

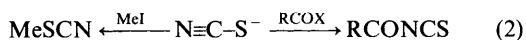
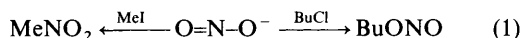
The Role of Reaction Energy and Transition State Bond Order on the Reactivity of Ambifunctional Compounds in Solution

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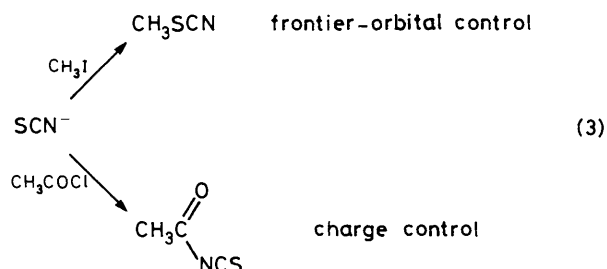
The ambident behaviour of some reagents, NO_2^- , SCN^- and ambident bases, in liquid solutions can be accounted for, quantitatively, in terms of the intersecting-state model. For many reactions changes in reactivity are dominated by the reaction energy, ΔG^0 , and the transition state bond order, n^\ddagger . A gain in polarity of the reactive bonds during the course of reaction leads to more negative ΔG^0 and to a decrease in n^\ddagger . This reveals that for the reaction energy barrier, ΔG^0 and n^\ddagger can work in opposite directions as a function of the electronegativity of the reaction sites and be responsible for ambident behaviour in 'charge control' reactions (ΔG^0) and 'frontier-orbital control' reactions (n^\ddagger). These concepts are employed to interpret the role of reagent, solvent, cation, and reaction mechanism on ambident reactivity.

A number of reagents contain two centres susceptible to nucleophilic or electrophilic attack but only one centre takes part in each transition state. The question of the reaction site of these ambident reagents is important in understanding chemical reactivity since such reactions are becoming increasingly important in synthetic organic chemistry;¹ the prediction of reaction sites for ambident reagents is relevant for the study of reaction mechanism and catalysis. The current interpretation¹⁻³ as to why a given reagent attacks a particular position rests on the factors which control the net transfer of electrons in chemical reactions: frontier-orbital control and charge (or Coulombic) control.^{3,4} Some examples of ambident reactions are shown in equations (1) and (2).



The charge control term is large when there is a large energy gap between the orbitals of the donor and those of the acceptor. In contrast, the orbital control term is important when the energy of the frontier orbitals of donor and acceptor are very close. These factors are also involved in the qualitative explanation of the hard and soft concepts, which deal with the specific affinity of some atoms for other atoms.^{3,5,6}

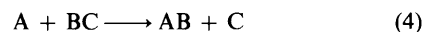
The greatest electron density in the HOMO of the thiocyanate ion is on the S atom, while the greatest total charge density is on the nitrogen.⁴ A frontier-orbital controlled reaction will involve bond formation at the sulphur atom, whereas the charge controlled process results in a new bond at the nitrogen atom. Two such divergent reactions are shown in equation (3).



A recently developed theoretical model of chemical reactivity, the intersecting-state model (ISM),⁷ which appears to have considerable generality, may provide a basis for the understanding of ambident behaviour. When the current interpretation of ambident reactions is compared with that which can be given by the ISM, charge control can be associated with the control of chemical reactivity by the reaction energy, ΔG^0 , and frontier-orbital control with the electronic factors of reactivity present within the ISM, *viz.*, the transition state bond order, n^\ddagger . In the present paper we consider whether this proposed hypothesis can provide a better quantitative understanding of ambident reactions.

Theory

Many chemical reactions can be satisfactorily explained in terms of independent bond-breaking of reactants and bond-formation of products [equation (4)].



