

Review Commentary

Reactivity trends and stereospecificity in nucleophilic substitution reactions[†]

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Received 6 January 2006; revised 28 February 2006; accepted 6 March 2006

ABSTRACT: To obtain the full overview of the mechanistic landscape of nucleophilic substitution reactions is a demanding pursuit. There are still many unexplored regions, and humility and carefulness should be exercised before drawing the final map. This review commentary emphasizes some recent findings of relevance to these questions. A critical account is given about commonly used concepts and practices for interpretation of reactivity trends. It is questioned whether the S_N2/S_N1 paradigm is fully appropriate for understanding the factors which govern the outcome of substitution reactions. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: reaction mechanism; S_N2, S_N1; nucleophilicity; frontside displacement; periodic trends; steric effect; Lewis basicity

INTRODUCTION

Hughes and Ingold postulated there are two mechanisms available to nucleophilic substitution reactions in solution; S_N1 (D_N + A_N) and S_N2 (A_ND_N).^{1–4}



In the S_N2 mechanism the R—X bond is broken and the R—Y bond is formed in a concerted manner, and consequently the reaction is bimolecular in the reactants, hence the label 2. Based on the ideas of among others Le Bel⁵ and London,⁶ following the experimental findings of Walden (Walden),⁷ Hughes and Ingold stated that the nucleophile attacks the substrate molecule from the diametrically opposite side of the leaving group, giving rise to the well-known [Y...R...X] transition structure, ultimately giving inversion of configuration around the central carbon atom. The S_N1 mechanism, probably originating from Lowry,⁸ is unimolecular, and requires two separate steps. The first is heterolytic cleavage of the R—X bond giving an intermediate carbocation R⁺, while the second is addition between of the nucleophile Y to the carbocation. If the substrate is enantiomerically pure, the stereochemical consequence of this mechanism is a racemic product mixture since the carbocation adopts a planar configuration around

the central carbon and the nucleophile may attack from both sides with equal probability.

The S_N2/S_N1 mechanistic scenario is one of the cornerstones of teaching modern organic chemistry, and generations of students have been confronted with it, and trained to understand experimental finding on the basis of the simple concepts outlined above. It is therefore relevant to question how solidly the mechanistic framework is founded. Any reaction mechanism is per definition open for challenge, and the postulates of Hughes and Ingold represent no exception. From accumulated experimental evidence it long ago became pertinent to adjust the original mechanistic scenario.^{9–11} For example numerous reports of product mixtures having enantiomer distributions different from the predicted 50:50 and 100:0 posed a particular difficulty. Winstein introduced the notion of ion pairs and a more complex reaction sequence, of which some of the elementary steps are reversible and other not.¹² More O'Ferrall and Jencks invented and elaborated on a gliding scale of mechanisms in-between S_N1 and S_N2.^{13–16}

Despite the popularity and apparent success of this extended scenario, there remain unresolved issues related to the basic assumptions of the theoretical construction. One obvious critical question is how a mechanism in-between S_N1 and S_N2 should be interpreted. It is unclear to which degree it is bimolecular or unimolecular. An elementary reaction must be one or the other. A related question is the debated issue of a third possible mechanism, a bimolecular retentive reaction^{17–20} – meaning that the

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[†]Selected paper presented at the 10th European Symposium on Organic Reactivity, 25–30 July 2005, Rome, Italy.

nucleophile attacks the substrate on the same face as the leaving group departs, in an essentially concerted bond breaking and bond formation process. These core issues will be discussed in the following.

