workers through their work on allyl transfer reactions [137] and on the reaction between benzyl chlorides and phenoxide and thiophenoxide nucleophiles [138].

### 3.3. Potential energy surfaces from ab initio methods

Theoretical ab initio methods are extremely valuable for the study of potential energy surfaces for the gas phase nucleophilic substitution reactions. This is due to the difficulties encountered in experimental work for many of these systems—in particular for the fundamentally important identity reactions—and in the interpretation of the experimental data in terms of potential energy surfaces and related concepts. Unfortunately, there appears to be some confusion in the literature about the relative accuracy of the various

theoretical approaches as well as their accuracy with respect to experimentally determined parameters.

It is well known that ion–dipole well depths and in particular reaction barriers are highly sensitive to the quality of the ab initio method, and it is thus mandatory that high quality methods are employed. Both fairly large basis sets and a proper treatment of electron correlation are necessary in order to obtain reliable results. For example, the results of Botschwina [86] show that the overall barrier height,  $\Delta H^\ddagger$ , for reaction (9) is overestimated by a factor of more than three at the Hartree–Fock level compared to the highly accurate coupled cluster approach including triple excitations perturbatively (CCSD(T)). Even the CCSD method gives results that are twice as high as the more accurate barrier [86]. Second order Møller–Plesset perturbation theory (MP2) gives surprisingly accurate results [86], most likely due to fortuitous cancellation of errors for this system. More typical examples of the accuracy of the MP2 method are given in Table 3—compare the experimental and calculated values for  $\Delta H^\ddagger$  for the reactions between water and protonated alcohols and  $\Delta H_{\text{cplx}}$  for the complexation energy of  $\text{Cl}^-$  and  $\text{RCl}$ .

With the current state of computational resources and theoretical algorithms it appears that for small system nucleophilic displacement reactions (less than six to eight non-hydrogens) the compound thermochemistry schemes such as G2 and G3 of Pople and co-workers [89,90], the complete basis set (CBS) methods of Petersson and co-workers [139–141] or W1 and W2 theory from the Martin group [34,142] should be employed (for examples, see [32–34,92]). These methods give errors of only a few kJ/mol for properties such as molecular total atomisation energies and proton and electron affinities for small stable molecules containing first and second row atoms. They are expected to give results of similar quality for  $S_{\text{N}}2$  reaction parameters since the critical points on the  $S_{\text{N}}2$  potential energy surface are dominated by dynamical correlation. This is also confirmed by the studies that already have been performed (see e.g., [32–34]), as discussed in Sections 3.1 and 3.2. Also the schemes for extrapolation of high level ab initio

results (e.g., CCSD(T) data) to the basis set limit is promising for small and medium-sized systems. An excellent example is the very recent study of Borisov et al. [48] on the reaction between the hydroxyl anion and  $\text{CH}_{(4-n)}\text{Cl}_n$  ( $n = 1-4$ ).

For larger systems, the MP2 method combined with polarised double-zeta quality basis sets (6-31G\*/6-31G\*\* [143,144] or cc-pVDZ [145,146]) for geometry optimisations and triple-zeta basis sets (6-311G\*\* [147] or cc-pVTZ [145,146]) for single point energy calculations appears to be the method of choice (see e.g., [62,148–152]). This procedure should be fairly reliable if one is mainly interested in comparing energy differences or trends among several systems. Geometry optimisations may also be performed employing density functional theory, in particular with modern hybrid functionals such as B3LYP [153] and mPW1K [154] (see [34,126,155,156]). However, one should note that density functional methods perform poorly for barrier height calculations for  $\text{S}_{\text{N}}2$  reactions, even with very recent functionals, and should be applied with care [34,60,155,157–159]. Baerends and co-workers have recently attributed the problem to spurious non-dynamical correlation for three-centre four-electron bonds (such as the  $\text{S}_{\text{N}}2$  transition state) [60,158].

Finally, for large systems where the high level ab initio methods cannot be employed for the whole molecular system, the multilayer “onion-like” methods appears to have great potential [160–162]. In conclusion, there is currently no reason to rely on data produced by the rather inaccurate semiempirical, Hartree–Fock, and density functional (without high quality functionals) methods. At the very least these methods must be carefully calibrated against high level calculations (or *reliable* experimental data) for reactions with very similar properties to the system in question.

### 3.4. Kinetic isotope effects

KIEs provide one of the most powerful means of obtaining information about the structure of transition states from experiments. A number of experimental

and theoretical studies on KIEs—in particular secondary deuterium KIEs—for gas phase nucleophilic substitution reactions have appeared in the literature, but the comprehensive review by Matsson and Westaway [163] covers the situation in this field until 1998. We here only give a very brief summary of the developments in this area the last decade.

Experimental deuterium KIEs have been reported for the reaction between  $\text{Cl}^-$  and  $\text{CH}_3\text{Br}$  [114,115] and  $\text{OH}^-(\text{H}_2\text{O})_{0-4}$  and  $\text{CH}_3\text{Br}$  [164] (temperature dependence) as well as for reaction (9) [68] (as a function of relative kinetic energy of reactants. See also [119] for a discussion). However, the largest compilation of experimental data comes from the Bierbaum group and comprises an extensive set of nucleophiles and methyl and larger alkyl halides [37,49,119]. All secondary  $\alpha$ -deuterium KIEs have been found to be inverse ( $k_{\text{H}}/k_{\text{D}} < 1.0$ ) or small and normal ( $k_{\text{H}}/k_{\text{D}} > 1.0$ ), usually in the range 0.6–1.2. For this reason it has been suggested the KIEs might be used to distinguish between  $\text{S}_{\text{N}}2$  and E2 pathways—E2 KIEs are normal and primary, and usually much larger [37]. It should be noted that significant KIEs only occur for reactions for which the central barrier is of importance for the reaction rate. For very fast reactions occurring at rates close to the collision frequency, the KIEs are absent [49,165].

Several groups have calculated secondary  $\alpha$ -deuterium KIEs from ab initio or semiempirical calculations and transition state theory [43,73,82,83,103,119,126,149,165–174]. Solvent KIEs for microsolvated systems have also been determined [83,119,166–168,175]. For systems where both experimental and theoretical data are available, there is good and in some cases excellent agreement (see e.g., [119,168,169]). This is also the case for systems that definitely behave non-statistically such as for reactions between halide ions and methyl halides (see Section 4), indicating that transition state theory is not necessarily unreliable for calculation of KIEs.

The total observable KIEs are often analysed

$$\frac{k_{\text{H}}}{k_{\text{D}}} = \left(\frac{k_{\text{H}}}{k_{\text{D}}}\right)_{\text{trans}} \left(\frac{k_{\text{H}}}{k_{\text{D}}}\right)_{\text{rot}} \prod_n \left(\frac{k_{\text{H}}}{k_{\text{D}}}\right)_{\text{vib},n}, \quad (19)$$

in terms of translational, rotational and vibrational contributions. The vibrational contributions may then be further factorised into low-, mid-, and high-frequency or similar groups of vibrational modes. It has generally been found that the translational contribution is small and normal, the rotational larger and normal, while the vibrations provide the inverse contributions that cause the overall inverse (or small normal) effect (see e.g., [119]). It is particularly the high- and low-frequency modes that contribute to the inverse effect, while the mid-frequency modes give a normal KIE contribution. For the rotational contribution in anionic  $S_N2$  reactions, Davico and Bierbaum have recently found that transition states with spatially widely distributed atoms produce a high value for  $(k_H/k_D)_{rot}$  as do heavy nucleophiles (reacting with the same neutral) [119].

There has been some controversy regarding the importance of the different vibrational contributions to  $k_H/k_D$ , in particular with respect to which vibrational modes determines the total KIE. The traditional view has been that the magnitude of the KIE is primarily the result of the changes in the  $\alpha$ -CH out-of-plane bending force constants  $(k_H/k_D)_{CHoop}$ , between the reactants and the transition state [163], since at the more crowded transition state there is interference between these  $\alpha$ -CH out-of-plane bending vibrations and the nucleophile and/or nucleofuge. As a measure of the amount of space available for the  $\alpha$ -hydrogens, various so-called “looseness” parameters (high looseness corresponds to a high degree of combined C–X and C–Y bond lengthening at the transition state. See [73,126,149] for a number of different definitions) have been proposed, and the conventional view has been that  $(k_H/k_D)_{CHoop}$  and consequently  $k_H/k_D$  increase with increasing transition state looseness. It was then pointed out that  $\alpha$ -CH bond stretching modes,  $(k_H/k_D)_{CHstr}$ , always give inverse KIE contributions, and it was suggested that these modes govern the  $S_N2$  reaction  $(k_H/k_D)_{vib}$  and overall KIEs [114,166,167,170–172]. However, other groups have defended the conventional view and disputed that looser transition states correspond to stronger inverse KIEs [149,173,174]. While the controversy does not

appear to have been resolved, the review of Matsson and Westaway [163] and the recent study of Davico and Bierbaum [119] sum up the current status as follows: the main inverse contributions to the KIE is  $(k_H/k_D)_{CHoop}$ ,  $(k_H/k_D)_{CHstr}$ , as well as the low-frequency vibrational modes. However, while the  $(k_H/k_D)_{CHstr}$  factor is nearly constant for a large set of reactions (0.69–0.80 for the set of 13 reactions of [119]) and low-frequency vibrational modes combined with rotational and translational modes give a small, nearly constant normal effect [119], the contribution from the out-of-plane bending modes varies significantly (0.72–1.08 [119]) and determines the overall KIE [119,163]. Glad and Jensen have analysed the various definitions of transition state looseness and argue that as expected from the conventional model, the overall KIEs do increase with transition state looseness through the influence on the  $\alpha$ -CH out-of-plane bending vibrations [149]. In this case the more reliable definition of the looseness is used. Unfortunately, it may turn out that looseness parameters are of limited value, since Davico and Bierbaum [119] have shown that they correlate with KIEs only for simple (not more than one non-hydrogen atom) nucleophiles. Instead the KIEs appear to correlate with the amount of space available for the  $\alpha$ -hydrogens at the transition state and depend on what these authors have termed the transition state “crowdedness”. It is not likely that a quantification of this concept will be simpler than for the transition state looseness. On the other hand, Glad and Jensen have cautioned that one should not view the KIEs as determined mainly by size-effects, but by changes in the force constants between the reactants and the transition state [149].

It should be noted, that as for reaction barriers, KIEs are best studied in identity reactions due to the higher symmetry of the transition state [149,171,172]. As the most recent contribution in this area, such an ab initio study has been performed by Ruggiero and Williams [73]. For a wide range of nucleophiles/nucleofuges (nine neutral and seven anionic), they find no correlation between KIEs and any of the suggested looseness parameters from the literature.



### 3.5. Trends and correlations in energetics and reactivity

Together with electron and proton transfer reactions, alkyl transfer nucleophilic substitution reactions have been of singular importance in the development of physical organic chemistry, and in particular in the development of linear free-energy relationships and relationships between thermodynamic properties of molecules and reaction rates (i.e., between static properties and dynamical processes). As described in the previous sections, there has been a large increase in the number of gas phase  $S_N2$  reactions for which highly reliable and accurate structure and energy data are available. Perhaps surprisingly, for structure–reactivity relationships, this development has at present only given a limited amount of new insight beyond what was known in the early 1990s [1,176–178]. In this chapter we will give a brief overview of the current situation. This field has also been reviewed recently by Brauman and co-workers [179], and discussed extensively in [1] (see also the reviews [52,180–182]).

The insight offered by the Marcus equation, is that a fundamental understanding of factors determining rate constants and derived properties such as barrier heights, may best be obtained by studying identity reactions without any thermodynamic driving force for the reaction. The properties of non-identity reactions are strongly affected by the exothermicity of the reaction, a fact that has been overlooked or ignored in many studies. Different rates for related reactions that have been ascribed to substituent effects, steric effects and so on, may actually be due to differences in exothermicity. Theories for determining intrinsic barriers is therefore of fundamental importance, but have proved to be very difficult to come up with [72,183].

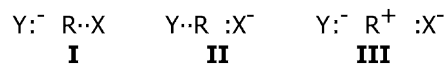
Among the most successful approaches for explaining reaction barriers and determining chemical reactivity is through the use of valence bond (VB) correlation diagrams [184]. Through the last two decades, this has been developed into a system of thought about chemical reactivity by Shaik Pross, and co-workers [1,176,177,180–182], and have been applied in many areas of chemistry. Of particular

interest for us is the application of these methods as a qualitative and quantitative model for nucleophilic substitution [1,176,177,180–182,185–202] and related reactions [46,203–207], where it has had considerable success both for gas phase reactions and reactions in solution. The VB diagrammatic methods and their application for nucleophilic substitution reactions have been extensively reviewed [1,176,177,180–182,189], and we will here only very briefly describe the approach and some of its applications. It should be noted that a related VB approach, involving the concept of increased-valence theory, has been developed independently by Harcourt. The theory has been applied for a large number of chemical systems, among them the  $S_N2$  reaction (see [208–211] and references therein).

The VB state correlation diagram (VBSCD) of Shaik and co-workers—based on VB theory (see e.g., [181,212])—describes the formation of the barrier for an elementary  $S_N2$  reaction step (between  $Y^-$  and  $RX$ ) as due to the avoided crossing of two curves containing the product-like and reactant-like Heitler–London VB states (**I** and **II** in Scheme 2) [181,182]. In addition to these two structures, additional ionic structures (e.g., **III** in Scheme 2) are mixed into the principal structures giving rise to the two VB state curves. The avoided crossing of these two VB state curves is the source of the  $S_N2$  transition state barrier at the lower energy profile. The barrier height,  $\Delta E_{CB}^\ddagger$  (in the gas phase identical to  $\Delta H_{CB}^\ddagger$  without zero-point vibrational energy), is given by the three-factor model (for an identity reaction)

$$\Delta E_{CB}^\ddagger = fG_r - B, \quad (20)$$

where  $G_r$  is the promotion gap,  $f$  is a curvature factor and  $B$  is the avoided crossing interaction (“resonance interaction energy”). While the VBSCD model has been applied for non-identity  $S_N2$  reactions (e.g., [1]), this leads to additional complicating parameters due



Scheme 2.

to the relationships expressed in Marcus theory. The most intriguing feature of the VBSCD model, however, is that it gives an expression for the intrinsic reaction barrier for which hardly any alternative model or understanding exist. For the barrier-crossing step of the reaction between  $X^-$  and  $RX$ , the promotion energy gap is the ion–dipole complex vertical charge transfer energy. It is usually approximated by

$$G_r = I_X - A_{RX}, \quad (21)$$

where  $I_X$  is the ionisation energy of  $X^-$  and  $A_{RX}$  the electron affinity of  $RX$ . According to the VBSCD model the promotion energy is the origin of the reaction barrier, but it is scaled and modified by the  $f$  and  $B$  factors. The factor  $f$  determines at which fraction of  $G_r$  the crossing of the VB state curves occurs and depends on the slope and curvature of the curves [195]. Thus, the height of the barrier is determined by the interplay of these gap and slope parameters, with a modification from the resonance energy  $B$ . Several reaction systems with similar  $B$  and  $f$  factors (belonging to the same reactivity family) have been shown to be governed by the promotion gap  $G_r$  [1,182,213,214], but complicated reactivity patterns and zig-zags may arise due to the interplay of the three factors. The factor  $f$  is a measure of the selectivity of the reaction to changes in the promotion energy, and is a complex function of the transition and promoted state properties. It has been shown that  $f$  is related to the ionic character of the bonds of the ground states of the VBSCD [1,181,182,196,215] and to the delocalisation properties of the promoted state [1,176,181,182,203,214]. For example,  $f_H/f_F = 2.8$ , for the reaction between  $X^-$  and  $CH_3X$  ( $X = H, F$ ), since the charge transfer state is highly localised and delocalised for fluoride and hydride exchange, respectively [182,196,215]. This explains the much lower  $S_N2$  reactivity of polyhalogenated alkanes (such as  $CH_2Cl_2$ ,  $CHCl_3$ , and  $CCl_4$  with  $Cl^-$  compared with  $CH_3Cl$ ), correlating with increased delocalisation of the charge transfer complexes for the polyhalogenated systems [176,182,190].