The barrier height to reaction, ΔG^\ddagger , can be found at the intersection of the potential energy curves representing the species AB, BC. For the reactant, approximated by a harmonic oscillator, it is shown in equation (5).

$$\Delta G^\ddagger = (1/2)f_i(l^\ddagger - l_r)^2 \quad (5)$$

If d is the distance between the minima of the two curves and the sum of the bond extensions of reactant and product at the transition state, it can be shown that,⁷

$$(1/2)f_i(l^\ddagger - l_r)^2 = (1/2)f_p[d - (l^\ddagger - l_r)]^2 + \Delta G^0 \quad (6)$$

where l_r and l^\ddagger are the bond lengths of the reactant and the transition state respectively, f_i are the stretching force constants, and ΔG^0 is the reaction energy.

We have shown⁷ that d is proportional to the sum of the equilibrium bond lengths of reactant and product [equation (7)]

$$d = [(a' \ln 2/n^\ddagger + (a'/2)(\Delta G^0/\lambda)^2](l_r + l_p) \quad (7)$$

The term, n^\ddagger , is the transition state bond order, λ is a parameter

Table 1. Nucleophile transition state bond order contributions, C_{n^\ddagger} , for methyl transfer reactions in solution.^a

X^-/Y^-	F^{-b}	Cl^{-b}	Br^{-b}	I^{-b}	H_2O^b	NO_3^{-b}	C_{n^\ddagger}		
							Water	Methanol	Acetone
F^-	—	0.27	0.28	0.25	0.29	—	$F^- = 0.27$		
Cl^-	0.30	0.30	0.30	0.30	0.31	0.29	$Cl^- = 0.30$	0.29	0.33
Br^-	0.33	0.32	—	0.30	0.32	0.29	$Br^- = 0.32$	0.33	0.38
I^-	0.33	—	0.35	0.35	0.34	—	$I^- = 0.35$	0.36	0.41
H_2O	0.25	0.24	0.23	0.22	—	0.24	$H_2O = 0.23$		
NO_3^-	—	0.28	0.29	0.28	0.30	—	$NO_3^- = 0.29$		

^a Calculated from the n^\ddagger values, ref. 8. ^b Reactions in water.

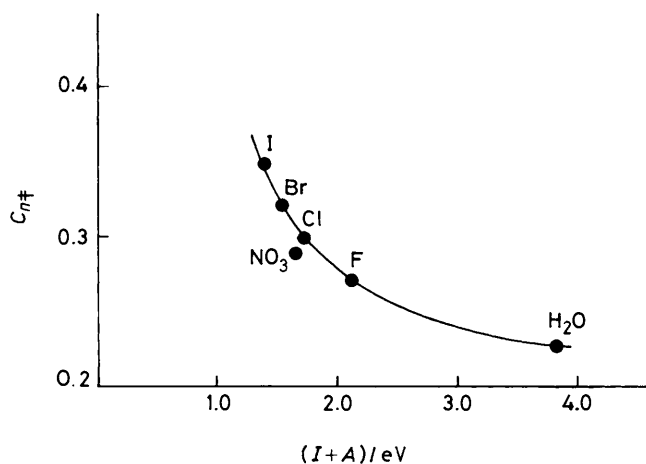


Figure 1. Correlation of the transition state bond order contributions, C_{n^\ddagger} , of different nucleophiles for the reactions $X^- + CH_3Y \rightarrow XCH_3 + Y^-$ (n^\ddagger data from ref. 8) with the sum of the ionization, I , and electron affinity, A , energies of the nucleophiles. I and A data from ref. 3 and 'Chemical Reactivity and Reaction Paths,' ed. G. Klopman, Wiley, New York, 1974, chap. 4; data for NO_3 , $I \approx 10.8$ e (solid state) M. Considine, J. A. Connor, and I. H. Hillier, *Inorg. Chem.*, 1977, **16**, 1392; $A = 4.0$ eV, R. G. Pearson, *J. Am. Chem. Soc.*, 1986, **108**, 6109.

with the dimensions of an energy which is associated with the concept of mixing entropy and a' is a constant ($a' = 0.156$).