In addition to these conceptual difficulties, there are other questions related to nucleophilic substitution reactions that yet have to be answered. According to the well-established textbook knowledge S_N reactions follow certain reactivity trends both in terms of substrate and nucleophile. It will become evident from the discussion that these patterns are of limited validity, and that the explanations are incomplete and even misleading. New insights into this highly fascinating and intricate topic are therefore welcome. It is illustrative that Hoz *et al.*—based on difficulties in interpreting S_N2 reactions on Br—concluded that current theories are inappropriate.²¹ They cited Ritchie: ‘... the search for an understanding [of] nucleophilic reactivity [is comparable] to the search for the Holy Grail.’²²

It is innate that mechanistic interpretation in organic chemistry is based on simplified and idealized gas phase models, since a mechanism represents a reduction of a vast set of empirical data. However, during this reduction process the essential features of the reaction must be correctly described. It is for example difficult to separate the properties of the molecules themselves from the effect of the solvent, and interpretation of trends in reactivity may easily be erroneous due to the neglect or misinterpretation of the solvent effect. In this respect, studies of the reaction in the gas phase are valuable. When such studies emerged in the 1960s, it became possible for the first time to directly study how the inherent properties of the molecules affect reactivity. As a result of this research, we are now in a much better situation for understanding the true nature and the full details of several reactions, in particular S_N reactions. Equally important, in parallel to the development in experimental methodology, there has been a revolution in quantum chemistry and modelling. It is now possible to calculate relative energies and structures of small molecules, and thereby reaction mechanisms, with high accuracy.²³

The purpose of this paper is to discuss some of the deficiencies in the S_N paradigm, and to demonstrate that important issues related to nucleophilicity at best are incompletely understood. The scope and the format of a review commentary does not allow for a comprehensive and fully balanced treatment. The critical reader should therefore consult the cited papers and recent reviews for more detail.^{23–26}

BACKSIDE SUBSTITUTION (TRADITIONAL S_N2)

Reactivity trends for nucleophile and leaving group

Nucleophilicity (from lat. *nucleus*, dim. of *nux nucis* nut, kernel and gr. *philos*, friend, to love) is the ability of an

attacking group, Y, to accommodate nucleophilic displacement in an S_N2 reaction, while nucleofugacity is the corresponding ability of a leaving group, X.

Swain and Scott²⁷ were first to give nucleophilicity a firm definition, which later has been approved by IUPAC. They defined nucleophilicity, n , through a linear free energy relationship:

$$\log(k/k_0) = ns \quad (2)$$

In this equation k_0 is the rate coefficient of a standard reaction, and k is the rate coefficient of the reaction of the given nucleophile. The slope s reflects the sensitivity of the given substrate. In their original work they studied the displacement of bromide using different nucleophiles and substrates, and their standard reaction was



Swain and Scott noticed that their approach did not reveal any direct connection between the kinetic concept of nucleophilicity and the thermodynamic concept of basicity. This is an unsettled state of affairs, since reactivity appears not to be correlated with the inherent properties of the reactants.^{27–37} In addition, it has turned out that there are a couple of other complications. Firstly, the equation is not universal, as first assumed. Secondly, the solvent masks the inherent properties of the reacting molecules. Wolfe and co-workers suggested the remedies to overcome these limitations.^{32,38} By studying the reaction in the gas phase, the solvent is literally lifted away. In addition, they noticed that the definition given by Eqns (2) and (3) fails to separate the intrinsic reactivity from the thermodynamical driving force. By analysing identity reactions,

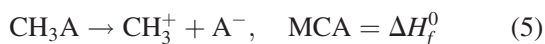


they also eliminated this factor. By making the attacking and leaving groups identical, there is no longer any distinction between inherent nucleophilicity and inherent nucleofugacity. The intrinsic barrier of a non-identity reaction can be expressed as the average of the intrinsic barriers of X and Y. The actual barrier can then be estimated, using a simple Marcus theory type expression to introduce the reaction exothermicity (determined by the relative heterolytic bond dissociation energies of $R-Y$ and $R-X$).^{32,38–41} The early work of Wolfe was not broad and systematic in its coverage of nucleophiles. More recent studies by Hoz^{42,43} and ourselves^{37,44} have a broader database, and we have therefore been able to draw wider conclusions than before.