In some of the early applications of the VBSCD scheme it was assumed that  $B$  was semi-constant, but more recent work have shown that also this parameter

may be of importance in order to explain trends. For the halide exchange reactions between  $X^-$  and  $CH_3X$  ( $X = F, Cl, Br, I$ ) consideration of only the first term of Eq. (20) leads to a predicted barrier height order  $F > Cl > Br > I$ . However, Shaik and Shurki [182] have recently shown that taking into account the counteraction of the  $B$  values,  $B_F > B_{Cl} > B_{Br} > B_I$ , leads to a levelling of the  $\Delta E_{CB}^\ddagger$  values which may explain the lower  $\Delta E_{CB}^\ddagger$  value for  $X = F$  compared with  $X = Cl$  (see Table 1). In many cases the  $B$  factor may be simplified to [1,181,182,197]

$$B = \frac{1}{2}(1 - S_{12})\Delta E_{HOMO-LUMO} \quad (22)$$

where  $\Delta E_{HOMO-LUMO}$  is the energy gap between the HOMO and LUMO at the transition state and  $S_{12}$  is the overlap between the VB states at the transition state geometry. It may be shown that for  $S_N2$  reactions,  $B$  is proportional to the mixing coefficient of VB structure **III** in Scheme 2 and consequently to the positive charge development at the central alkyl moiety at the transition state [197].  $B$  is also related to the “looseness” of the transition state and the deviation from linearity at the transition state: a “loose” or bent transition state generally gives low  $B$  values [197].

While the VBSCD model has been applied to explain a number of reactivity trends, its most impressive achievements is in predicting trends and correlations that have been shown to be correct at a later stage. An example is the ‘mini periodic table’ of reactivity patterns for the reaction between  $X^-$  and  $RX$ , which predicts that the central energy barriers increase in going up and to the left in the periodic table (groups 15–17) [177]. These trends were confirmed (for  $RX = CH_3X$ ) by high quality G2 theoretical calculations a decade later (groups 14–17) by Hoz et al. [72], although first and second row elements have very similar barriers (most likely due to the influence of  $B$ ). In the 1980s the VBSCD model was also used to predict that the barriers for the reaction between chloride and benzyl chlorides might be semi-constant for a variety of aryl substituents due to competition between  $f$  and  $G_r$  [190]. This prediction was confirmed in 1994 through combined experimental and theoretical work [70].

An alternative VB diagram to the two-curve VB-SCD model is the many-curve VB configuration mixing (VBCMD) diagram [181,182]. It is completely equivalent to the VBSCD model, as any VBSCD may be written as a multicurve VBCMD. However, its main strength is for qualitative, illustrative purposes when ‘foreign’ states govern the reactivity. It has for example been used to explain the differences in the  $S_N2$  reactivity of  $X^-$  and  $ML_3X$  (L: ligand,  $M = C$  or  $Si$ ) where the transition state for the alkyl reaction is transformed into a penta-coordinated reaction intermediate for the silyl case due to the much lower lying tri-ionic structure (**III** of Scheme 2) for  $M = Si$  [182,216,217]. For an alternative view on the relative  $S_N2$  reactivity of carbon and silicon, see Shi and Boyd [218].

The ab initio G2(+) results of Glukhovtsev and co-workers for the identity [32] and non-identity [33]  $S_N2$  reactions (5) ( $X, Y = F, Cl, Br, \text{ and } I$ ) and  $Wn$  results of the Martin group [34] ( $X, Y = F, Cl, \text{ and } Br$ ) are currently among the most important sources of information about correlation between barriers and structural and electronic parameters. A fairly large number of reactions have been treated employing the same very accurate theoretical model. Among the findings in [32,33] is good linear correlation between  $\Delta H_{\text{cpl}}$  (Table 1) and the halogen electronegativity for  $X = Y$  and between  $\Delta H_{\text{Rcpl}}$  (Table 2) and the electronegativity of  $Y$  for a given  $CH_3X$ . It was also found, in agreement with earlier work [31,219,220], that the bonding in the complexes is mainly of ion/dipole and ion/induced dipole in character with very little charge transfer. On the other hand, the strongest interactions between a given halogen anion and  $CH_3X$  is for  $CH_3Br$  and  $CH_3I$ , indicating that these interactions are not the only contributing factor to the bonding enthalpies (the largest dipole moment is that of  $CH_3F$ ).

Glukhovtsev et al. [32] find that both the central and overall barriers lie within quite narrow ranges (less than 20 kJ/mol) compared with the large variation in bond strengths  $D_{C-X}$  (230 kJ/mol) for the four identity reactions (9)–(12). One would tend to attribute this to the  $S_N2$  reaction being a simultaneous process of bond breaking and formation for the passage over the transi-

tion barrier. Interestingly, Glukhovtsev et al. [32] and Parthiban et al. [34] find that neither the central barrier, nor the overall barrier for the identity reactions, correlate with the periodic table ordering of the halogen atoms. The highest barriers are found for  $X = Cl$ . As noted by Vetter and Zülicke [221], the barrier height decreases monotonously with periodic table ordering at the Hartree–Fock level and the loss of this trend is essentially an effect of different electron correlation energies for the reactions (i.e., going beyond the independent particle treatment of Hartree–Fock theory). Presently, the only model that appears to be able to elucidate these trends is the VBSCD, where the opposing effects of the two terms in Eq. (20) recently have been shown [182] to reproduce the high level theoretical results [32,34] for the barrier. When it comes to alternative models, one may draw the important conclusion that models for the trends in reactivity based on concepts such as molecular orbitals (MOs) at the Hartree–Fock level will not be adequate since they do not take into account the dominating contribution of electron correlation. It is possible that explanations based on high quality calculated electron densities or density functional theory related concepts might fare better (see e.g., [222,223]). However, great care should be applied when dealing with density functionals that currently are inaccurate for  $S_N2$  reaction barriers (see discussion in Section 3.3). Another illustrating example of the breakdown of the Hartree–Fock approximation has been given by Wladkowski et al. [31]: the  $\alpha$ -effect stabilisation of the  $S_N2$  transition state for the  $Cl^- + CH_2ClCN$  with respect to the  $Cl^- + CH_3Cl$  reaction (by approximately 30 kJ/mol) is purely due to electron correlation. Lee et al. have found similar effects in allyl transfer reactions [150].

It has been noted by Brauman and co-workers [75] that the gas phase results for the identity  $S_N2$  reactions between  $X^-$  and  $CH_3X$  ( $X = F, Cl, Br, I$  in Table 1) (reactions for which one would expect the barrier heights to be proportional to the reaction rates) are in stark contrast to the situation in solution where the reactivity appears to follow the order  $RI > RBr > RCl \gg RF$  [224–226]. Consequently, this solution reactivity order is due to differential

solvation effects and cannot be attributed to differences in C–X bond strengths. In agreement with the above identity reaction results [32,34],  $\Delta H^\ddagger$  is found to be lower for X = Br than for X = Cl for two other S<sub>N</sub>2 identity reactions where reliable data are available—the  $\alpha$ -substituted reactants XCH<sub>2</sub>CN and C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>X (Table 3) [31,69,70].

Glukhovtsev et al. find their data to be in agreement with the Leffler–Hammond postulate in that there is a correlation between the geometrical asymmetry of the transition state ( $d_{C-X}^\ddagger/d_{C-X}^{\text{comp}} - d_{C-Y}^\ddagger/d_{C-Y}^{\text{comp}}$ , where  $d_{C-M}^\ddagger$  and  $d_{C-M}^{\text{comp}}$  are the C–M bond lengths in the transition state and ion–dipole complexes, respectively) and the reaction exothermicity [33]. This has also been found earlier by Wolfe and co-workers [131]. Whether there also is a correlation between the degree of charge development on the nucleophile/nucleofuge, and reaction exothermicity or geometrical transition state asymmetry has been the subject of some controversy in the literature. Shaik and co-workers have suggested—as a more chemically intuitive model for the transition state—what has been termed the avoided crossing state (ACS) or perfectly resonating state (PRS) [200–202]. It is characterised as having equal weights of the reactant and product Heitler–London structures. This model was criticised by Shi and Boyd [227,228] on the grounds that the entering and leaving groups have identical charges in the ACS/PRS for any exothermicity of the reaction, and it was argued that this was at odds with the Leffler–Hammond postulate prediction of early/late transition states being reactant/product-like (see also [136,229]). However, the proponents of the ACS/PRS model have in a number of publications shown that the ACS/PRS and transition state lie very close both geometrically as well as energetically [187,200–202], and have argued that there is no necessarily simple linkage between transition state geometry and charge. On the other hand, in the recent high quality G2 study of Glukhovtsev et al. [33], excellent correlation is found between the charge asymmetry ( $q(X) - q(Y)$ , where  $q(M)$  is the MP2 natural population analysis charge for M) and the geometrical asymmetry. It appears that further investigations are necessary in order to clarify the

possible correlation between charge development and earliness/lateness of the transition structure.

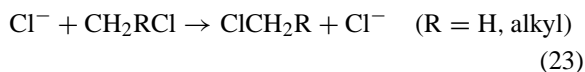
A correlation between transition state “looseness” and transition state barriers has been found in the recent G2 studies [32,33], confirming earlier work [193,194,230]. However, in a very recent identity reaction study of Ruggiero and Williams [73] for a wide range of neutral and anionic nucleophiles/nucleofuges, no such correlation was found for any of the definitions of looseness that was applied. In related work, Lee et al. [231] have found the transition state “tightness” to be nearly constant within the groups of primary and secondary reaction centre carbon. A fairly low-level theoretical study by Anh et al. [232–234], also provide some information on the relationship between reaction barriers and transition state structure.

In contrast with earlier suggestions [66,178], Glukhovtsev et al. [32] find no correlation between  $\Delta H^\ddagger$  or  $\Delta H_{CB}^\ddagger$  for the identity reactions (5) (X = Y = F, Cl, Br, and I) and methyl cation or proton affinities of the halogen anions. This is confirmed in the recent study of Uggerud [152], where a wider range of nucleophiles has been studied (X = Y = NH<sub>3</sub>, H<sub>2</sub>O, HF, NH<sub>2</sub><sup>−</sup>, OH<sup>−</sup>, and F<sup>−</sup>) with methyl cation affinities between approximately 125 and 1150 kJ/mol. On the other hand, a linear relationship was found between the enthalpy for the symmetric dissociation  $M \cdots CH_3^+ \cdots M \rightarrow M + CH_3^+ + M$  and the proton or methyl cation affinity of M within three groups of similar M; (NH<sub>3</sub>, H<sub>2</sub>O, and HF), (NH<sub>2</sub><sup>−</sup>, OH<sup>−</sup>, and F<sup>−</sup>), and (F<sup>−</sup>, Cl<sup>−</sup>, Br<sup>−</sup>, and I<sup>−</sup>) [152]. Further investigations into this relationship might be rewarding.

A number of studies from Brauman’s group [179] give valuable suggestions about the relationship between structure and energetics on reactivity. FT-ICR mass spectrometry experiments combined with RRKM theory and AM1 semiempirical calculations give similar trends for the barriers for the S<sub>N</sub>2 identity reaction between Cl<sup>−</sup> and X-C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>Cl for the series X = H, *m*-CH<sub>3</sub>, *m*-OCH<sub>3</sub>, *m*-F, *m*-Cl, and *m*-CF<sub>3</sub> [70]. As expected, the RRKM  $\Delta H^\ddagger$  values vary consistently with the reaction rate coefficients, but there also appears to be a trend connecting  $\Delta H^\ddagger$  and

Hammett  $\sigma$  constants for the electron-withdrawing substituents. Interestingly, a similar connection is found between  $\Delta H_{\text{cpl}}$  and  $\sigma$ , while  $\Delta H_{\text{CB}}^\ddagger$  is constant for the reactions considered. Compared with the reaction between  $\text{Cl}^-$  and  $\text{CH}_3\text{Cl}$  the  $\alpha$ -effect of the benzyl group is found to lower both  $\Delta H^\ddagger$  and  $\Delta H_{\text{cpl}}$  by at least 10 kJ/mol and leads to an increase in the rate constant by several orders of magnitude. A similar  $\alpha$ -effect was found for  $\text{ClCH}_2\text{CN}$  [31]. The lack of an  $\alpha$ -effect for  $\Delta H_{\text{CB}}^\ddagger$  indicates that no special resonance or similar electronic effects are present in the transition state compared with the ion–dipole complex [179].

The well known trend for the rate of  $\text{S}_{\text{N}}2$  displacement reactions at alkyl derivatives,  $\text{RX}$ , in solution—methyl  $\text{R} >$  primary  $\text{R} >$  secondary  $\text{R} \gg$  tertiary  $\text{R}$ —is traditionally ascribed to *steric hindrance* [3,224,235–237]. For the reactivity of corresponding systems in the gas phase, only a limited number of studies are available. For the identity reactions



Jensen [148] (Table 3) and Ruggiero and Williams [159] have calculated barrier heights for a number of different alkyl groups. They find that increased branching at  $\alpha$ - and  $\beta$ -carbon leads to a higher barrier for the reaction in correspondence with the textbook examples.

Disregarding exothermicity effects that may be of importance, a number of studies have found reaction rates and transition state barriers to be sensitive to alkyl substitution for non-identity  $\text{S}_{\text{N}}2$  reactions. Bierbaum and co-workers [35,37] have found the reaction rates for nucleophilic attack on alkyl halides to be significantly reduced upon increased branching at  $\alpha$ -carbon. Similar conclusions have been reached from high-pressure mass spectrometric experiments by Caldwell et al. [54] and recently by Li et al. [88]. The overall reaction barrier,  $\Delta H^\ddagger$ , for the reaction of chloride ion with alkyl bromide is negative ( $\text{CH}_3\text{Br}$ ), close to zero ( $\text{C}_2\text{H}_5\text{Br}$ ), or positive ( $i\text{-C}_3\text{H}_7\text{Br}$ ,  $t\text{-C}_4\text{H}_9\text{Br}$ ) [88]. Grimsrud and co-workers [19,55,56,112] have performed experiments on  $\text{S}_{\text{N}}2$

reactions between chloride ion and alkyl bromide in a buffer gas at atmospheric pressure. The reactants and intermediates are in thermal equilibrium with the environment eliminating an important source of experimental error. In agreement with textbook solution data they find increased  $\alpha$ -carbon branching to give lower reaction rates. The reaction barrier is found to be  $-9.2$ ,  $0.0$ ,  $-5.4$ , and  $6.7$  kJ/mol for the reaction between  $\text{Cl}^-$  and  $\text{CH}_3\text{Br}$ ,  $\text{C}_2\text{H}_5\text{Br}$ ,  $n\text{-C}_4\text{H}_9\text{Br}$ , and  $i\text{-C}_3\text{H}_7\text{Br}$ , respectively [56].