The term bond order has a specific technical meaning. Here the bond order, n , is estimated simply by counting the number of electrons (in the bond forming process). For single bonds, $n = 1$, and the conservation of the total bond order along the reaction co-ordinates, $n_r + n_p = 1$, leads to $n^\ddagger = 1/2$ (the transition state bond order) for the thermoneutral situation. However, for electron rich molecular species the total bond order may not be conserved at the transition state and for several chemical reactions $n^\ddagger > 1/2$.⁷ For example, when a non-bonding pair of a reactant is converted into a bonding pair at the transition state then $n^\ddagger = 1$.

Nucleophilic substitutions on methyl [equation (8)]



where X and Y are halogen atoms, have $n^\ddagger = 1$ in the vapour phase,⁸ almost independently of the nature of X and Y , due to the conversion of a non-bonding pair of electrons from the reactants to a pair with bonding character at the transition state. However, in liquid solutions, $n^\ddagger < 1$, approaching the limit of $n^\ddagger = 0.5$ when $X = Y = F$ (in water); in this limit the total bond order is conserved along the reaction co-ordinate, and the non-bonding pair of electrons is no longer free to increase n^\ddagger because of strong interactions with the water molecules. Nevertheless, this variation in transition state bond

order depends on the nature of the solvent; n^\ddagger is higher ($\rightarrow < 1$) with poor acceptor solvents (e.g. acetone, dimethylformamide) and lower ($\leftarrow < 1$) with good acceptor solvents such as water and methanol.

The transition state bond order is also dependent on the nature of the substituents. The value of n^\ddagger decreases with increasing electronegativity as measured by the sum, $E_i + E_{ea}$ (E_i ionization and E_{ea} electron affinity energies). For a symmetrical reaction one can divide the overall n^\ddagger value into equal contributions of the nucleophiles X . From that data and the values of n^\ddagger of the asymmetrical reactions the Y contributions for the transition state bond order are calculated. The constancy of the values found (horizontal lines in Table 1) shows that n^\ddagger can be viewed as the sum of the contributions, C_{n^\ddagger} , of the nucleophiles X and Y .

$$n^\ddagger = C_{n^\ddagger}(X) + C_{n^\ddagger}(Y) \quad (9)$$

As Figure 1 shows, the C_{n^\ddagger} values correlate well with $E_i + E_{ea}$. Correlations with other parameters such as $E_i - E_{ea}$ and the Klopman indices³ were poor.

Since n^\ddagger is solvent dependent, the same is valid for C_{n^\ddagger} . For comparative purposes Table 1 also includes some C_{n^\ddagger} values in methanol and acetone.

In liquid solutions, reactivity may also depend on the nature of the counter-ion. For example, the order of reactivity of the halides towards butyl brosylate in acetone is $Cl^- > Br^- > I^-$ when $(C_4H_9)_4N^+$ is the counter-cation, but is $I^- > Br^- > Cl^-$ when Li^+ is the counter-ion. A hard cation such as Li^+ interacts more strongly with hard anions in ion-pairs and can make variation of n^\ddagger the dominant factor for the overall reactivity.⁸

At the transition state, the reaction energy ΔG^0 has to be accommodated internally. If the activated complexes have few ways (internal degrees of freedom) and, consequently, a small capacity (λ energy capacity) to store ΔG^0 ($\lambda \ll |\Delta G^0|$), this energy has to be stored in the reactive bonds, through further bond extensions, i.e. d increases with an increase in $|\Delta G^0|$. However, if the activated complexes have many accessible rovibrational states and, consequently, a large capacity to store the reaction energy ($\lambda \gg |\Delta G^0|$), then virtually no reaction energy will be stored in the reactive bonds and d is independent of $|\Delta G^0|$. For chemical reactions λ ranges typically between 100 and 300 kJ mol^{-1} .⁷⁻⁹