Using G2 compound quantum chemical calculations, we modelled the most relevant features of the potential energy profiles for 18 different identity S_N2 reactions: $X^- + \text{CH}_3-X \rightarrow X-CH_3 + X^-$ and $\text{XH} + \text{CH}_3-X \rightarrow \text{XH} + \text{CH}_3-X$ ($X = \text{NH}_2, \text{OH}, \text{F}, \text{PH}_2, \text{SH}, \text{Cl}, \text{AsH}_2, \text{SeH}, \text{Br}$).⁴⁴ It was surprising to find that despite the charge difference, the barrier heights and the geometrical requirements upon going from the reactant

to the transition structure are directly comparable for X^- and XH . The intrinsic barrier heights decrease from left to right in the periodic table, thereby following the trend in decreasing electron donating ability (Lewis basicity). Increasing ionisation energy (of X^- and XH , respectively) is strongly correlated with decreasing barrier. This relationship can be explained by comparing the electronic distribution of the transition structure and the reactants (i.e. the substrate molecule alone). A nucleophile with a high IE , for example F^- , has a strongly polar $C-X$ bond in the substrate, where little electron density is donated from the nucleophile to the methyl cation. The bond, therefore, has a high electrostatic character. The road to the TS will be quite easy, since entrance of the second F^- from the rear will not be hampered much by electron repulsion due to the electron cloud of the first.

The remaining question is how this intrinsic nucleophilicity, defined only for identity reactions, relates to over-all nucleophilicity as defined by Swain and Scott. We will not go into detail here, but the relationship is quite straightforward.⁴⁴ On the one hand, the periodic trends in intrinsic nucleophilicity and Lewis basicity are inverse, as stated above. This means that F^- , in this strict sense, is a better nucleophile than OH^- . On the other hand, nucleophilicity and basicity draw in the same direction with regard to the thermochemical force. Heterolytic bond dissociation energies define carbon basicity, for example in terms of the methyl cation affinity, MCA



On this basis the thermochemical driving force is due to the difference in the $C-X$ and $C-Y$ bond energies – as implicit in the Marcus formulation – an increasingly stronger base will lead to an increased rate of substitution. Over-all nucleophilicity will, therefore, be determined by the relative contribution of these opposite intrinsic and the thermochemical factors. For thermoneutral and weakly exothermic reactions intrinsic nucleophilicity will dominate, while for sufficiently exothermic reactions basicity and nucleophilicity will merge.

Reactivity trends for substrate

The structure of the alkyl group of the substrate has a strong influence on reactivity. All textbooks of organic chemistry quote the well-known solution trends in S_N2 reaction rates which is methyl > primary > secondary > tertiary. This trend is often – and somewhat misleadingly – referred to as steric hindrance.^{4,11,45} Few systematic studies of gas phase reactions exist, but for anionic nucleophiles the situation in the gas phase and solution phase appears to be the same. Experimental^{46–52} and computational data^{53,54} agree on this. Exothermicity may, however, be an issue of concern, as inferred above, since most reactions studied are non-identity reactions.

Table 1. Calculated transition structure (TS) relative potential energies (kJ mol^{-1}) for cationic identity reactions with backside displacement, Eqn (6)^{55–57}

HX	CH_3	CH_3CH_2	$(CH_3)_2CH$	$(CH_3)_3C$
NH_3	56 (100)	73 (105)	86 (–)	101 (130)
H_2O	3 (38)	8 (46)	–1 (35)	–28 (6)
HF	–37 (5)	–28 (14)	–37 (0)	–34 (0)

Energies of TS are given relative to the separated reactants. The numbers in parenthesis corresponds to the energy of the TS relative to the reactant complex $HX \dots R-XH^+$. In the case of HF the method is MP2/6-31 ++ G(d,p), while for H_2O and NH_3 the others are G3_m.

For neutral nucleophiles the situation appears different.^{55–57} Table 1 shows the calculated barrier heights for normal backside substitution for the given identity reactions.



Out of the three nucleophiles considered here, only ammonia shows the expected behaviour, since a larger alkyl group gives a higher barrier. For hydrogen fluoride, the backside displacement is extremely favourable, but shows relatively little variation with the alkyl group. For water, the situation is somewhere in-between the two others, and the trend in barrier height with irregular size, essentially opposite to the textbook order. The calculated figures agree well with experimental FT-ICR mass spectrometry data,⁵⁸ both qualitatively and quantitatively in that the relative reaction rates are $R = C(CH_3)_3 > CH(CH_3)_2 > CH_3 > CH_2CH_3$ (Fig. 1).