The limited number of  $\text{S}_{\text{N}}2$  reactions described above all involve fairly strong nucleophiles, and they all support the solution phase textbook view of steric hindrance—increased alkyl substitution at  $\alpha$ -carbon reduces reaction rates and increases the reaction enthalpy barrier. Recent experimental and theoretical work on identity  $\text{S}_{\text{N}}2$  reactions for protonated alcohols indicate that this is not a universal law since the trends are different for weaker nucleophiles such as water [62,159]. The experimental FT-ICR mass spectrometry data for the reaction of  $\text{H}_2\text{O}$  and  $\text{ROH}_2^+$  suggest that the relative reaction rates are  $\text{R} = \text{C}(\text{CH}_3)_3 > \text{CH}(\text{CH}_3)_2 > \text{CH}_3 > \text{CH}_2\text{CH}_3$ . Accompanying theoretical calculations reflect this trend. This is clearly at odds with the naïve view of steric hindrance (as being due to  $\alpha$ -alkyl substituents giving a crowded transition state as would macroscopic solid objects). Recent theoretical work on identity  $\text{S}_{\text{N}}2$  reactions for protonated amines and fluorides indicate that while the behaviour in the former case ( $\text{NH}_3$  being a stronger nucleophile than  $\text{H}_2\text{O}$ ) is the traditional [238], the reaction of  $\text{HF}$  and  $\text{RFH}^+$  is more in accordance with the situation for protonated alcohols ( $\text{HF}$  being a weaker nucleophile than  $\text{H}_2\text{O}$ ) [239]. Clearly, more work is needed to obtain a better understanding of the factors guiding what traditionally has been termed “steric hindrance”.

The VB diagram approach of Shaik and co-workers [1,181,182] has been quite successful in explaining and predicting reactivity patterns, at least compared with the very limited success of alternative systems of thought. However, most of the work done on  $\text{S}_{\text{N}}2$  reactions applying the VBSCD model and relationships such as that of Eq. (20) was done in the 1980s

and early 1990s when  $S_N2$  reactions barriers for most identity reactions were known with quite low accuracy. It is possible that more insight into these matters might come out of the application of these methods on high quality (mainly theoretical) reaction barriers that have been published (Table 1) or which now may be routinely calculated (see Sections 3.1–3.3). While the VBSCD model is by far the most successful model for  $S_N2$  identity reaction barriers, it may be seen as problematic that it contains several factors (three in Eq. (20)) that are derived from VB theory and that cannot be easily determined from experiment or MO theory. These parameters are not observables, in the sense that they cannot be measured directly by experiment. While one of these parameters, the promotion energy  $G_r$ , usually is estimated by the measurable quantity indicated by Eq. (21) this is only a rough approximation to the true promotion energy for the pre-reaction complex of the gas phase  $S_N2$  elementary step across the reaction barrier. It has been shown that for the  $S_N2$  reaction between  $F^-$  and  $CH_3F$ , application of Eq. (21) gives an error of approximately 7 kJ/mol compared with the promotion energy for the  $F^- \cdots CH_3F$  ion–dipole complex [199]. The parameters such as  $G_r$ ,  $f$ , and  $B$  may indeed be calculated from VB theory (e.g., [196,199]), but this is by no means routine. Even if VB and MO theory with the same basis sets of course in principle may yield results of identical quality, the VB methods are currently less developed. As long as this is the situation, alternative or supplemental views on  $S_N2$  reactivity might be seen as welcome.

In addition to the comprehensive work by Shaik and co-workers involving VB diagrams, there have been some other attempts on explaining intrinsic reaction barriers, in particular by Shi and Boyd [240] and by Lee and co-workers [241]. For example, Lee et al. [150] have found similar trends as Hoz et al. [72] for a small number of identity reactions, and they have attributed this to electronegativity trends of the nucleophile/nucleofuge and substituents. They were able to explain the trends in the barrier heights (see also Lee et al. [231]). The model is, however, based on a number of assumptions and on the treatment of the

Hartree–Fock and correlation effects separately, which might be viewed as not fully satisfactory. Some very recent publications involve electron density concepts that may turn out to be promising [223,242]. However, the researchers behind this work would greatly benefit from performing their analysis based on structural and energetic parameters from modern experimental and in particular theoretical approaches that are readily available. Note also that other simple, qualitative models are being developed in this field [243].

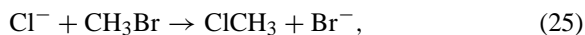
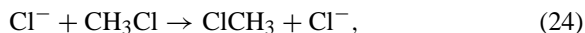
#### 4. Dynamical features of gas phase nucleophilic substitution

Theoretical and experimental studies during the last decade have given a deeper insight into the detailed reaction dynamics at the microscopic level for nucleophilic substitution reactions in the gas phase. One has been particularly interested in testing the accuracy of the so-called statistical theories [244–246], such as transition state theory, RRKM theory, and phase space theory (PST), for describing these reactions. The group of Hase and co-workers has provided a large number of theoretical studies [80,102,103,247–264], in particular classical trajectory calculations, which have elucidated this topic and brought the suitability of the statistical methods into question. Other important contributions have come from quantum dynamics studies that recently have become feasible for models of  $S_N2$  reactions [85,87,113,265–269]. In addition, a number of experimental studies have supported the theoretical findings of the Hase group (e.g., [68,71,76,105–109,115,116,270–273]). Since several review articles have dealt with these dynamical studies [179,252,262], we will here only give a brief summary.

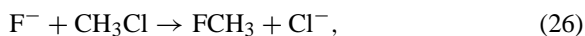
For most chemical reactions, it is difficult to study the detailed dynamics experimentally. Theoretical studies may only be performed by means of quantum mechanical or classical trajectory methods for systems consisting of a small number of atoms. For this reason the so-called statistical methods are widely used for the study of chemical rate constants and other

attributes of chemical reactions. For reactions with a free-energy barrier separating reactants and products, transition state theory [245] is frequently employed. The reaction rate constant is proportional to the statistical partition function at the transition state, and it is assumed that no recrossing of the transition state barrier occurs. Gas phase bimolecular ion–molecule reactions are usually interpreted in terms of unimolecular reaction rate theory, since it may be assumed that upon association of the reactants, the complexes have lifetimes that are sufficiently long for energy to be redistributed statistically to all available internal degrees of freedom by intramolecular vibrational energy redistribution (IVR). The dynamics may then be modelled by PST or by RRKM theory as that of a microcanonical ensemble at equilibrium. Again it is assumed that recrossing of the central barrier does not occur in the standard formulations of the theories.

The picture that has emerged from the theoretical and experimental studies of the 1990s is that the dynamics, at least for the reactions



and



is decidedly non-statistical. This is partially due to a dynamical bottleneck in the transfer of energy from the relative translational degrees of freedom to the vibrational degrees of freedom corresponding to the breaking of the bond between the products. In addition there is a possibility of extensive barrier recrossing and an alternative direct substitution mechanism. These small systems appear to have too short lifetimes for the reactant ion–dipole complexes for IVR to occur, and nonergodic behaviour is consequently observed. A central question is to what degree the ergodic hypothesis is fulfilled for other  $\text{S}_{\text{N}}2$  reactions as well as organic reactions in general for which detailed molecular dynamics studies are prohibitively difficult and computationally expensive.

The dynamical model that has been developed by Hase and co-workers may be summarised as follows [252,262]: when the reactants  $\text{Y}^-$  and  $\text{CH}_3\text{X}$  collide, the relative translational energy must be transferred to vibrational ( $\text{T} \rightarrow \text{V}$ ) or rotational ( $\text{T} \rightarrow \text{R}$ ) energy of the  $\text{CH}_3\text{X}$  moiety for complexation to occur. Trajectory calculations for the reaction between  $\text{Cl}^-$  and  $\text{CH}_3\text{Cl}$  (Eq. (24)) have shown that ( $\text{T} \rightarrow \text{V}$ ) is unimportant for complex formation and that only ( $\text{T} \rightarrow \text{R}$ ) gives stable complexes [251,264]. Reaction path Hamiltonian studies for the reaction between  $\text{Cl}^-$  and  $\text{CH}_3\text{Br}$  (Eq. (25)) [256] relate the lack of ( $\text{T} \rightarrow \text{V}$ ) to the very small coupling terms between the  $\text{Cl}^- + \text{CH}_3\text{Br}$  relative translational and the  $\text{CH}_3\text{Br}$  vibrational modes. Classical trajectory studies for both the reactions (24) and (26) have shown that the reactants orient themselves such that the anion attacks from the backside in the association process, but that trajectories that collide with a  $\text{X}-\text{C}-\text{Y}$  angle in the range of  $170$ – $140^\circ$  are most likely to form long-lived complexes [248,251,261] and consequently lead to product formation. At elevated rotational temperatures a much wider range of  $\text{X}-\text{C}-\text{Y}$  collision angles give rise to stable complexes [248,251]. At low rotational temperatures, trajectories with collisions at  $\text{X}-\text{C}-\text{Y}$  collision angles close to  $180^\circ$  tend to rebound due to the lack of ( $\text{T} \rightarrow \text{V}$ ) energy transfer [251,264]. For this reason, the association rate of the reactants forming the pre-reaction complex is lower than that determined by a simple ion capture model. This is supported by experimental data of Su et al. [274] for the highly exothermic reactions of  $\text{F}^-$  with  $\text{CH}_3\text{Cl}$ ,  $\text{CH}_3\text{Br}$ , and  $\text{CH}_3\text{I}$ , for the reaction between  $\text{F}^-$  and  $\text{CH}_3\text{Cl}$  by Angel and Ervin [61], and by the theoretical study of Wang and Hase [257] on the same reaction. The reaction rate was found to be only a fraction of the capture rate constant, and even the very low central energy barrier was found to have a significant effect on the reaction rate.

After the association of the pre-reaction ion–dipole complex by ( $\text{T} \rightarrow \text{R}$ ) the exothermicity and the height of the central barrier determine the fate of the system. For high barriers (e.g., Eq. (24)) the most likely process is re-dissociation to the reactants

[248,249]. Hase and co-workers have termed these initially formed complexes “intermolecular complexes” [250,252] since only the three low-frequency intermolecular modes (the  $\text{Cl}^- \cdots \text{CH}_3\text{Cl}$  stretching and bending modes of frequencies below  $120\text{ cm}^{-1}$  [262]) are excited. For complexes with long lifetimes the unlikely ( $\text{R} \rightarrow \text{V}$ ) process may occur with energy redistribution into the higher frequency modes of the  $\text{CH}_3\text{Cl}$  moiety (frequencies above  $500\text{ cm}^{-1}$  for  $\text{Cl}^- \cdots \text{CH}_3\text{Cl}$  [262]). However, there is a significant bottleneck for the transformation into these “intramolecular complexes” [250,252] where the energy is distributed so that passage over the central barrier may occur. Illustrating figures of the mismatch between the vibrational frequencies for the  $\text{Cl}^- \cdots \text{C}$  and  $\text{Cl}-\text{C}$  stretching modes is given in [264]. Due to the dynamical bottlenecks at both the reactant and product side, several recrossings may occur before a transformation into an intermolecular product (or reactant) complex and finally products (or reactants) takes place [264]. For reactions with a large exothermicity and low barrier (e.g., Eq. (26)) the formation of products is a much more likely process. However, there is still a bottleneck for the energy transfer between low and high-frequency modes causing the products to be vibrationally hot [261].

A direct substitution channel where the reaction occurs at a  $\text{Cl}-\text{C}-\text{Cl}$  angle close to  $180^\circ$  and without formation of an ion-dipole complex has been demonstrated for reaction (24) [248,251]. However, this channel only opens up if a substantial amount of energy is deposited into the  $\text{C}-\text{Cl}$  stretch mode of  $\text{CH}_3\text{Cl}$  (at least three quanta) [248] and it is also strongly suppressed at rotational temperatures as low as 300 K [251]. Consequently, this mechanism does not seem to be of importance for this reaction under thermal conditions at room temperature. It has been argued that this mechanism may be more important for more exothermic reactions with lower barriers. The recent studies of Su et al. [261] and by Angel and Erwin [61] for the reaction between  $\text{F}^-$  and  $\text{CH}_3\text{Cl}$  appear to support this view, especially for reactants with high relative translational energy. Unlike reaction (24), energy added to the  $\text{C}-\text{Cl}$  stretch mode of

$\text{CH}_3\text{Cl}$  does not alter the reaction rate significantly. Recent trajectory studies of translational activation by Mann and Hase [260] have also demonstrated that a direct mechanism process (24) becomes important at high translational energies. The translational energy threshold was found [260], in agreement with the experiments of DeTuri et al. [68], to be approximately a factor five higher than the barrier of the potential energy surface. Simple statistical models cannot easily account for this highly elevated threshold for translational activation for the reaction [68]. A kinematic collision model has also been applied, but it can only partially explain the experimental results [275].

The presence of attributes such as multiple barrier recrossings and dynamical barriers for the IVR strongly suggests that statistical methods are unreliable for these reactions. This has also been demonstrated in a number of studies where these methods have been applied [103,116,253,255,262]. The model described above is supported by experimental work in which energy partitioning in different degrees of freedom has been studied. Viggiano, Morris, and co-workers performed variable temperature-selected ion flow drift tube experiments [276] and showed that the reaction rate decreased with both temperature and average center-of-mass kinetic energy, but was independent of the internal energy for reaction (25) [115]. Later FT-ICR experiments by Craig and Brauman [111] are in good agreement with the results of Viggiano et al. [115]. It was concluded that vibrational and translational energy have a different effect on the rate constant, this being an indication of non-statistical behaviour [103,115]. This has been interpreted as being caused by the dynamical bottleneck for energy transfer between internal modes of  $\text{CH}_3\text{Br}$  and the intermolecular low-frequency modes at the timescale of the reaction. The results of Viggiano et al. [115] and Craig and Brauman [111] both disagree with statistical RRKM calculations by Wang and Hase [103] (see also Fig. 6 and ref. 29 of ref. [111]).

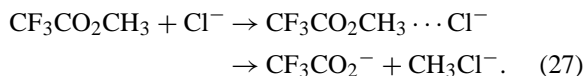
The work of Graul and Bowers on the dissociation of metastable  $\text{Y}^- \cdots \text{CH}_3\text{X}$  complexes also seem to indicate non-statistical features and weak coupling



between inter- and intramolecular modes for these reactions. For the dissociation of the metastable reactant ion–dipole complexes  $\text{Cl}^- \cdots \text{CH}_3\text{Br}$ ,  $\text{Cl}^- \cdots \text{CH}_3\text{I}$ , and  $\text{Br}^- \cdots \text{CH}_3\text{I}$  it was concluded that the products  $\text{YCH}_3$  are vibrationally hot [105,106]. This is in agreement with modelling trajectory studies of Wang et al. [253] (see also [255]), but seems to be in disagreement with a statistical product energy distribution according to PST [106]. Using the same methods, similar behaviour was recently also inferred for four other systems:  $\text{Cl}^- \cdots \text{CF}_3\text{CO}_2\text{CH}_3$ ,  $\text{CN}^- \cdots \text{CF}_3\text{CO}_2\text{CH}_3$ ,  $\text{F}^- \cdots \text{C}_6\text{H}_5\text{OCH}_3$ , and  $\text{Cl}^- \cdots \text{C}_2\text{H}_5\text{I}$  comprising larger reactants and a variety of leaving and entering groups [116]. The dissociation of  $\text{Cl}^- \cdots \text{CH}_3\text{Br}$  has also been studied by Cyr et al. [107] and by Seeley et al. [108]. An analysis and comparison of the different experiments have been provided in [108]. Here it is concluded that RRKM indeed may model the dissociation of  $\text{Cl}^- \cdots \text{CH}_3\text{Br}$  correctly for complexes that have been prepared with low energy, resulting in intermediate lifetimes several orders of magnitude larger than in the case of the substitution reaction.