Control of Kinetic Reactivity by n^\ddagger and ΔG^0 .—ISM is a semi-empirical model of chemical reactivity which uses equilibrium data and transition state concepts to replace the missing potential energy surface information, and to relate similar systems. Semiempirical theories involve transition state concepts and, therefore, suffer from some of the limitations of the current transition state theory (TST), as discussed in detail elsewhere,¹⁰ but strictly speaking they are not TST. As Kreevoy and Truhlar have pointed out,¹⁰ one should also be aware that the concept of free energy of activation and other quasi-

Table 2. Effect of the transition state bond order, n^\ddagger , and the reaction energy, ΔG^0 , on the reaction energy barrier, ΔG^\ddagger .^a

Effect	f_r/f_p	$\Delta G^0/\text{kJ mol}^{-1}$	n^\ddagger	$\delta\Delta G^\ddagger/\delta n^\ddagger$	$\delta\Delta G^\ddagger/\delta\Delta G^0$
ΔG^0	1	0	0.75	155	0.5
	1	+40	0.75	151	0.585
	1	-40	0.75	151	0.414
n^\ddagger		-80	0.75	138	0.328
	1	0	0.5	523	0.5
f	1	0	1.0	65.5	0.5
	4	0	0.75	277	0.67
	2	0	0.75	213	0.59
	0.4	0	0.75	93	0.39
	0.2	0	0.75	60	0.31

^a Calculations with $f_p = 2.5 \times 10^3 \text{ kJ mol}^{-1} \text{ \AA}^{-2}$, $l_r + l_p = 3 \text{ \AA}$ and $\lambda \gg |\Delta G^0|$; equations (1)–(3).

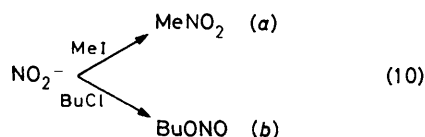
thermodynamic activation parameters are merely conventions established by analogy to the relations between changes in real thermodynamic variables and real equilibrium constants. Nevertheless, semiempirical models are important to characterize TS structures, to establish structure–reactivity relations, namely linear free-energy relations (LFER), and predict novel features of chemical reactivity. ISM is not just a reparametrization of LFER.¹¹ This is particularly notorious for reactions where $\Delta G^0 = 0$, such as electron exchange reactions.¹²

Within the ISM, chemical reactivity can be controlled by several molecular factors, namely n^\ddagger , ΔG^0 , f , l and λ . Some of these parameters, ΔG^0 , f , and l , can be obtained from fields outside chemical kinetics, namely from thermodynamic and spectroscopic data. The parameter λ is an empirical kinetic-parameter, significant only for reactions where $|\Delta G^0|$ is not very low. The parameter n^\ddagger , for reactions in the vapour phase and for reactions in solution where electronic interactions with the solvent molecules can be neglected, can be estimated by simple molecular orbital theory arguments;^{7,8,11} otherwise n^\ddagger is also an empirical kinetic parameter.

The parameter n^\ddagger is the electronic parameter of reactivity, and the one which can be associated normally with the orbital control of ambident reactions. In principle all the other parameters could be associated with the charge control contribution. However, a longer chemical bond usually has a lower force constant than a shorter bond. This factor introduces a compensating effect of f and l in the barrier height, when $|\Delta G^0|$ is not very large.¹¹ Consequently, we will neglect such a contribution in ambident behaviour and will only consider the effect of the remaining molecular parameters, ΔG^0 and λ .