It is illustrative to analyse the transition structures for the water case. As found for other substrate molecules $R-X$, the $C-O$ bond of ROH_2^+ becomes longer with the size of the alkyl group. The same tendency is found in the TS, where the $C-O$ bonds are even longer. For the *t*-butyl case, the two bonds are each around 2.7 Å in the TS, and it is highly questionable whether they are covalent bonds at all. More than anything, the situation resembles a carbocation sandwiched between two water molecules, bonded by electrostatic forces.

We observed from the data in Table 1 that the stronger base, ammonia shows textbook behaviour in how the barrier height increases with the size of the alkyl group. This may give a clue to the reason behind the trend in the alcohol data.⁵⁹ A water molecule, $PA(H_2O) = 697 \text{ kJ mol}^{-1}$, is less basic than ammonia, $PA(NH_3) = 854 \text{ kJ mol}^{-1}$, but the water dimer is of the similar base strength. Larger clusters are even more basic, approaching bulk water with $PA(H_2O)_\infty = 1130 \text{ kJ mol}^{-1}$. *Ab initio* calculations including four additional water molecules to mimic water solvation show the textbook order, methyl > primary > secondary > tertiary. In other words, this solvent effect seems to be a result of the differences in the interaction between nearest neighbours of the first solvation shell and the reacting unit in the TS and reactant configurations.⁵⁸ The increased basicity of the water clusters compared to single waters appears to be the controlling factor.

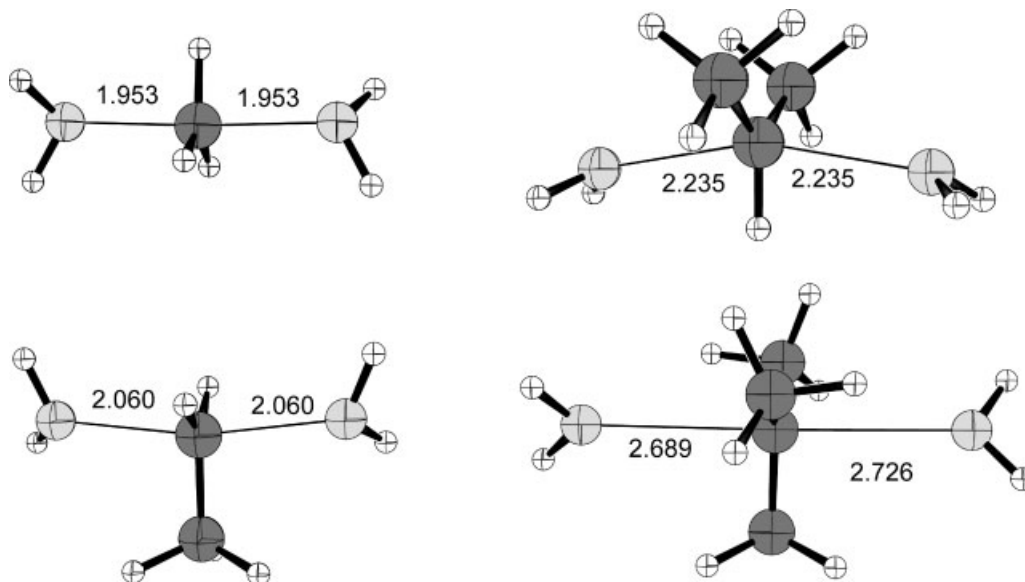


Figure 1. Transition structures (MP2/6-31G(d)) for identity reactions $\text{H}_2\text{O} + \text{R}-\text{OH}_2^+ \rightarrow {}^+\text{H}_2\text{O}-\text{R} + \text{OH}_2$. Bond lengths are given in Å units. For the substrate molecules, $\text{R}-\text{OH}_2^+$, the C–O bond lengths are 1.518 Å (Me), 1.549 Å (Et), 1.580 Å (*i*Pr), and 1.611 Å (*t*Bu)