Further insight has recently been gained from the experiments of Tonner and McMahon [109]. After preparation of cold  $\text{Cl}^- \cdots \text{CH}_3\text{Br}$  complexes, excitation of the high-frequency modes of the  $\text{CH}_3\text{Br}$  moiety by a CW  $\text{CO}_2$  laser exclusively gave dissociation into  $\text{Cl}^-$  and  $\text{CH}_3\text{Br}$  as should be expected from the trajectory studies of Hase and co-workers [253,255]. In the absence of laser activation the ratio between  $\text{Cl}^-$  and  $\text{Br}^-$  production is approximately 0.2 from which a reaction barrier of  $\Delta H^\ddagger = -5.5$  kJ/mol has been derived [109], in reasonable agreement with the benchmark ab initio data of Table 2.

Craig et al. [272] have recently reported non-statistical behaviour for the  $\text{S}_{\text{N}}2$  reaction



For this bimolecular collision reaction the efficiency is approximately 0.02. However, when the pre-reaction complex,  $\text{CF}_3\text{CO}_2\text{CH}_3 \cdots \text{Cl}^-$  is generated with a

large amount of vibrational energy the efficiency is increased by at least a factor four. This change in reactivity is not consistent with the properties of the potential energy surface, and in disagreement with a RRKM analysis [272]. The non-statistical behaviour arises because of the short lifetime for the energised intermediate compared with the IVR timescale.

The non-statistical behaviour of reactions (24)–(26) makes it problematic to interpret reactions rate constants in terms of the properties of the potential energy surface. The kinetic ion mobility mass spectrometric method developed by Grimsrud and co-workers circumvents this problem by carrying out the reactions at high buffer gas pressures (atmospheric pressure and above) [19,55,56,112,277]. At sufficiently high-pressures—known as the high-pressure limit—all the reaction intermediates have a Boltzmann energy distribution and are maintained at thermal equilibrium during reaction. Accurate energy barriers have been determined in this fashion for the reactions between  $\text{Cl}^-$  and  $\text{RBr}$  ( $\text{R}$  = methyl, ethyl, *i*-propyl, and *n*-butyl) [55,56]. While the high-pressure limit for the larger reactants is well below atmospheric pressure [55,56,112], the limit for  $\text{CH}_3\text{Br}$  appears to lie above 1100 Torr [112]. Nevertheless, a barrier in excellent agreement with the most recent benchmark ab initio results was obtained from these experiments (see Table 2).

The main problem with the classical trajectory studies is that zero-point energy quantisation and tunnelling effects are not treated in a formally correct way. The solution to these problems is to apply quantum dynamical calculations, which recently have been very successful in determining detailed state-to-state reaction dynamics for small systems containing three to four atoms [278]. These methods are unfortunately too computationally expensive for treating even the simplest  $\text{S}_{\text{N}}2$  reaction systems without employing a significantly reduced dimensionality model. Early two-dimensional studies were performed by Basilevsky and Ryaboy [265,279], while Billing introduced an approximate zero-point energy treatment for a study of reaction (24) by performing a semiclassical

calculation employing the reaction path Hamiltonian model [84]. Clary and Palma then performed quantum scattering calculations for the reaction (24) where the two C–Cl stretching modes and the CH<sub>3</sub> umbrella mode were treated explicitly [266]. A similar study was recently performed by Yu and Nyman [280]. Both studies conclude that vibrational excitation of the C–Cl bond greatly enhances the reaction while the umbrella mode may be viewed as a spectator. Several recent studies have revealed a wealth of details for these reactions [85,87,259,267,269,281] for example by focusing on the temperature dependence for the rate constant of reaction (25) [113], and on rotational excitation [267]. The high sensitivity of the results to the details of the potential energy surface has also been considered [85,87,269], and scattering resonances have been found to play an important role in the dynamics [85,268]. While the potential of the quantum dynamics studies is far-reaching, one currently has to restrict oneself to models of only a few active degrees of freedom. For this reason it is unclear to what degree these methods at present can elucidate the detailed dynamics of the model developed by Hase and co-workers, for example by discriminating between direct and non-direct substitutions, model high angular momentum collisions and determine probabilities for (T → R) association and (R → V) energy flow.

Schettino and co-workers have recently employed Car-Parrinello first principles molecular dynamics theory [282] in studies of the reaction between Cl<sup>−</sup> and CH<sub>3</sub>Br (Eq. (25)) [283,284] and between Cl<sup>−</sup> and ClCH<sub>2</sub>CN [285], while Ensing et al. [60] have performed a similar study for the identity reaction between Cl<sup>−</sup> and CH<sub>3</sub>Cl (Eq. (24)). Calculations of this type have been extremely successful the last years in studying gas and condensed phase systems at finite temperatures (see e.g., [286,287]), and they are very promising for the study of solvent effects for organic chemistry reactions. Unfortunately, the techniques are hampered by the currently poor performance of density functionals for S<sub>N</sub>2 reactions [158]. Nevertheless, Ensing et al. [60] obtain very impressive results for reaction (24) in both gas phase and in solution. They

have carefully tested the various approximations inherent in the theory, as has Pagliai et al. [285] for the reaction between Cl<sup>−</sup> and ClCH<sub>2</sub>CN, and demonstrate that while the application of Car-Parrinello molecular dynamics theory for the study of substitution reactions is still in its infancy, the method will undoubtedly be very important in the development of this field in the future.

While a large number of studies during the 1990s have demonstrated non-statistical dynamics for several gas phase S<sub>N</sub>2 reactions, there are indications that the non-statistical systems may be special cases, and that statistical theories are reliable for most S<sub>N</sub>2 reactions. This is very fortunate since accurate trajectory studies are both computationally very expensive and to a large degree dependent on the details of large regions of the potential energy surface [87,255,269]. The special cases that show non-statistical dynamical behaviour all seem to be rather small systems without deep minima for the intermediates and ion-dipole complex lifetimes of a few tens of picoseconds [88,248,255]. For the reaction between Y<sup>−</sup> and RX this is too short for efficient energy redistribution into the intramolecular vibrational modes of the RX moiety. Examples are the reactions (24)–(26) and very energetic systems such as the intermediate of reaction (27). Brauman and co-workers [70,71,76,77,270] have shown that larger systems such as benzyl- and cyano-substituted alkyl chlorides do behave statistically and that RRKM calculations give results in agreement with experiments [71]. Lifetimes of these systems are tens of nanoseconds [71], which is sufficient for efficient energy transfer between the relevant internal modes of the intermediates.

Morris and Viggiano [121] have also found the reactions of F<sup>−</sup> with CF<sub>3</sub>Br and CF<sub>3</sub>I to behave statistically, and again this is attributed to the long lifetimes of the intermediates. For these two systems, association is the dominating reaction pathway, and a correlation between the amount of association and intermediate lifetime can be expected [121]. For the non-statistical reaction between F<sup>−</sup> and CH<sub>3</sub>X (X = Cl, Br, I), which is known to involve very short-lived intermediates, no association was observed [115,274]. Other examples

of systems that most likely behave statistically due to their complexity and the lifetimes of the intermediates (of the order of  $10^{-7}$  s) is given by the reaction between  $\text{Cl}^-$  and  $\text{C}_2\text{H}_5\text{Br}$  and  $n\text{-C}_3\text{H}_7\text{Br}$  [271]. The work of Grimsrud and co-workers also lends support to the view that slightly larger systems have significantly longer lifetimes for the ion–dipole complexes than the reactions between halide ions and halomethanes. While  $\text{Cl}^- \cdots \text{RBr}$  ( $\text{R} = \text{methyl}$ ) is only significantly quenched by buffer gas collisions above atmospheric pressure [112] the high-pressure limit is below a few Torr for  $\text{R} = \text{ethyl}$ ,  $i\text{-propyl}$ , and  $n\text{-butyl}$  [55,56].

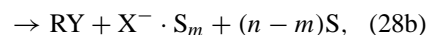
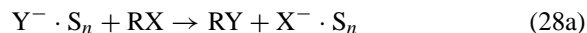
In conclusion, the limits of poor energy transfer is not known, but it appears that most gas phase substitution reactions at thermal conditions and not very high temperatures are complex enough and have sufficient lifetimes for the intermediates for the simplifying assumptions of statistical theories to be valid. Non-statistical dynamics is restricted to small or highly energised systems with short lifetimes of the order of tens of picoseconds for the ion–dipole complex intermediates.

## 5. Microsolvation, clusters and the transition to solution

Since the first studies of gas phase nucleophilic substitution in the 1970s, gas phase reaction rates have been known to be much higher—in some cases by 20 orders of magnitude—than the corresponding rates in solution [7,20]. The reason for this is well known: all points on the potential energy profile (e.g., Fig. 1a and b) are stabilised by solvation, but the regions of localised electronic charge is stabilised to a greater extent than the more charge-delocalised regions. As a consequence the stabilisation is the greatest for the reactants, less for the ion–dipole complexes and the least for the transition state. This means that the energy barrier becomes higher in solution, and higher in the stronger than in the weaker solvating media. The ion–dipole complexes may disappear altogether in strongly solvating media, and the double-well

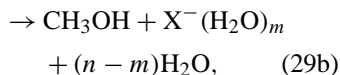
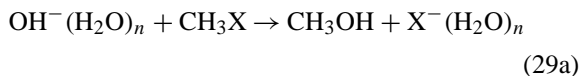
potential is replaced by a single unimodal reaction barrier [20,288]. In addition the dynamics of solvent motion has a large influence on kinetics and dynamical details. Theoretical modelling of nucleophilic substitution in solution confirms the disappearance of the energy minima and the higher free-energy barrier compared with vacuum [58–60,62,151,159,289–293]. We also mention that changes in reactivity trends and the preferred reaction pathways upon solvation have been the subject of recent work (see e.g., [53,62,159,294]). In a theoretical study on alkyl substitution effects for  $\text{Cl}^- + \text{RCl}$   $\text{S}_{\text{N}}2$  reactions in water and various organic solvents ( $\text{R} = \text{methyl}$ , ethyl,  $i\text{-propyl}$ , and  $t\text{-butyl}$ ), Mohamed and Jensen [294] have shown that these effects are reduced by solvation and microsolvation. This is due to an increased stabilisation of the transition state mediated by the electron donating methyl groups.

While attempting to bridge the gap between gas phase and solution reactivity, many researchers have studied microsolvated systems, i.e., systems that are progressively solvated in the gas phase with a low number  $n$  of solvent molecules  $\text{S}$ , for example



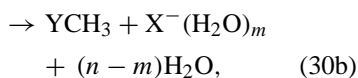
with  $m \leq n$ . There have been many variations in the results and experimental conditions, but the general trends appear to be as follows: (1) increasing the number of solvent molecules  $n$  progressively leads to reduced reaction rates and higher energy barriers,  $\Delta H^\ddagger$ , for the reactions; (2) the reactions lead to both solvated and unsolvated leaving groups (as in Eq. (28b)) with the branching dependent on the exothermicity of the reactions and the ability of the solvent molecules to be “boiled off”. However, the detailed dynamics in the neighbourhood of the transition state appears to be equally important for the product distribution. In most cases unsolvated  $\text{X}^-$  appears to be the main product; (3) in the absence of a fast  $\text{S}_{\text{N}}2$  reaction channel other reaction mechanisms become dominant. Several recent reviews have covered parts of this research field [179,295,296].

One of the most studied reactions is



with  $X = \text{Br}$  ( $m \leq n$ ), where work has been performed with  $n = 0\text{--}4$  [35,164,288,296–299]. In the most recent study, by Viggiano et al. [164,296], the  $\text{S}_{\text{N}}2$  reaction rate has been found to be close to the collision rate for  $n = 0$ . For  $n = 1$  the reaction rate is reduced by approximately a factor 1.5, and further by two orders of magnitude for  $n = 2$ . The reaction then becomes another order of magnitude slower and finally undetectably slow for  $n = 3$  and 4, respectively. A small change in reactivity upon mono-hydration with a more pronounced effect of di-hydration has also been observed for other systems (e.g., [299–301]), while larger solvents (e.g., methanol or ethanol) appear to give significantly reduced rates already upon mono-solvation [297]. The reaction of Eq. (29) with  $X = \text{Cl}$  has also been the subject of a number of studies, both experimental [35,297,299,300,302,303] and theoretical [162,304] (see also [305] for hydrolysis of  $\text{CH}_3\text{Cl}$ ). The trends appear to be similar to the reaction with  $X = \text{Br}$ . The reactions related to Eq. (29), but with  $\text{CH}_3\text{X}$  replaced by larger alkyl bromides and chlorides, have also been investigated ( $n = 0, 1$ ) [35].

A large number of publications have dealt with the exothermic reactions



where  $X$  and  $Y$  are halogens. The reactions with  $\text{F}^-(\text{H}_2\text{O})_n$  have been studied for  $X = \text{Cl}$  [49,168,306–309],  $X = \text{Br}$  [49,301,306], and  $X = \text{I}$  [49]. For  $n = 0$  they all occur close to the encounter rate, as expected for highly exothermic reactions with low central barriers. Seeley et al. [301] have determined that for the reaction between  $\text{CH}_3\text{Br}$  and  $\text{F}^-(\text{H}_2\text{O})_n$ , the mechanism changes twice upon going from  $n = 0$

to  $n = 5$ . The only significant reaction for  $n \leq 1$  is through the  $\text{S}_{\text{N}}2$  channel, while for  $n = 2$  there is competition with an association mechanism. While there is no observed reaction for  $n = 3$ ,  $n = 4$  and 5 appear to proceed by ligand switching followed by thermal decomposition [296,301]. This example is illustrative for the problems that are encountered in attempts to bridge the gap between gas phase and solution by microsolvation experiments. While the rate is close to the collision frequency for  $n = 0$ , already at  $n = 3$  the barrier is too high to allow for any observable  $\text{S}_{\text{N}}2$  reaction. Unfortunately, similar problems are invariably encountered in these studies. For  $n \geq 2\text{--}3$  the substitution reactions become so slow that competing reactions take over, for example, ligand switching, association, or proton transfer. Also, thermal decomposition of the  $\text{Y}^-(\text{H}_2\text{O})_n$  species is, as one might expect, observed for large  $n$  (e.g., for  $n \geq 3$  for  $\text{OH}^-(\text{H}_2\text{O})_n$  above 163 K [164]). The reactions between  $\text{F}^-$  and  $\text{CH}_3\text{X}$  ( $X = \text{Cl}, \text{Br}, \text{I}$ ) have also been studied in electron beam activated binary clusters [310,311].

Reaction (30) between  $\text{CH}_3\text{Br}$  and  $\text{Cl}^-(\text{H}_2\text{O})_n$  has also been the subject of several studies [108,284], and has been observed upon microsolvation in  $\text{CHCl}_3$  (as has  $\text{CH}_3\text{I} + \text{Cl}^-(\text{CHCl}_3)_n$ ) [277] and in other organic solvents [306]. Seeley et al. [108] found evidence that ligand switching replaces the  $\text{S}_{\text{N}}2$  channel already for  $n = 1$  for this reaction, a result that finds support in a recent Car–Parrinello molecular dynamics study for this reaction [284].

Since identity  $\text{S}_{\text{N}}2$  reactions are slow, microsolvated identity reactions are expected to be even slower, and there does not appear to be any reports in the literature of experimental work on reactions of the type in Eq. (30) with  $X = Y$ . The identity “intramolecularly solvated” reactions of Craig and Brauman [78,79] provide an example where solvation increases the reaction rates, but these reactions are rather uncharacteristic, since, unlike Eq. (30), the transition state is solvated while the nucleophile is not. The lack of experimental work on identity reactions is partially compensated by a large amount of theoretical work for the reaction between  $\text{Cl}^-(\text{H}_2\text{O})_n$  and  $\text{CH}_3\text{Cl}$

[166,167,175,294,312–317], including molecular dynamics studies [314,317] and a full potential energy surface [313]. The Monte Carlo simulations and illustrations of Asada et al. [316] demonstrate that not only does  $\Delta H^\ddagger$  increase upon mono- and di-hydration, but also the density of states for passage over the transition barrier is reduced.