Table 2 presents calculations of $\delta\Delta G^\ddagger/\delta n^\ddagger$ and $\delta\Delta G^\ddagger/\delta\Delta G^0$ as a function of several molecular parameters. The coefficient $\delta\Delta G^\ddagger/\delta n^\ddagger$ is very sensitive to values of n^\ddagger and is quite insensitive to ΔG^0 . In contrast $\delta\Delta G^\ddagger/\delta\Delta G^0$ is quite sensitive to ΔG^0 , but is independent of n^\ddagger . Both coefficients depend on the asymmetry of the potential energy curves, f_r/f_p . These calculations suggest that typical variations of n^\ddagger and ΔG^0 can have opposite effects on the energy barriers for the chemical reactions and can explain ambident reactivity.

Applications.—Nitrite ion. The following sections discuss some concrete examples of ambident reactivity within the ISM frame-

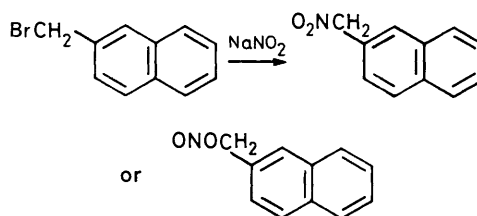


work. The first reaction is the nucleophilic reaction of nitrite ion [equation (10)]. For the calculations of ΔG^\ddagger , the following transition state bond order contributions, typical of nucleophilic substitutions in poor acceptor solvents, were employed: $C_n(\text{I}) = 0.4$, $C_n(\text{Cl}) = C_n(\text{N}) = 0.35$ and $C_n(\text{O}) = 0.3$ (Table 1). The relevant force constant (f_r, f_p) and bond length (l_r, l_p) data were taken from reference 13 which lists sets of stretching force constants and lengths for bonds typical of organic compounds. Reaction energies were approximated by ΔH^0 , and were obtained from typical bond dissociation energies.¹⁴

Since some reactions are very exothermic, it is not possible to assume $\lambda \gg |\Delta G^0|$. In this treatment, $\lambda = 300 \text{ kJ mol}^{-1}$, corresponding to the weakest dependence of d on $(\Delta G^0)^2$ for chemical reactions. In the present case, the effect of the mixing entropy (λ) diminishes the effect of ΔG^0 and, consequently, enhances the dominance of n^\ddagger . The calculations are presented in Table 3 and the correct ambident behaviour of NO_2^- is quantitatively confirmed, because CH_3NO_2 is calculated to be formed at a rate some thirty times faster than that of its isomer, CH_3ONO , in the reaction between NO_2^- and CH_3I , but the isonitrite, BuONO , is formed almost two orders of magnitude faster than BuNO_2 in the reaction of NO_2^- with BuCl .

Solvents can alter n^\ddagger and ΔG^0 and consequently can affect ambident reactivity. For example, a good acceptor solvent such as water decreases ΔG^0 with respect to acetone by about 20 kJ mol^{-1} and decreases n^\ddagger by 0.06 (Table 1). Using these modified terms, and assuming f , l , and λ to be constant, the ambident reactivity of BuCl towards NO_2^- decreases drastically with the rate of reaction at oxygen becoming only 3.5 times the rate of reaction at nitrogen in water as solvent; conversely, for methyl iodide the discrimination between the two possible reaction sites is enhanced, with $k_{(\text{N})}/k_{(\text{O})} = 580$.

The calculations described above suggest that solvents can affect the reactive site of an ambident reagent. An interesting example lies in the reaction of bromomethylnaphthalene with the ambident anion NO_2^- which is catalysed by a macrocyclic



azacyclophane.¹⁵ The most remarkable feature of this reaction is the increase in the product ratio of RNO_2/RONO (ca. 4–5 times), which corresponds exactly to the overall rate constant increase as a function of the catalyst:substrate concentration ratio.

The encapsulation of the reagents in the less polar environment existing within the cyclophane allows n^\ddagger to increase and therefore increases the n^\ddagger -controlled product, RNO_2 as calculated in Table 3. In contrast, the opposite effect is observed upon addition of open-chain alkylammonium salts.¹⁵ The interaction of the lone-pairs of NO_2^- with the added cation in a polar medium decreases n^\ddagger and ΔG^0 , and enhances the ΔG^0 -controlled product, RONO .