FRONTSIDE SUBSTITUTION

The idea of a frontside substitution, a controversial issue among physical organic chemists, was approached by Glukhovtsec *et al.*⁶⁰ by applying quantum chemical methods. By calculating the barriers for reaction for $\text{X}^- + \text{CH}_3\text{X}$, they found that frontside displacement with barriers in the range 171–194 kJ mol^{-1} is highly unfavourable compared to backside displacement. However, frontside substitution has rarely been advocated for this type of substrates or nucleophiles. Instead we chose to investigate more prototype reactions, namely $\text{XH} + \text{R}-\text{XH}^+$, thereby including activated substrates and larger alkyl groups than methyl.^{55–58} It turns out that this investigation was very successful. It is not only possible to locate transition structures for the retentive mechanism, but it is far more favourable than anticipated. In the case of the protonated alcohols ($\text{HX} = \text{H}_2\text{O}$) we found that for identity reactions the energy difference between the TSs for frontside and backside substitution decreases with increasing size of the R group. In the case of *t*-butyl, the TS for frontside substitution is only 10 kJ mol^{-1} above that for backside substitution, both transition structures being lower in potential energy than the separated reactants. The same trend is also found for the protonated amines ($\text{HX} = \text{NH}_3$). In the case of $\text{R} = (\text{CH}_3)_3\text{C}$, no TS for the frontside displacement was found, and the reaction most likely occurs via a two step process ($\text{A}_\text{N} + \text{D}_\text{N}$), being only marginally more energy demanding than the backside mechanism. In the case of $\text{HX} = \text{HF}$ even the methyl substrate demonstrates potential frontside reactivity, with a barrier at 18 kJ mol^{-1} . For the larger substrates, that is upon increased methyl substitution at the α -carbon, no genuine

TS for frontside nucleophilic substitution TS could be found. The protonated alkyl fluorides ($\text{R} = \text{ethyl}$) are extremely loosely bonded, and should be regarded as weakly interacting ion–molecule complexes of the type $\text{R}^+ \cdots \text{FH}$. In fact, they are very close to the borderline of forming stable carbocations, thereby approaching very closely the limiting $\text{S}_\text{N}1$ reaction. Born–Oppenheimer reaction dynamics simulation have demonstrated that both frontside and backside substitution is feasible, despite there is no TS for the former⁶¹ (Table 2).

Ab initio model calculations clearly show that protonated cyclopropanol ring opens upon frontside attack of a water molecule. The ring is, however, stabilized by alkyl substitution. This is demonstrated by calculations of the $\text{S}_\text{N}2$ mechanisms of protonated bicyclo[3.1.0]hexanol (Scheme 1).⁶² It is remarkable that the found TS for frontside substitution in this case is even lower in potential energy than the corresponding TS for backside substitution. Another feature is that a compound with the same essential structural features was

Table 2. Calculated transition structure (TS) relative potential energies (kJ mol^{-1}) for cationic identity reactions with frontside displacement^{55–57}

HX	CH ₃	CH ₃ CH ₂	(CH ₃) ₂ CH	(CH ₃) ₃ C
NH ₃	227 (317)	191 (277)	150 (232)	—
H ₂ O	120 (231)	55 (157)	10 (106)	–18 (106)
HF	15 (103)	—	—	—

Energies of TS are given relative to the separated reactants. The numbers in parenthesis corresponds to the energy of the TS relative to the reactant complex $\text{R}-\text{XH}^+ \cdots \text{XH}$. In the case of HF the method is MP2/6-31++G(d,p), while for H₂O and NH₃ it is G3_m. No entry means that TS could not be located.