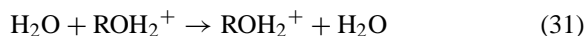
## 6. Frontside vs. backside $S_N2$ reactions

While the limiting  $S_N1$  mechanism only yields racemic products through a carbocationic intermediate, the classical  $S_N2$  mechanism can only give inverted products. On this background the idea of a retentive  $S_N2$  mechanism has been met by much scepticism. A report from 1978 on the reaction between lithium ethoxide and 3-chlorobut-1-ene in ethanol [318] seems to be the first to provide solid experimental support for retention of configuration in  $S_N2$ . On the other hand, the ion pair theory of Winstein [319] permits partial retention in  $S_N1$  nucleophilic substitution. In this mode, an ion pair is first formed unimolecularly. Then the nucleophile attacks the ion pair on the front side, upon which the leaving group disappears. Alternatively, backside attack of the ion pair will give the inverted product. The problem with this picture is that the term ion pair is rather poorly defined. It is difficult to distinguish experimentally, and also conceptually, between a solvolytic  $S_N1$  ion pair frontside substitution mechanism and a retentive  $S_N2$  mechanism with a late transition state. Moreover, it is difficult to envisage truly unimolecular behaviour in solution, since solvent molecules always will participate actively. For this reason, a discussion about frontside vs. backside substitution may easily turn into a war of words. Again gas phase studies may assist to clarify the discussion.

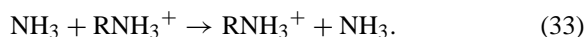
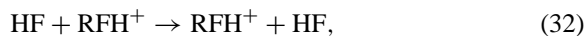
Harder et al. studied the influence of lithium salts on gas phase models of substitution reactions [320]. They were able to demonstrate, through fourth order Møller–Plesset perturbation theoretical (MP4) calculations employing double-zeta basis sets, that e.g., in the case of  $\text{LiCl} + \text{CH}_3\text{Cl}$ , a retentive transition state in

which the lithium ion interacts equally with both chlorides had approximately the same energy as the corresponding invertive transition state (see also [321,322]). On the other hand, [320] and a G2 study by Glukhovtsev et al. [92] demonstrated that in the absence of the lithium cation, the retentive mechanism is far higher in energy than the invertive, at least for methyl substrates and strong nucleophiles.

Uggerud and Bache-Andreassen [62] approached the same problem by looking at identity reactions between water and protonated alcohols.



In the case of protonated methanol it was found that the retentive  $S_N2$  transition structure is unfavourably high in energy compared to the invertive. However, this energy difference drops gradually down the homologous series of  $\text{CH}_3\text{OH}_2^+$ ,  $\text{CH}_3\text{CH}_2\text{OH}_2^+$ ,  $(\text{CH}_3)_2\text{CHOH}_2^+$ , and  $(\text{CH}_3)_3\text{COH}_2^+$ . In the latter case the difference is only 10 kJ/mol, which means that the two—in this case only in principle—stereochemical antipodes are produced in direct competition. Similar trends are found for the analogous reactions [238,239],



Since a nucleophilic substitution in the gas phase must be bimolecular by necessity, we have introduced the terms  $S_{NB}$  and  $S_{NF}$  to distinguish the two alternative mechanisms. The classical  $S_N1/S_N2$  paradigm with its relationship between stereochemistry and reaction order is at best very complicated. It is thus, tempting to suggest that an alternative view, with also solution reactions categorised according to  $S_{NB}$  and  $S_{NF}$ , might be more beneficial.

Another example comes from a detailed survey of the potential energy surface of the reaction between water and the exo- and the endo-forms of protonated norcaryl alcohol [323]. This ab initio study revealed that while the latter rearranges to the allylic isomer, the former prefers a retentive exchange of waters, even over the alternative  $S_{NB}$  route to give the endo-isomer.

These findings are in accord with solution experiments on this class of substances [324–327].

## 7. A note on solvolysis and the limiting $S_N1$ reaction

For nucleophilic reactions in solution, it is generally believed that there is a trend in reactivity such that primary substrates follow  $S_N2$  ( $S_{NB}$ ), while tertiary aliphatic compounds give rise to carbocations in solution, according to the limiting  $S_N1$  mechanism of Eq. (2). Few have questioned the basis of the postulate stating that there is a direct relationship between the molecularity of the rate determining step and the stereoselectivity, despite the fact that many supposedly  $S_N1$  reactions give rise to non-racemic product mixtures with variable enantiomeric composition [328]. Instead, considerable effort has been put into the task of containing these intermediate and deviating cases in the classical  $S_N1/S_N2$  regime. The most influential contributors have been Winstein, More O'Ferrall, Schleyer, Jencks and Bentley, who have introduced various ion pair mechanisms in the landscape in-between  $S_N1$  and  $S_N2$  [319,329–334].

Despite the apparent success of these ideas, there appear to be unresolved problems. The main question is whether or not a carbocation, or more precisely a solvated carbocation, may exist as an intermediate under the reaction conditions given. Recently, Müller and Rossier showed that alcohol solvolysis of tertiary chloride species ((*R*)-3-chloro-3,7-dimethyloctane and related compounds) proceed with up to 87% inversion of configuration [335]. They pointed out that there could be two explanations for their observation; solvent attack on the substrate or attack on an intermediate intimate ion pair. They were not able to distinguish between these mechanistic variants. The amount of retention observed was ascribed to electrophilic solvent catalysis, and they wrote: “The departure of the leaving group may be assisted by hydrogen bonding to the solvent, and this will result in an ion pair having a solvent molecule in close proximity to the leaving group. Breakdown of this intermediate ion pair may

occur with preferential incorporation of this solvent molecule rather than of bulk solvent”. The relationship between this scenario, and the  $S_NF$  mechanism is evident, but it is also clear that if the postulated ion pair really exists, this is an indication of a solvated carbocation and hints further towards an  $S_N1$  type mechanism.

Solvated carbocations are known indirectly from numerous gas phase studies of unimolecular decomposition reactions. The term ion/neutral complex has been used, and a number of remarkable experimental studies have been published in the literature [336–339]. Also in this context, it has been debated intensively to which degree complexes of the type  $X \cdots R^+$  play a role, having a measurable lifetime (minimum a couple of vibrational periods) during the decomposition  $RX^+ \rightarrow R^+ + X$ . The general idea of ion/neutral complexes finds support in quantum chemical calculations for  $CH_3CH_2OH_2^+$  [340,341],  $CH_3CH_2CH_2NH_3^+$  [342],  $CH_3CH_2CNH^+$  [343],  $C(CH_3)_3OH_2^+$  [344], to mention a few selected examples.

The distinction between covalently and hydrogen bonded isomers does not fully account for the genuine nature of energetic ion-neutral complexes  $X \cdots R^+$ . A dynamic perspective must be taken. Morton was early to notice the importance of discrete chemical processes occurring within such complexes. He noticed the similarity to solution chemistry, and introduced the term “gas phase solvolysis” to describe the phenomenon [336]. Morton's criterion for identifying such processes is that one of the two partners ( $R^+$  or  $X$ ) is free to reorient (“flip”) relative to the other during the short lifetime of the complex. During this period of time the structures of  $R^+$  and  $X$  may also isomerise before further reaction takes place.

However, it can also be deduced from the aforementioned papers on ion/neutral complexes that the relative proton affinity of the neutral molecule and the corresponding alkene of the carbocation is a key factor. In the case of  $CH_3CH_2OH_2^+$ , either formed by protonation of ethanol or by reaction between the ethyl cation and water, it turns out that the ion has two

isomers, corresponding to the two minima of the potential energy surface,  $C_2H_5OH_2^+$  and  $(C_2H_4) \cdots H-OH_2^+$ . The hydrogen bonded isomer is 99 kJ/mol above the covalently bonded. On the other hand, there is no minimum corresponding to  $C_2H_5^+ \cdots OH_2$ , simply because the proton affinity of water ( $PA = 697$  kJ/mol) is slightly above that of ethylene ( $PA = 680$  kJ/mol). This is a key point, since even if carbocations are stabilised in solution we may infer from this that bulk water in many cases is too basic ( $PA = 1130$  kJ/mol) to accommodate alkyl cations with  $\beta$ -hydrogens. In the literal sense, as implicated by Eq. (2),  $S_N1$  is therefore not realistic for this kind of substrate in water and most other solvents. Despite this lack of stability, it may still be argued that carbocations have transient existence in aqueous solution. It is very difficult to assess this problem directly by measurement, but recent kinetic studies cast serious doubt on the existence of the tertiary butyl cation in water. The lifetime appears to be significantly below 1 ps [345,346]. On the other hand, it is well established that carbocations without  $\beta$ -hydrogens that benefit from unusually high stabilisation (for example, the triphenylmethyl cation) do exist both in the liquid and the solid states. It is also established that carbocationic species prevail in superacids, and IR, NMR and ESCA spectra have been recorded [347–349].

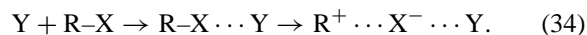
Although, they are not energy minima, extremely shortly lived hydrogen bonded complexes of carbocations should not be ruled out as a transient situation during proton abstraction and thereby elimination. However, as true intermediates in the literal sense of Eq. (2) it seems unrealistic that they could play any role, and for this reason the gas phase  $S_NB/S_NF$  paradigm provides a more satisfactory description also for typical solution behaviour—at least until spectroscopic or structural evidence can be presented for solvated carbocations in the given solvent. In this sense the limiting  $S_N1$  reaction is best regarded as the asymptotic limit that is approached when the bulk solvent has a lower proton affinity than the alkene corresponding to the carbocation in question.

In the case that there is no intermediate carbocation, Morton's reorientation can be reformulated to be com-

patible with the  $S_NB/S_NF$  paradigm. Direct encounter between a nucleophile  $Y$  and a substrate  $RX$  may give two topologically distinct complexes,  $Y \cdots R-X$  (**a**) or  $R-X \cdots Y$  (**b**), corresponding to the structures **2** and **3** of Scheme 1, respectively. For the many gas phase examples discussed in this review, structure **a** is the reactive configuration which leads directly to the transition state of the invertive  $S_NB$  reaction (corresponding to the classical  $S_N2$ ), while **b** is the immediate precursor for the retentive  $S_NF$  reaction. Depending on the details of the potential energy surface, and the initial conditions, **a** may rearrange to **b** (or vice versa). This may either be regarded as “space walk” by the nucleophile, or a Morton type reorientation of the substrate  $R-X$  relative to  $Y$ . In any case, the actual outcome of an encounter by  $Y$  and  $R-X$  will depend intimately on the potential energies of **a** and **b**, on the barrier between them, and the barriers for  $S_NB$  relative to  $S_NF$ .

A nice example which outlines some of these ideas was recently provided by Filippi and Speranza on the reaction between (*R*)-1-phenyl-ethanol and protonated  $^{18}O$ -methanol, which they studied by a gas phase radiolysis technique [350]. Based on the observed kinetics and an analysis of the enantiomer composition of the ether product formed, they concluded that at low temperature there is a preference for a retentive pathway. They coined the term “troposelectivity” to describe the phenomenon observed.

Based on the discussion of the preceding paragraphs, one question remains, namely whether the rate determining step of a reaction of this type is unimolecular. According to the ion pair hypothesis formation of a hydrogen bonded carbocationic intermediate should occur in two steps according to



Unless the reaction is diffusion controlled, and as long as  $R-X \cdots Y$  exist as a minimum of the potential energy surface, the second step would normally be rate determining, and consequently this is a bimolecular reaction. Of course, the ion pair is surrounded by several  $Y$  molecules in the case of solvolysis, and it is therefore impossible to infer the true molecularity of the rate determining step. It is interesting that

Ingold noticed this possibility when he formulated his theory, but this did not hinder him in using the term unimolecular for this reaction type [3].

## 8. Conclusion and outlook

The concepts and language of physical organic chemistry used to describe reactivity often confuse rather than clarify. Interesting, but timeless discussions is a part of the somewhat dubious reputation of physical organic chemistry. We hope that the present review has taken away some of the misconceptions introduced in this way. It should be evident that simplified models based on accumulated knowledge in the field of gas phase chemistry is a rich and inspiring source of ideas and information to the rest of chemistry and science, and all signs point towards a future where this will continue to be so.

## Acknowledgements

The authors wish to thank L. Bache-Andreassen for fruitful discussion and comments on the manuscript, and we are grateful to the Norwegian Research Council (NFR) for the grants that made this work possible. We are also in great debt to all the living and non-living chemists who have guided our curiosity into this field, some by their clear and inspiring thoughts, some by their incomprehensible explanations. Those who generated the facts are too numerous to be mentioned by name here, but most of the names will be found in the list of references given below. Upon writing this article the authors had to make decisions about which sub-topics and literature they should cover. Scientifically rewarding material has been left out realising that the separation process, to some extent, is subjective. We need to apologise to negatively affected colleagues for all our misjudgements and ignorance.

## Notes added in proof

Since submission of the manuscript a number of important articles have appeared in the literature,

illustrating the fast development of new insight in this field. In order to make our survey as up to date as possible they are listed below with brief comments.

[A1] L.A. Angel, S.P. Garcia, K.M. Ervin, *J. Am. Chem. Soc.* 124 (2002) 336. Mass spectrometric study of the endothermic  $S_N2$  reaction between  $Cl^-$  and  $CH_3F$  and competing reactions. The reaction dynamics has been elucidated and the experimental results compared with results from ab initio calculations of the potential energy surface.

[A2] J.M. Gonzales, R.S. Cox III, S.T. Brown, W.D. Allen, H.F. Schaefer III, *J. Phys. Chem. A* 105 (2001) 11327. An assessment of density functional theory (DFT) for the  $S_N2$  reactions between  $F^-$  and  $CH_3X$  ( $X = F, Cl, CN, OH, SH, NH_2$  and  $PH_2$ ) which show that DFT performs fairly well for geometries and complexation energies, but severely underestimates  $S_N2$  activation barriers. This is essentially the same result as found in earlier work (Section 3.3).

[A3] I. Lee, C.K. Kim, C.K. Sohn, H.G. Li, H.W. Lee, *J. Phys. Chem. A* 106 (2002) 1081. High level ab initio study of the identity methyl transfer reactions  $X^- + CH_3X \rightarrow XCH_3 + X^-$  ( $X = H, F, Cl$  and  $Br$ ). It is found that the stronger the nucleophile, the greater is the bond formation at the transition state.

[A4] M. Pagliai, S. Raugei, G. Cardini, V. Schettino, *Phys. Chem. Chem. Phys.* 3 (2001) 4870. Car-Parrinello DFT molecular dynamics study of the  $S_N2$  reactions between  $Cl^-$  and  $CH_2Cl_2$ .

[A5] S. Kato, G.E. Davico, H.S. Lee, C.H. DePuy, V.M. Bierbaum, *Int. J. Mass Spectrom.* 210/211 (2001) 223. Flowing afterglow study of reaction rates and  $\alpha$ -deuterium KIEs for the  $S_N2$  reaction between  $Y^-$  and  $CH_3X$  ( $X \neq Y = Cl, Br, I$ ). The experimentally observed KIEs are significantly smaller than KIEs earlier derived from transition state theory (TST). These reactions are believed to behave non-statistically (Section 4) making statistical theories such as TST unreliable. These new and more accurate experimental data show that TST might be unreliable also for the calculation of KIEs in these systems, contrary to our statement in Section 3.4.