Sulphocyanate ion. Similar calculations have been performed for SCN^- . From the value of $E_i + E_{\text{ea}}$ sulphur, $C_n(\text{S}) = 0.55$ can be estimated (Figure 1). With this value and the other relevant molecular data⁸ presented in Table 4, the intersecting-state model produces results in agreement with the experimental ambident behaviour *viz.* bond order control is important in the reaction with methyl iodide (leading to attack at S) and orbital energy control becomes important in reaction with acetyl chloride (leading to attack at N).

Table 3. Calculations for the ambident reactivity of NO_2^- .

Reaction	$f/10^3 \text{ kJ mol}^{-1} \text{ \AA}^{-2}$		$l/\text{\AA}$	$\Delta G^0/\text{kJ mol}^{-1}$	n^\ddagger	$\Delta G^\ddagger/\text{kJ mol}^{-1}$	
	reactant	product					
$\text{CH}_3\text{I} + \text{NO}_2^- \longrightarrow \text{CH}_3\text{NO}_2 + \text{I}^-$	1.6 (C-I)	2.8 (C-N)	3.679	-96	0.75	46.2	$\frac{k(\text{N})}{k(\text{O})} \approx 32$
$\longrightarrow \text{CH}_3\text{ONO} + \text{I}^-$	1.6 (C-I)	3.0 (C-O)	3.633	-148.5	0.70	54.8	(n^\ddagger control)
$\text{BuCl} + \text{NO}_2^- \longrightarrow \text{BuNO}_2 + \text{Cl}^-$	2.2 (C-Cl)	2.8 (C-N)	3.239	19	0.70	86.7	$\frac{k(\text{O})}{k(\text{N})} \approx 77$
$\longrightarrow \text{BuONO} + \text{Cl}^-$	2.2 (C-Cl)	3.0 (C-O)	3.193	-34	0.65	76.0	(ΔG^0 control)

^a $C_{n^\ddagger}(\text{I}) = 0.40$, $C_{n^\ddagger}(\text{N}) = C_{n^\ddagger}(\text{Cl}) = 0.35$, $C_{n^\ddagger}(\text{O}) = 0.3$; $\lambda = 300 \text{ kJ mol}^{-1}$

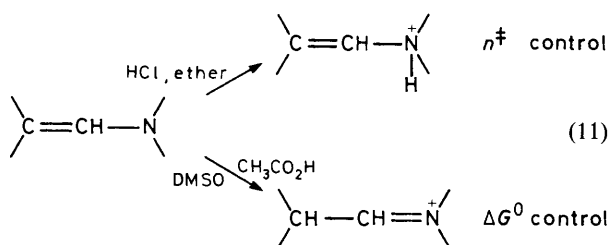
Table 4. Calculations for the ambident reactivity of SCN^- .

Reaction	$f/10^3 \text{ kJ mol}^{-1} \text{ \AA}^{-2}$		$l/\text{\AA}$	$\Delta G^0/\text{kJ mol}^{-1}$	n^\ddagger	$\Delta G^\ddagger/\text{kJ mol}^{-1}$	
	reactant	product					
$\text{CH}_3\text{I} + \text{SCN}^- \longrightarrow \text{CH}_3\text{SCN} + \text{I}^-$	1.6 (C-I)	2.2 (C-S)	4.024	-17	0.95	41.3	$\frac{k(\text{S})}{k(\text{N})} \approx 7$
$\longrightarrow \text{CH}_3\text{NCS} + \text{I}^-$	1.6 (C-I)	2.8 (C-N)	3.679	-96	0.75	46.2	(n^\ddagger control)
$\text{SCN}^- + \text{CH}_3\text{COCl} \longrightarrow \text{CH}_3\text{C(=O)SCN} + \text{Cl}^-$	2.2 (C-Cl)	2.2 (C-S)	3.584	98	0.90	121	$\frac{k(\text{N})}{k(\text{S})} = 10^6$
$\longrightarrow \text{CH}_3\text{C(=O)NCS} + \text{Cl}^-$	2.2 (C-Cl)	2.8 (C-N)	3.239	19	0.70	86.4	(ΔG^0 control)

^a $C_{n^\ddagger}(\text{S}) = 0.55$ and the other values as in Table 3.