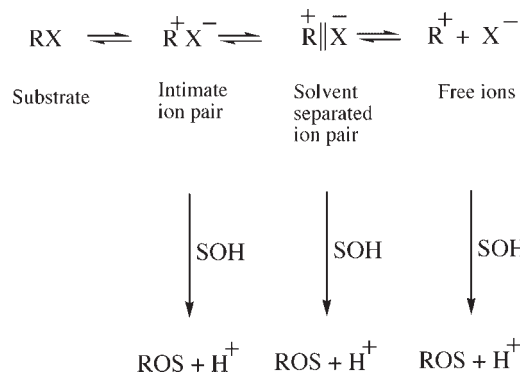
Scheme 1.

noted already in 1979 to undergo retentive nucleophilic substitution under typical S_N2 conditions.¹⁷

Most substrates become activated by protonation in the sense that an $R-XH^+$ bond is longer than an $R-X$ bond. This bond elongation is accompanied by a considerable decrease in the heterolytic bond dissociation energy. However, different substrates and X groups display great variability in their susceptibility to this effect. Generally, a more electronegative group will be more strongly affected than a less electronegative, and a more substituted alkyl group will be more affected than a less substituted. All this is in full accordance with how these substrates respond to conditions usually associated with the S_N1 mechanism, for example in acidic solvolysis. In the rational Hughes/Ingold interpretation, this means that the more strongly the molecule becomes activated by protonation in this way, the closer does it approach a weakly bonded carbocation and thereby the true S_N1 situation. From our study on the S_N2 reactivity, discussed above, we learned that protonation affect reactivity in a different way in terms of barrier heights. But we noticed that TS geometries for S_N2 also are expanded, resembling a sandwiched carbocation for tertiary substrates.

CONCLUSIVE REMARKS

How should these findings be interpreted, and what are the consequences? The obvious weakness of the Ingold/Hughes model is the intimate coupling between stereochemistry and molecularity – a bimolecular substitution gives inversion, and a unimolecular gives racemization. Only elementary gas phase reactions are simple in this respect, since they are either bimolecular or unimolecular. In solution, the situation is much more complex. In principle, the molecularity cannot be defined, since it is impossible to draw a firm line separating which solvent molecules are involved in the rate determining step and which are not. The kinetic order of a reaction, which is different from its molecularity, can of course be determined but is of limited use. A majority of reactions classified to be S_N1 are solvolysis reactions, for which it is impossible to determine neither order nor molecularity. This writer is free to speculate that the rate-determining step in any nucleophilic solvolysis involves more than one molecule. It would be difficult to provide convincing counter arguments. It is only possible to isolate carbocations under the extreme conditions of a superacid or high vacuum. Crystals of salts of carbocations can only be realized with



Scheme 2.

the most extremely weakly coordinating anions. To this end, methyl and ethyl cations are unknown even in super acid. Our first conclusion is that reactions in normal solvents will always be at least bimolecular. True unimolecular events are rare and short-lived carbocationic species whether they exist as shallow potential energy minima or represents transition structures are essentially the result of direct solvent assistance Scheme 2.

Winstein extended the Ingold/Hughes model to incorporate salt-effects and variable enantiomeric product distributions apparently in-between 50 and 100%.^{12,63} By introducing the intimate ion pair, the solvent separated ion pair and the free ions along the reaction coordinate, they were able to rationalize a large body of experimental observations. The model is also flexible since it involves several elementary steps, and can therefore be applied for quite complicated kinetics. Despite these positive sides, the model is of limited value in predicting the stereospecificity of a solvolytic reaction, and it makes some quite dubious assumptions regarding the existence of various energy minima (the ion pairs) and the heights of the barriers separating them. Another major limitation of this and similar models is that it does not include the obvious option of frontside bimolecular substitution as an elementary step. Our second conclusion is therefore that an improved mechanistic paradigm should not only include real intermediates as minima but also incorporate transition structures for frontside and backside substitutions. As demonstrated above, a much simpler and more realistic picture is obtained by invoking the topographically distinct backside and frontside substitution situations, and realising that frontside substitution becomes gradually more competitive when the alkyl group becomes bigger and the leaving group/nucleophile becomes better.

Acknowledgements

The author is indebted to Dr. Jon K. Lærdahl for his valuable contributions to our work in this field and for the drawings of Figure 1.

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