[A6] K. Ohmiya, S. Kato, *Chem. Phys. Lett.* 348 (2001) 75. Reference interaction site model



self-consistent field (RISM-SCF) study of the  $S_N2$  reaction  $Cl^- + CH_3Cl$  in water.

[A7] J. Grinblat, M. Ben-Zion, S. Hoz, *J. Am. Chem. Soc.* 123 (2001) 10738. A study of  $S_N2$ -like bromine transfer reactions with implications for proton, halogen and alkyl transfer ( $S_N2$ ) reactions.

[A8] J.P. Richard, T.L. Amyes, M.A. Toteva, *Acc. Chem. Res.* 34 (2001) 981. Experimental study of lifetimes and dynamics of carbocations (and carbanions) in water.

[A9] S. Gronert, G.N. Merrill, S.R. Kass, *J. Org. Chem.* 60 (1995) 488. Early study questioning the ability of the DFT approach in determining reaction barriers for  $S_N2$  reactions.

## References

- [1] S.S. Shaik, H.B. Schlegel, S. Wolfe, *Theoretical Aspects of Physical Organic Chemistry: The  $S_N2$  Reaction*, Wiley, New York, 1992.
- [2] P. Walden, *Ber.* 26 (1893) 210.
- [3] C.K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, NY, 1953.
- [4] D.K. Bohme, L.B. Young, *J. Am. Chem. Soc.* 92 (1970) 7354.
- [5] L.B. Young, E. Lee-Ruff, D.K. Bohme, *J. Chem. Soc., Chem. Commun.* (1973) 35.
- [6] D.K. Bohme, G.I. Mackay, J.D. Payzant, *J. Am. Chem. Soc.* 96 (1974) 4027.
- [7] K. Tanaka, G.I. MacKay, J.D. Payzant, D.K. Bohme, *Can. J. Chem.* 54 (1976) 1643.
- [8] C.A. Lieder, J.I. Brauman, *J. Am. Chem. Soc.* 96 (1974) 4028.
- [9] J.I. Brauman, W.N. Olmstead, C.A. Lieder, *J. Am. Chem. Soc.* 96 (1974) 4030.
- [10] C.A. Lieder, J.I. Brauman, *Int. J. Mass Spectrom. Ion. Phys.* 16 (1975) 307.
- [11] E.E. Ferguson, F.C. Fehsenfeld, A.L. Schmeltekopf, *Adv. At. Mol. Phys.* 5 (1969) 1.
- [12] N.G. Adams, D. Smith, in: J.M. Farrar, W.H. Sanders (Eds.), *Techniques for the study of ion molecule reactions*, Wiley, New York, 1988, p. 165.
- [13] M.B. Comisarov, A.G. Marshall, *Chem. Phys. Lett.* 25 (1974) 282.
- [14] M.B. Comisarov, A.G. Marshall, *Chem. Phys. Lett.* 26 (1974) 489.
- [15] A.G. Marshall, C.L. Hendrickson, G.S. Jackson, *Mass Spectrom. Rev.* 17 (1998) 1.
- [16] J.P. Briggs, R. Yamdagni, P. Kebarle, *J. Am. Chem. Soc.* 94 (1972) 5128.
- [17] P. Kebarle, in: J.M. Farrar, W.H. Sanders (Eds.), *Techniques for the study of ion molecule reactions*, Wiley, New York, 1988, p. 221.
- [18] M. Meot-Ner, L.W. Sieck, *J. Am. Chem. Soc.* 113 (1991) 4448.
- [19] K. Giles, E.P. Grimsrud, *J. Phys. Chem.* 96 (1992) 6680.
- [20] W.N. Olmstead, J.I. Brauman, *J. Am. Chem. Soc.* 99 (1977) 4219.
- [21] J.I. Brauman, *J. Mass Spectrom.* 30 (1995) 1649.
- [22] P. Langevin, *Ann. Chim. Phys.* 5 (1905) 245.
- [23] G. Giomousis, D.P. Stevenson, *J. Chem. Phys.* 29 (1958) 294.
- [24] T. Su, M.T. Bowers, in: M.T. Bowers (Ed.), *Gas Phase Ion Chemistry*, Vol. 1, Academic Press, New York, 1979, p. 83.
- [25] W.J. Chesnavich, T. Su, M.T. Bowers, *J. Chem. Phys.* 72 (1980) 2641.
- [26] T. Su, W.J. Chesnavich, *J. Chem. Phys.* 76 (1982) 5183.
- [27] T. Su, *J. Chem. Phys.* 82 (1985) 2164.
- [28] T. Su, *J. Chem. Phys.* 100 (1994) 4703.
- [29] J. Troe, *J. Chem. Phys.* 105 (1996) 6249.
- [30] M.J. Pellerite, J.I. Brauman, *J. Am. Chem. Soc.* 102 (1980) 5993.
- [31] B.D. Wladkowski, K.F. Lim, W.D. Allen, J.I. Brauman, *J. Am. Chem. Soc.* 114 (1992) 9136.
- [32] M.N. Glukhovtsev, A. Pross, L. Radom, *J. Am. Chem. Soc.* 117 (1995) 2024.
- [33] M.N. Glukhovtsev, A. Pross, L. Radom, *J. Am. Chem. Soc.* 118 (1996) 6273.
- [34] S. Parthiban, G. de Oliveira, J.M.L. Martin, *J. Phys. Chem. A* 105 (2001) 895.
- [35] C.H. DePuy, S. Gronert, A. Mullin, V.M. Bierbaum, *J. Am. Chem. Soc.* 112 (1990) 8650.
- [36] M.J.S. Dewar, Y.-C. Yuan, *J. Am. Chem. Soc.* 112 (1990) 2095.
- [37] S. Gronert, C.H. DePuy, V.M. Bierbaum, *J. Am. Chem. Soc.* 113 (1991) 4009.
- [38] S. Gronert, *J. Am. Chem. Soc.* 115 (1993) 652.
- [39] D.S. Chung, C.K. Kim, B.-S. Lee, I. Lee, *J. Phys. Chem. A* 101 (1997) 9097.
- [40] F.M. Bickelhaupt, E.J. Baerends, N.M.M. Nibbering, T. Ziegler, *J. Am. Chem. Soc.* 115 (1993) 9160.
- [41] F.M. Bickelhaupt, *J. Comput. Chem.* 20 (1999) 114.
- [42] B.D. Wladkowski, J.I. Brauman, *J. Am. Chem. Soc.* 114 (1992) 10643.
- [43] G.E. Davico, *Org. Lett.* 1 (1999) 1675.
- [44] P.O. Staneke, G. Groothuis, S. Ingemann, N.M.M. Nibbering, *J. Phys. Org. Chem.* 9 (1996) 471.
- [45] R.A. Morris, A.A. Viggiano, T.M. Miller, J.V. Seeley, S.T. Arnold, J.F. Paulson, J.M. Van Doren, *J. Phys. Chem.* 100 (1996) 10641.
- [46] G.N. Sastry, S. Shaik, *J. Am. Chem. Soc.* 120 (1998) 2131.
- [47] V. Bakken, D. Danovich, S. Shaik, H.B. Schlegel, *J. Am. Chem. Soc.* 123 (2001) 130.
- [48] Y.A. Borisov, E.E. Arcia, S.L. Mielke, B.C. Garrett, T.H. Dunning Jr., *J. Phys. Chem. A* 105 (2001) 7724.
- [49] R.A.J. O'Hair, G.E. Davico, J. Hacıoglu, T.T. Dang, C.H. DePuy, V.M. Bierbaum, *J. Am. Chem. Soc.* 116 (1994) 3609.

- [50] S. Gronert, L.-M. Fong, *Int. J. Mass Spectrom.* 192 (1999) 185.
- [51] A.E. Flores, S. Gronert, *J. Am. Chem. Soc.* 121 (1999) 2627.
- [52] S. Gronert, *Chem. Rev.* 101 (2001) 329.
- [53] S. Gronert, L.M. Pratt, S. Mogali, *J. Am. Chem. Soc.* 123 (2001) 3081.
- [54] G. Caldwell, T.F. Magnera, P. Kebarle, *J. Am. Chem. Soc.* 106 (1984) 959.
- [55] W.B. Knighton, J.A. Bognar, P.M. O'Connor, E.P. Grimsrud, *J. Am. Chem. Soc.* 115 (1993) 12079.
- [56] K.E. Sahlstrom, W.B. Knighton, E.P. Grimsrud, *J. Phys. Chem. A* 101 (1997) 1501.
- [57] C.H. DePuy, *Int. J. Mass Spectrom.* 200 (2000) 79.
- [58] J. Chandrasekhar, S.F. Smith, W.L. Jorgensen, *J. Am. Chem. Soc.* 106 (1984) 3049.
- [59] J. Chandrasekhar, S.F. Smith, W.L. Jorgensen, *J. Am. Chem. Soc.* 107 (1985) 154.
- [60] B. Ensing, E.J. Meijer, P.E. Blöchl, E.J. Baerends, *J. Phys. Chem. A* 105 (2001) 3300.
- [61] L.A. Angel, K.M. Ervin, *J. Phys. Chem. A* 105 (2001) 4042.
- [62] E. Uggerud, L. Bache-Andreassen, *Chem. Eur. J.* 5 (1999) 1917.
- [63] R.A. Marcus, *Ann. Rev. Phys. Chem.* 15 (1964) 155.
- [64] R.A. Marcus, *J. Phys. Chem.* 72 (1968) 891.
- [65] R.A. Marcus, *J. Phys. Chem. A* 101 (1997) 4072.
- [66] M.J. Pellerite, J.I. Brauman, *J. Am. Chem. Soc.* 105 (1983) 2672.
- [67] S.E. Barlow, J.M. Van Doren, V.M. Bierbaum, *J. Am. Chem. Soc.* 110 (1988) 7240.
- [68] V.F. DeTuri, P.A. Hintz, K.M. Ervin, *J. Phys. Chem. A* 101 (1997) 5969.
- [69] B.D. Wladkowski, J.I. Brauman, *J. Phys. Chem.* 97 (1993) 13158.
- [70] B.D. Wladkowski, J.L. Wilbur, J.I. Brauman, *J. Am. Chem. Soc.* 116 (1994) 2471.
- [71] S.L. Craig, M. Zhong, J.I. Brauman, *J. Am. Chem. Soc.* 121 (1999) 11790.
- [72] S. Hoz, H. Basch, J.L. Wolk, T. Hoz, E. Rozental, *J. Am. Chem. Soc.* 121 (1999) 7724.
- [73] G.D. Ruggiero, I.H. Williams, *J. Chem. Soc., Perkin Trans. 2*, in press.
- [74] J.M. Van Doren, C.H. DePuy, V.M. Bierbaum, *J. Phys. Chem.* 93 (1989) 1130.
- [75] B.D. Wladkowski, W.D. Allen, J.I. Brauman, *J. Phys. Chem.* 98 (1994) 13532.
- [76] S.L. Craig, J.I. Brauman, *Science* 276 (1997) 1536.
- [77] S.L. Craig, J.I. Brauman, *Ber. Bunsenges. Phys. Chem.* 101 (1997) 510.
- [78] S.L. Craig, J.I. Brauman, *J. Am. Chem. Soc.* 118 (1996) 6786.
- [79] S.L. Craig, J.I. Brauman, *J. Am. Chem. Soc.* 121 (1999) 6690.
- [80] S.R. Vande Linde, W.L. Hase, *J. Phys. Chem.* 94 (1990) 2778.
- [81] S.C. Tucker, D.G. Truhlar, *J. Phys. Chem.* 93 (1989) 8138.
- [82] S.C. Tucker, D.G. Truhlar, *J. Am. Chem. Soc.* 112 (1990) 3338.
- [83] A. Gonzalez-Lafont, T.N. Truong, D.G. Truhlar, *J. Phys. Chem.* 95 (1991) 4618.
- [84] G.D. Billing, *Chem. Phys.* 159 (1992) 109.
- [85] S. Schmatz, P. Botschwina, J. Hauschildt, R. Schinke, *J. Chem. Phys.* 114 (2001) 5233.
- [86] P. Botschwina, *Theor. Chem. Acc.* 99 (1998) 426.
- [87] S. Schmatz, *Chem. Phys. Lett.* 330 (2000) 188.
- [88] C. Li, P. Ross, J.E. Szulejko, T.B. McMahon, *J. Am. Chem. Soc.* 118 (1996) 9360.
- [89] L.A. Curtiss, K. Raghavachari, G.W. Trucks, J.A. Pople, *J. Chem. Phys.* 94 (1991) 7221.
- [90] L.A. Curtiss, K. Raghavachari, P.C. Redfern, V. Rassolov, J.A. Pople, *J. Chem. Phys.* 109 (1998) 7764.
- [91] J.K. Laerdahl, unpublished results.
- [92] M.N. Glukhovtsev, A. Pross, H.B. Schlegel, R.D. Bach, L. Radom, *J. Am. Chem. Soc.* 118 (1996) 11258.
- [93] D.M. Cyr, M.G. Scarton, M.A. Johnson, *J. Chem. Phys.* 99 (1993) 4869.
- [94] W.-P. Hu, D.G. Truhlar, *J. Phys. Chem.* 98 (1994) 1049.
- [95] D.M. Cyr, G.A. Bishea, M.G. Scarton, M.A. Johnson, *J. Chem. Phys.* 97 (1992) 5911.
- [96] D.M. Cyr, C.G. Bailey, D. Serxner, M.G. Scarton, M.A. Johnson, *J. Chem. Phys.* 101 (1994) 10507.
- [97] C.C. Arnold, D.M. Neumark, D.M. Cyr, M.A. Johnson, *J. Phys. Chem.* 99 (1995) 1633.
- [98] C.E.H. Dessent, C.G. Bailey, M.A. Johnson, *J. Chem. Phys.* 105 (1996) 10416.
- [99] C.E.H. Dessent, M.A. Johnson, *J. Am. Chem. Soc.* 119 (1997) 5067.
- [100] P. Botschwina, M. Horn, S. Seeger, R. Oswald, *Ber. Bunsenges. Phys. Chem.* 101 (1997) 387.
- [101] S. Schmatz, P. Botschwina, H. Stoll, *Int. J. Mass Spectrom.* 201 (2000) 277.
- [102] H. Wang, L. Zhu, W.L. Hase, *J. Phys. Chem.* 98 (1994) 1608.
- [103] H. Wang, W.L. Hase, *J. Am. Chem. Soc.* 117 (1995) 9347.
- [104] E. Uggerud, *J. Chem. Soc., Perkin Trans. 2* (1999) 1465.
- [105] S.T. Graul, M.T. Bowers, *J. Am. Chem. Soc.* 113 (1991) 9696.
- [106] S.T. Graul, M.T. Bowers, *J. Am. Chem. Soc.* 116 (1994) 3875.
- [107] D.M. Cyr, L.A. Posey, G.A. Bishea, C.-C. Han, M.A. Johnson, *J. Am. Chem. Soc.* 113 (1991) 9697.
- [108] J.V. Seeley, R.A. Morris, A.A. Viggiano, H. Wang, W.L. Hase, *J. Am. Chem. Soc.* 119 (1997) 577.
- [109] D.S. Tonner, T.B. McMahon, *J. Am. Chem. Soc.* 122 (2000) 8783.
- [110] P. Ayotte, J. Kim, J.A. Kelley, S.B. Nielsen, M.A. Johnson, *J. Am. Chem. Soc.* 121 (1999) 6950.
- [111] S.L. Craig, J.I. Brauman, *J. Phys. Chem. A* 101 (1997) 4745.
- [112] K.E. Sahlstrom, W.B. Knighton, E.P. Grimsrud, *J. Phys. Chem. A* 101 (1997) 5543.
- [113] J.-L. Le Garrec, B.R. Rowe, J.L. Queffelec, J.B.A. Mitchell, D.C. Clary, *J. Chem. Phys.* 107 (1997) 1021.
- [114] A.A. Viggiano, J.S. Paschkewitz, R.A. Morris, J.F. Paulson, A. Gonzalez-Lafont, D.G. Truhlar, *J. Am. Chem. Soc.* 113 (1991) 9404.