The first conclusion that can be made from these calculations is that the IS model is able to account quantitatively for ambident behaviour in kinetic terms.

Proton transfers. The alternative proton sites in proton transfer reactions are also examples of ambident behaviour.¹⁶ An interesting reaction reported by Alais *et al.*¹⁷ refers to the protonation of *N,N*-dimethyl-2-methylprop-1-enylamine

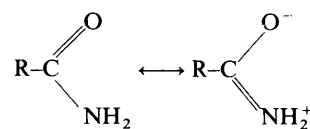


[equation (11)]. In all solvents the C-protonated immonium ion is the more stable ion. This ion is formed directly with carboxylic acids (acetic, trifluoroacetic) in DMSO and CDCl_3 ; these proton transfers are reaction-energy controlled. However, when HCl in ether is employed, the N-protonated enammonium ion is formed, reverting subsequently to the protonated carbon form. We have found that n^\ddagger of amines in water is higher than that of carbon acids.⁹ Such a difference, enhanced by less polar media and associated with the lone-pair contribution of the chlorine atom of HCl, can make the reaction n^\ddagger -controlled.

Amides provide another interesting case of ambident behaviour in the field of proton transfer, but some of the reactions require a quantitative study within the ISM frame-

work, because they are not easily interpretable in frontier-orbital terms.

The site of protonation of primary amides has been the subject of a prolonged controversy.^{16,17} It is now recognized that both N- and O-protonation may occur depending on experimental conditions, but the acidities of these sites remain controversial. The resonance interaction



decreases the basicity of nitrogen and enhances the basicity of oxygen. Although it has been stated that the most basic site of an amide is the oxygen atom¹⁸ and the $\text{p}K_a$ values of protonated amides have long been correlated with the $\text{p}K_a$ of the corresponding carboxylic acids,¹⁹ recent evidence based on a common correlation between ΔG^0 and ΔH^0 for primary ammonium ions and amide cations²⁰ led to the proposal of N-protonated as the dominant form of amide cations in aqueous acids.

Further studies carried out for methacrylamide were claimed to support the tautomeric change from the dominant N-protonated amide at low acid concentration, to the O-protonated amide at high acid concentration.²¹ The N-protonated amide $\text{p}K^N$ was proposed to be -1.8. Kinetic studies of proton transfers involving acrylamide, seriously questioned this $\text{p}K^N$ value and indicate that it should be close to -7.0,²² supporting earlier estimates.²³

According to the frontier-orbital approach, protonation of amides on oxygen or nitrogen may be explained in terms of charge or orbital control of the reactions; under charge control

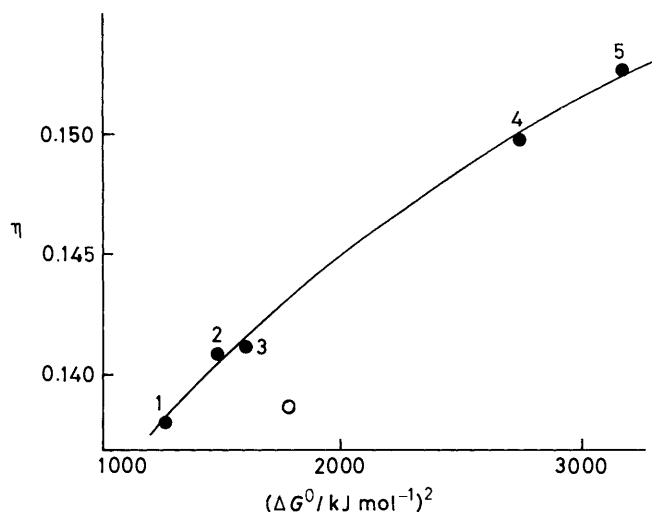
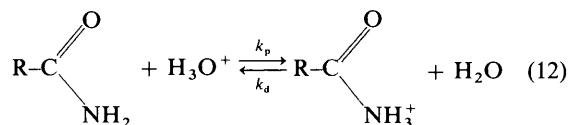