- [115] A.A. Viggiano, R.A. Morris, J.S. Paschkewitz, J.F. Paulson, *J. Am. Chem. Soc.* 114 (1992) 10477.
- [116] S.T. Graul, C.J. Carpenter, J.E. Bushnell, P.A.M. van Koppen, M.T. Bowers, *J. Am. Chem. Soc.* 120 (1998) 6785.
- [117] A.H. Maulitz, F.C. Lightstone, Y.-J. Zheng, T.C. Bruice, *Proc. Natl. Acad. Sci. U.S.A.* 94 (1997) 6591.
- [118] K.S. Strode, E.P. Grimsrud, *Int. J. Mass Spectrom. Ion. Processes* 130 (1994) 227.
- [119] G.E. Davico, V.M. Bierbaum, *J. Am. Chem. Soc.* 122 (2000) 1740.
- [120] C.E.C.A. Hop, T.B. McMahon, *J. Phys. Chem.* 95 (1991) 10582.
- [121] R.A. Morris, A.A. Viggiano, *J. Phys. Chem.* 98 (1994) 3740.
- [122] R.A. Morris, A.A. Viggiano, J.F. Paulson, *Int. Rev. Phys. Chem.* 15 (1996) 183.
- [123] R.N. McDonald, A.K. Chowdhury, *J. Am. Chem. Soc.* 107 (1985) 4123.
- [124] G.G. Gatev, M. Zhong, J.I. Brauman, *J. Phys. Org. Chem.* 10 (1997) 531.
- [125] J.L. Wilbur, J.I. Brauman, *J. Am. Chem. Soc.* 113 (1991) 9699.
- [126] V. Moliner, I.H. Williams, *J. Am. Chem. Soc.* 122 (2000) 10895.
- [127] M.L. McKee, *J. Org. Chem.* 62 (1997) 7942.
- [128] I.-S. Han, C.K. Kim, C.K. Kim, B.-S. Lee, I. Lee, *J. Comput. Chem.* 18 (1997) 1773.
- [129] A.R. Katritzky, R.D. Burton, M. Qi, P.A. Shipkova, C.H. Watson, Z. Dega-Szafran, J.R. Eyler, M. Karelson, U. Maran, M.C. Zerner, *J. Chem. Soc., Perkin Trans. 2* (1998) 825.
- [130] G. Bouchoux, N. Choret, *Rapid Commun. Mass Spectrom.* 11 (1997) 1799.
- [131] S. Wolfe, D.J. Mitchell, H.B. Schlegel, *J. Am. Chem. Soc.* 103 (1981) 7692.
- [132] S. Wolfe, D.J. Mitchell, H.B. Schlegel, *J. Am. Chem. Soc.* 103 (1981) 7694.
- [133] J.A. Dodd, J.I. Brauman, *J. Phys. Chem.* 90 (1986) 3559.
- [134] R.P. Bell, *Proc. R. Soc. London Ser. A* 154 (1936) 414.
- [135] M.G. Evans, M. Polanyi, *Trans. Faraday Soc.* 34 (1938) 11.
- [136] Z. Shi, R.J. Boyd, *Can. J. Chem.* 70 (1992) 450.
- [137] I. Lee, C.K. Kim, B.-S. Lee, *J. Comput. Chem.* 16 (1995) 1045.
- [138] W.K. Kim, W.S. Ryu, I.-S. Han, C.K. Kim, I. Lee, *J. Phys. Org. Chem.* 11 (1998) 115.
- [139] J.A. Montgomery Jr., J.W. Ochterski, G.A. Petersson, *J. Chem. Phys.* 101 (1994) 5900.
- [140] J.W. Ochterski, G.A. Petersson, J.A. Montgomery Jr., *J. Chem. Phys.* 104 (1996) 2598.
- [141] J.A. Montgomery Jr., M.J. Frisch, J.W. Ochterski, G.A. Petersson, *J. Chem. Phys.* 110 (1999) 2822.
- [142] J.M.L. Martin, G. de Oliveira, *J. Chem. Phys.* 111 (1999) 1843.
- [143] W.J. Hehre, R. Ditchfield, J.A. Pople, *J. Chem. Phys.* 56 (1972) 2257.
- [144] P.C. Hariharan, J.A. Pople, *Theoret. Chim. Acta* 28 (1973) 213.
- [145] T.H. Dunning Jr., *J. Chem. Phys.* 90 (1989) 1007.
- [146] D.E. Woon, T.H. Dunning Jr., *J. Chem. Phys.* 98 (1993) 1358.
- [147] R. Krishnan, J.S. Binkley, R. Seeger, J.A. Pople, *J. Chem. Phys.* 72 (1980) 650.
- [148] F. Jensen, *Chem. Phys. Lett.* 196 (1992) 368.
- [149] S.S. Glad, F. Jensen, *J. Am. Chem. Soc.* 119 (1997) 227.
- [150] I. Lee, C.K. Kim, B.-S. Lee, *J. Phys. Org. Chem.* 8 (1995) 473.
- [151] E. Uggerud, *Int. J. Mass Spectrom.* 182/183 (1999) 13.
- [152] E. Uggerud, *J. Chem. Soc., Perkin Trans. 2* (1999) 1459.
- [153] A.D. Becke, *J. Chem. Phys.* 98 (1993) 5648.
- [154] B.J. Lynch, P.L. Fast, M. Harris, D.G. Truhlar, *J. Phys. Chem. A* 104 (2000) 4811.
- [155] M.N. Glukhovtsev, R.D. Bach, A. Pross, L. Radom, *Chem. Phys. Lett.* 260 (1996) 558.
- [156] L. Deng, V. Branchadell, T. Ziegler, *J. Am. Chem. Soc.* 116 (1994) 10645.
- [157] C. Adamo, V. Barone, *J. Chem. Phys.* 108 (1998) 664.
- [158] O.V. Gritsenko, B. Ensing, P.R.T. Schipper, E.J. Baerends, *J. Phys. Chem. A* 104 (2000) 8558.
- [159] G.D. Ruggiero, I.H. Williams, *J. Chem. Soc., Perkin Trans. 2* (2001) 448.
- [160] S. Humbel, S. Sieber, K. Morokuma, *J. Chem. Phys.* 105 (1996) 1959.
- [161] M. Svensson, S. Humbel, K. Morokuma, *J. Chem. Phys.* 105 (1996) 3654.
- [162] S. Re, K. Morokuma, *J. Phys. Chem. A* 105 (2001) 7185.
- [163] O. Matsson, K.C. Westaway, *Adv. Phys. Org. Chem.* 31 (1998) 143.
- [164] A.A. Viggiano, S.T. Arnold, R.A. Morris, A.F. Ahrens, P.M. Hierl, *J. Phys. Chem.* 100 (1996) 14397.
- [165] W.-P. Hu, D.G. Truhlar, *J. Am. Chem. Soc.* 118 (1996) 860.
- [166] X.G. Zhao, S.C. Tucker, D.G. Truhlar, *J. Am. Chem. Soc.* 113 (1991) 826.
- [167] X.G. Zhao, D.-H. Lu, Y.-P. Liu, G.C. Lynch, D.G. Truhlar, *J. Chem. Phys.* 97 (1992) 6369.
- [168] W.-P. Hu, D.G. Truhlar, *J. Am. Chem. Soc.* 116 (1994) 7797.
- [169] W.-P. Hu, D.G. Truhlar, *J. Am. Chem. Soc.* 117 (1995) 10726.
- [170] S. Wolfe, C.-K. Kim, *J. Am. Chem. Soc.* 113 (1991) 8056.
- [171] R.J. Boyd, C.-K. Kim, Z. Shi, N. Weinberg, S. Wolfe, *J. Am. Chem. Soc.* 115 (1993) 10147.
- [172] S. Wolfe, C.-K. Kim, K. Yang, N. Weinberg, Z. Shi, *Can. J. Chem.* 76 (1998) 359.
- [173] J.A. Barnes, I.H. Williams, *J. Chem. Soc., Chem. Commun.* (1993) 1286.
- [174] R.A. Poirier, Y. Wang, K.C. Westaway, *J. Am. Chem. Soc.* 116 (1994) 2526.
- [175] Y. Okuno, *Chem. Phys. Lett.* 264 (1997) 120.
- [176] S. Shaik, *Prog. Phys. Org. Chem.* 15 (1985) 197.
- [177] S. Shaik, *Acta Chem. Scand.* 44 (1990) 205.
- [178] C.-C. Han, J.A. Dodd, J.I. Brauman, *J. Phys. Chem.* 90 (1986) 471.
- [179] M.L. Chabinyk, S.L. Craig, C.K. Regan, J.I. Brauman, *Science* 279 (1998) 1882.
- [180] S. Shaik, P.C. Hiberty, *Adv. Quantum Chem.* 26 (1995) 99.

- [181] S. Shaik, in: P.v.R. Schleyer (Ed.), *Encyclopedia of Computational Chemistry*, Vol. 5, Wiley, Chichester, UK, 1998, p. 3143.
- [182] S. Shaik, A. Shurki, *Angew. Chem. Int. Ed. Engl.* 38 (1999) 586.
- [183] R.G. Pearson, *J. Org. Chem.* 54 (1989) 1423.
- [184] S. Shaik, *J. Am. Chem. Soc.* 103 (1981) 3692.
- [185] A. Pross, S. Shaik, *J. Am. Chem. Soc.* 103 (1981) 3702.
- [186] S. Shaik, A. Pross, *J. Am. Chem. Soc.* 104 (1982) 2708.
- [187] A. Pross, S. Shaik, *Tetrahedron Lett.* 23 (1982) 5467.
- [188] S. Shaik, *Nouv. J. Chim.* 6 (1982) 159.
- [189] A. Pross, S. Shaik, *Acc. Chem. Res.* 16 (1983) 363.
- [190] S. Shaik, *J. Am. Chem. Soc.* 105 (1983) 4359.
- [191] S. Shaik, *Nouv. J. Chim.* 7 (1983) 201.
- [192] S. Shaik, *J. Am. Chem. Soc.* 106 (1984) 1227.
- [193] D.J. Mitchell, H.B. Schlegel, S. Shaik, S. Wolfe, *Can. J. Chem.* 63 (1985) 1642.
- [194] S. Shaik, *Isr. J. Chem.* 26 (1985) 367.
- [195] S. Shaik, *Can. J. Chem.* 64 (1986) 96.
- [196] G. Sini, S. Shaik, J.-M. Lefour, G. Ohanessian, P.C. Hiberty, *J. Phys. Chem.* 93 (1989) 5661.
- [197] S. Shaik, E. Duzy, A. Bartuv, *J. Phys. Chem.* 94 (1990) 6574.
- [198] A. Pross, S. Shaik, *Croat. Chem. Acta* 65 (1992) 625.
- [199] G. Sini, S. Shaik, P.C. Hiberty, *J. Chem. Soc., Perkin Trans. 2* (1992) 1019.
- [200] S. Shaik, A. Ioffe, A.C. Reddy, A. Pross, *J. Am. Chem. Soc.* 116 (1994) 262.
- [201] S. Shaik, A.C. Reddy, *J. Chem. Soc., Faraday Trans.* 90 (1994) 1631.
- [202] A. Shurki, S. Shaik, *J. Mol. Struct. (Theochem)*. 424 (1998) 37.
- [203] D. Cohen, R. Bar, S. Shaik, *J. Am. Chem. Soc.* 108 (1986) 231.
- [204] S. Shaik, A.C. Reddy, A. Ioffe, J.P. Dinnocenzo, D. Danovich, J.K. Cho, *J. Am. Chem. Soc.* 117 (1995) 3205.
- [205] G.N. Sastry, S. Shaik, *J. Am. Chem. Soc.* 117 (1995) 3290.
- [206] G.N. Sastry, S. Shaik, *J. Phys. Chem.* 100 (1996) 12241.
- [207] G.N. Sastry, D. Danovich, S. Shaik, *Angew. Chem. Int. Ed. Engl.* 35 (1996) 1098.
- [208] R.D. Harcourt, *J. Mol. Struct. (Theochem)*. 253 (1992) 363.
- [209] R.D. Harcourt, *Int. J. Quantum Chem.* 60 (1996) 553.
- [210] R.D. Harcourt, *J. Mol. Struct. (Theochem)*. 398/399 (1997) 93.
- [211] R.D. Harcourt, *Eur. J. Inorg. Chem.* (2000) 1901.
- [212] R. McWeeny, *Methods of molecular quantum mechanics*, Academic Press, London, 1989.
- [213] S. Shaik, *J. Org. Chem.* 52 (1987) 1563.
- [214] E. Buncel, S. Shaik, I.-H. Um, S. Wolfe, *J. Am. Chem. Soc.* 110 (1988) 1275.
- [215] G. Sini, P. Maitre, P.C. Hiberty, S. Shaik, *J. Mol. Struct. (Theochem)*. 229 (1991) 163.
- [216] D. Lauvergnat, P.C. Hiberty, D. Danovich, S. Shaik, *J. Phys. Chem.* 100 (1996) 5715.
- [217] A. Shurki, P.C. Hiberty, S. Shaik, *J. Am. Chem. Soc.* 121 (1999) 822.
- [218] Z. Shi, R.J. Boyd, *J. Phys. Chem.* 95 (1991) 4698.
- [219] J.W. Larson, T.B. McMahon, *J. Am. Chem. Soc.* 106 (1984) 517.
- [220] J.W. Larson, T.B. McMahon, *J. Am. Chem. Soc.* 107 (1985) 766.
- [221] R. Vetter, L. Zülicke, *J. Am. Chem. Soc.* 112 (1990) 5136.
- [222] P. Sand, J. Bergman, E. Lindholm, *J. Phys. Chem.* 92 (1988) 2039.
- [223] B. Safi, K. Choho, P. Geerlings, *J. Phys. Chem. A* 105 (2001) 591.
- [224] J. March, *Advanced Organic Chemistry*, Wiley, New York, 1992.
- [225] W.J. Albery, M.M. Kreevoy, *Adv. Phys. Org. Chem.* 16 (1978) 87.
- [226] W.J. Albery, *Ann. Rev. Phys. Chem.* 31 (1980) 227.
- [227] Z. Shi, R.J. Boyd, *J. Am. Chem. Soc.* 111 (1989) 1575.
- [228] Z. Shi, R.J. Boyd, *J. Am. Chem. Soc.* 113 (1991) 1072.
- [229] Z. Shi, R.J. Boyd, *J. Am. Chem. Soc.* 112 (1990) 6789.
- [230] S. Shaik, H.B. Schlegel, S. Wolfe, *J. Chem. Soc., Chem. Commun.* (1988) 1322.
- [231] I. Lee, C.K. Kim, D.S. Chung, B.-S. Lee, *J. Org. Chem.* 59 (1994) 4490.
- [232] N.T. Anh, F. Maurel, B.T. Thanh, H.H. Thao, Y.T. N'Guessan, *New J. Chem.* 18 (1994) 473.
- [233] N.T. Anh, F. Maurel, H.H. Thao, Y.T. N'Guessan, *New J. Chem.* 18 (1994) 483.
- [234] N.T. Anh, B.T. Thanh, H.H. Thao, Y.T. N'Guessan, *New J. Chem.* 18 (1994) 489.
- [235] E.D. Hughes, *Trans. Faraday Soc.* 37 (1941) 603.
- [236] A.G. Evans, M. Polanyi, *Nature* 149 (1942) 608.
- [237] J.D. Roberts, M.C. Caserio, *Basic Principles of Organic Chemistry*, W.A. Benjamin, Menlo Park, California, 1977.
- [238] J.K. Laerdahl, E. Uggerud, unpublished results.
- [239] P.U. Civcir, L. Bache-Andreassen, J.K. Laerdahl, K. Faegri, Jr., E. Uggerud, in preparation.
- [240] Z. Shi, R.J. Boyd, *J. Am. Chem. Soc.* 113 (1991) 2434.
- [241] I. Lee, *Chem. Soc. Rev.* 19 (1990) 133.
- [242] E.H. Knoerr, M.E. Eberhart, *J. Phys. Chem. A* 105 (2001) 880.
- [243] V. Gineityte, *J. Mol. Struct. (Theochem)*. 541 (2001) 1.
- [244] T. Baer, W.L. Hase, *Unimolecular Reaction Dynamics*, Oxford University Press, New York, 1996.
- [245] D.G. Truhlar, B.C. Garrett, S.J. Klippenstein, *J. Phys. Chem.* 100 (1996) 12771.
- [246] R.A. Marcus, in: V. Sundström (Ed.), *Femtochemistry and femtobiology: ultrafast reaction dynamics at the atomic scale resolutions*, Nobel Symposium 101, Imperial College Press, London, 1997, p. 54.
- [247] S.R. Vande Linde, W.L. Hase, *J. Am. Chem. Soc.* 111 (1989) 2349.
- [248] S.R. Vande Linde, W.L. Hase, *J. Chem. Phys.* 93 (1990) 7962.
- [249] S.R. Vande Linde, W.L. Hase, *J. Phys. Chem.* 94 (1990) 6148.
- [250] Y.J. Cho, S.R. Vande Linde, L. Zhu, W.L. Hase, *J. Chem. Phys.* 96 (1992) 8275.
- [251] W.L. Hase, Y.J. Cho, *J. Chem. Phys.* 98 (1993) 8626.
- [252] W.L. Hase, *Science* 266 (1994) 998.

- [253] H. Wang, G.H. Peslherbe, W.L. Hase, *J. Am. Chem. Soc.* 116 (1994) 9644.
- [254] G.H. Peslherbe, H. Wang, W.L. Hase, *J. Chem. Phys.* 102 (1995) 5626.
- [255] G.H. Peslherbe, H. Wang, W.L. Hase, *J. Am. Chem. Soc.* 118 (1996) 2257.
- [256] H. Wang, W.L. Hase, *Chem. Phys.* 212 (1996) 247.
- [257] H. Wang, W.L. Hase, *J. Am. Chem. Soc.* 119 (1997) 3093.
- [258] H. Wang, W.L. Hase, *Int. J. Mass Spectrom.* 167/168 (1997) 573.
- [259] H. Wang, E.M. Goldfield, W.L. Hase, *J. Chem. Soc., Faraday Trans.* 93 (1997) 737.
- [260] D.J. Mann, W.J. Hase, *J. Phys. Chem. A* 102 (1998) 6208.
- [261] T. Su, H. Wang, W.L. Hase, *J. Phys. Chem. A* 102 (1998) 9819.
- [262] W.L. Hase, H. Wang, G.H. Peslherbe, in: N.G. Adams, L.M. Babock (Eds.), *Advances in Gas-Phase Ion Chemistry*, Vol. 3, JAI Press, Greenwich, CT, 1998, p. 125.
- [263] G. Li, W.L. Hase, *J. Am. Chem. Soc.* 121 (1999) 7124.
- [264] L. Sun, W.L. Hase, K. Song, *J. Am. Chem. Soc.* 123 (2001) 5753.
- [265] M.V. Basilevsky, V.M. Ryaboy, *Chem. Phys. Lett.* 129 (1986) 71.
- [266] D.C. Clary, J. Palma, *J. Chem. Phys.* 106 (1997) 575.
- [267] S. Schmatz, D.C. Clary, *J. Chem. Phys.* 109 (1998) 8200.
- [268] M.I. Hernández, J. Campos-Martínez, P. Villarreal, S. Schmatz, D.C. Clary, *Phys. Chem. Chem. Phys.* 1 (1999) 1197.
- [269] S. Schmatz, D.C. Clary, *J. Chem. Phys.* 110 (1999) 9483.
- [270] A.A. Viggiano, R.A. Morris, T. Su, B.D. Wladkowski, S.L. Craig, M. Zhong, J.I. Brauman, *J. Am. Chem. Soc.* 116 (1994) 2213.
- [271] A.A. Viggiano, A.J. Midey, *J. Phys. Chem. A* 104 (2000) 6786.
- [272] S.L. Craig, M. Zhong, J.I. Brauman, *J. Am. Chem. Soc.* 120 (1998) 12125.
- [273] J.L. Wilbur, B.D. Wladkowski, J.I. Brauman, *J. Am. Chem. Soc.* 115 (1993) 10823.
- [274] T. Su, R.A. Morris, A.A. Viggiano, J.F. Paulson, *J. Phys. Chem.* 94 (1990) 8426.
- [275] K.M. Ervin, *Int. J. Mass Spectrom.* 185/186/187 (1999) 343.
- [276] A.A. Viggiano, R.A. Morris, *J. Phys. Chem.* 100 (1996) 19227.
- [277] K. Giles, E.P. Grimsrud, *J. Phys. Chem.* 97 (1993) 1318.
- [278] D.C. Clary, *Science* 279 (1998) 1879.
- [279] V.M. Ryaboy, *Chem. Phys. Lett.* 159 (1989) 371.
- [280] H.-G. Yu, G. Nyman, *Chem. Phys. Lett.* 312 (1999) 585.
- [281] J. Hauschildt, R. Schinke, S. Schmatz, P. Botschwina, *Phys. Chem. Chem. Phys.* 3 (2001) 2275.
- [282] R. Car, M. Parrinello, *Phys. Rev. Lett.* 55 (1985) 2471.
- [283] S. Raugei, G. Cardini, V. Schettino, *J. Chem. Phys.* 111 (1999) 10887.
- [284] S. Raugei, G. Cardini, V. Schettino, *J. Chem. Phys.* 114 (2001) 4089.
- [285] M. Pagliai, S. Raugei, G. Cardini, V. Schettino, *Phys. Chem. Chem. Phys.* 3 (2001) 2559.
- [286] D. Marx, M.E. Tuckerman, J. Hutter, M. Parrinello, *Nature* 397 (1999) 601.
- [287] P.L. Geissler, C. Dellago, D. Chandler, J. Hutter, M. Parrinello, *Science* 291 (2001) 2121.
- [288] D.K. Bohme, G.I. Mackay, *J. Am. Chem. Soc.* 103 (1981) 978.
- [289] T.N. Truong, E.V. Stefanovich, *J. Phys. Chem.* 99 (1995) 14700.
- [290] O. Takahashi, H. Sawahata, Y. Ogawa, O. Kikuchi, *J. Mol. Struct. (Theochem)*. 393 (1997) 141.
- [291] C.S. Pomelli, J. Tomasi, *J. Phys. Chem. A* 101 (1997) 3561.
- [292] T. Mineva, N. Russo, E. Sicilia, *J. Comput. Chem.* 19 (1998) 290.
- [293] Y. Mo, J. Gao, *J. Comput. Chem.* 21 (2000) 1458.
- [294] A.A. Mohamed, F. Jensen, *J. Phys. Chem. A* 105 (2001) 3259.
- [295] K. Takashima, J.M. Riveros, *Mass Spectrom. Rev.* 17 (1998) 409.
- [296] A.A. Viggiano, S.T. Arnold, R.A. Morris, *Int. Rev. Phys. Chem.* 17 (1998) 147.
- [297] D.K. Bohme, A.B. Raksit, *J. Am. Chem. Soc.* 106 (1984) 3447.
- [298] M. Henchman, J.F. Paulson, P.M. Hierl, *J. Am. Chem. Soc.* 105 (1983) 5509.
- [299] P.M. Hierl, J.F. Paulson, M.J. Henchman, *J. Phys. Chem.* 99 (1995) 15655.
- [300] P.M. Hierl, A.F. Ahrens, M. Henchman, A.A. Viggiano, J.F. Paulson, D.C. Clary, *J. Am. Chem. Soc.* 108 (1986) 3142.
- [301] J.V. Seeley, R.A. Morris, A.A. Viggiano, *J. Phys. Chem. A* 101 (1997) 4598.
- [302] M. Henchman, P.M. Hierl, J.F. Paulson, *J. Am. Chem. Soc.* 107 (1985) 2812.
- [303] P.M. Hierl, A.F. Ahrens, M.J. Henchman, A.A. Viggiano, J.F. Paulson, D.C. Clary, *Faraday Discuss. Chem. Soc.* 85 (1988) 37.
- [304] K. Ohta, K. Morokuma, *J. Phys. Chem.* 89 (1985) 5845.
- [305] M. Aida, H. Yamataka, *J. Mol. Struct. (Theochem)*. 461/462 (1999) 417.
- [306] D.K. Bohme, A.B. Raksit, *Can. J. Chem.* 63 (1985) 3007.
- [307] Y. Okuno, *J. Am. Chem. Soc.* 122 (2000) 2925.
- [308] H. Tachikawa, *J. Phys. Chem. A* 104 (2000) 497.
- [309] H. Tachikawa, *J. Phys. Chem. A* 105 (2001) 1260.
- [310] L. Lehmann, E. Illenberger, *Int. J. Mass Spectrom.* 185/186/187 (1999) 463.
- [311] J. Langer, S. Matejcek, E. Illenberger, *Phys. Chem. Chem. Phys.* 2 (2000) 1001.
- [312] K. Morokuma, *J. Am. Chem. Soc.* 104 (1982) 3732.
- [313] S.C. Tucker, D.G. Truhlar, *J. Am. Chem. Soc.* 112 (1990) 3347.
- [314] M. Re, D. Laria, *J. Chem. Phys.* 105 (1996) 4584.
- [315] Y. Okuno, *J. Chem. Phys.* 105 (1996) 5817.
- [316] T. Asada, N. Kato, K. Kitaura, *J. Mol. Struct. (Theochem)*. 461/462 (1999) 493.
- [317] T. Nyman, K.V. Mikkelsen, P.-O. Åstrand, G.D. Billing, *Acta Chem. Scand.* 53 (1999) 1043.
- [318] P. Cayzergues, C. Georgoulis, G. Ville, *J. Chem. Res. (S)* (1978) 325.

- [319] S. Winstein, E. Clippinger, A.H. Fainberg, R. Heck, G.C. Robinson, *J. Am. Chem. Soc.* 78 (1956) 328.
- [320] S. Harder, A. Streitwieser, J.T. Petty, P.v.R. Schleyer, *J. Am. Chem. Soc.* 117 (1995) 3253.
- [321] A. Streitwieser, G.S.-C. Choy, F. Abu-Hasanayn, *J. Am. Chem. Soc.* 119 (1997) 5013.
- [322] P.R. Schreiner, P.v.R. Schleyer, R.K. Hill, *J. Org. Chem.* 59 (1994) 1849.
- [323] E. Uggerud, *J. Org. Chem.* 66 (2001) 7084.
- [324] P.v.R. Schleyer, M. Bremer, *J. Org. Chem.* 53 (1988) 2362.
- [325] U. Schöllkopf, K. Fellenberger, M. Patsch, P.v.R. Schleyer, T. Su, G.W. van Dine, *Tetrahedron Lett.* 37 (1967) 3639.
- [326] H. Dauner, D. Lenoir, I. Ugi, *Z. Naturforsch.* 34b (1979) 1745.
- [327] W.-D. Stohre, K.R. Schmieder, *Chem. Ber.* 109 (1976) 285.
- [328] J. Dale, *J. Chem. Edu.* 75 (1998) 1482.
- [329] R.A. More O'Ferrall, *J. Chem. Soc. B* (1970) 274.
- [330] D.J. Raber, R.C. Bingham, J. Milton Harris, J.L. Fry, P.v.R. Schleyer, *J. Am. Chem. Soc.* 92 (1970) 5977.
- [331] W.P. Jencks, *Chem. Rev.* 72 (1972) 705.
- [332] W.P. Jencks, *Chem. Soc. Rev.* 10 (1981) 345.
- [333] W.P. Jencks, *Chem. Rev.* 85 (1985) 511.
- [334] T.W. Bentley, G. Llewellyn, *Prog. Phys. Org. Chem.* 17 (1990) 121.
- [335] P. Müller, J.-C. Rossier, *J. Chem. Soc., Perkin Trans. 2* (2000) 2232.
- [336] T.H. Morton, *Tetrahedron* 38 (1982) 3195.
- [337] P. Longevialle, R. Botter, *J. Chem. Soc., Chem. Commun.* (1980) 823.
- [338] D.H. Williams, B.J. Stapleton, R.D. Bowen, *Tetrahedron Lett.* 32 (1978) 2919.
- [339] R.D. Bowen, D.H. Williams, H. Schwarz, C. Wesdemiotis, *J. Chem. Soc., Chem. Commun.* (1979) 261.
- [340] G. Bouchoux, Y. Hoppilliard, *J. Am. Chem. Soc.* 112 (1990) 9110.
- [341] D.J. Swanton, D.C.J. Marsden, L. Radom, *Org. Mass Spectrom.* 26 (1991) 227.
- [342] H.E. Audier, T.H. Morton, *Org. Mass Spectrom.* 28 (1993) 1218.
- [343] G. Bouchoux, M.T. Nguyen, P. Longevialle, *J. Am. Chem. Soc.* 114 (1992) 10000.
- [344] D. Berthomieu, H.-E. Audier, *Eur. Mass Spectrom.* 3 (1997) 19.
- [345] M.M. Toteva, J.P. Richard, *J. Am. Chem. Soc.* 118 (1996) 11434.
- [346] Q. Meng, A. Thibblin, *J. Chem. Soc., Perkin Trans. 2* (1999) 1397.
- [347] G. Olah, *Angew. Chem. Int. Ed. Engl.* 34 (1995) 1393.
- [348] P. Vogel, *Carbocation Chemistry*, Elsevier, Amsterdam, 1985.
- [349] G.A. Olah, *J. Org. Chem.* 66 (2001) 5943.
- [350] A. Filippi, M. Speranza, *J. Am. Chem. Soc.* 123 (2001) 6077.
- [351] Y. Okuno, *Int. J. Quantum Chem.* 68 (1998) 261.
- [352] S.L. VanOrden, R.M. Pope, S.W. Buckner, *Org. Mass Spectrom.* 26 (1991) 1003.
- [353] H. Tachikawa, M. Igarashi, *Chem. Phys. Lett.* 303 (1999) 81.
- [354] M. Igarashi, H. Tachikawa, *Int. J. Mass Spectrom.* 181 (1998) 151.
- [355] J.M.L. Martin, personal communication.
- [356] D.M. Cyr, M.G. Scarton, K.B. Wiberg, M.A. Johnson, S. Nonose, J. Hirokawa, H. Tanaka, T. Kondow, R.A. Morris, A.A. Viggiano, *J. Am. Chem. Soc.* 117 (1995) 1828.