Figure 2. Calculated reduced bond extensions, η , as function of $(\Delta G^0)^2$ for proton exchanges of amides in water for mechanism (a); for benzamide (○) the solvent is 60% aqueous methanol. Amides: 1, methacrylamide; 2, acetamide; 3, acrylamide; 4, cyanoacetamide; 5, trifluoroacetamide.

the most negatively charged atom is the most reactive site, and under orbital control the atom with the highest coefficient of electron density in the HOMO ought to be the most reactive.²⁴ Calculations show that, contrary to expectation, the N atom bears the greater atomic charge and should be more reactive, under charge control; alternatively, the highest occupied amide π -orbital lies very close in energy to the n_o orbital which corresponds to an oxygen lone-pair.²⁴ Consequently, frontier orbital theory cannot easily explain the site of protonation of amides.

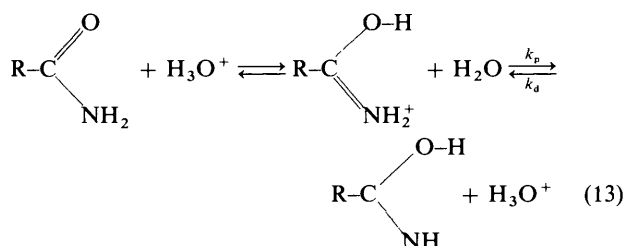
In the application of ISM to the protonation of amides, we attempt to address the following questions: which are the most reasonable pK_a^N and pK_a^O values for amides, and the influence of the medium and substituents on the rates and proton exchanges between *N*- and *O*-protonated amides? In order to solve these problems we have tested the three most likely mechanisms of amide protonation.

(a) The protonation and proton exchange with the solvent occurs at the N-atom,

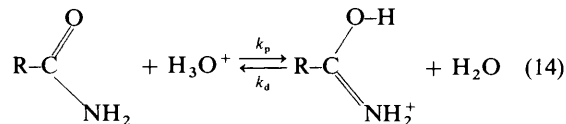


with either a pK_a close to -7 or -1 [equation (12)].

(b) The protonation occurs at the O-atom, but it is the N-atom which exchanges protons with the solvent *via* the imidic acid; the first equilibrium involves two slow and almost isoenergetic reactions [equation (13)].



(c) The protonation and proton exchange with the solvent occurs at the O-atom with a pK_a^o ca. -1 (or -5.8 for benzamide¹⁶) [equation (14)].



The results of our calculations are shown in Table 5. If we set the deprotonation rate constant, k_d for mechanism (a) to $6 \times 10^{10} \text{ s}^{-2}$, based on the data for acrylamide,²² and use this value together with the protonation rate constant, k_p , to calculate the pK_a^N values for acetamide, acrylamide, and methacrylamide, the application of the ISM formalism to this bond-breaking-bond-forming process involving only the O-H bond in the reactants and a N-H bond in the products, leads to $n^\ddagger = 0.86$; this value coincides with the value previously reported for nitrogen acids.⁹ Similar calculations for benzamide, cyanoacetamide and trifluoroacetamide lead to higher n^\ddagger values. The deviation of benzamide from the correlation in Figure 2 may be assigned to the solvent used (60% aqueous methanol); we have shown that the decrease of water content in solvent mixtures leads to an increase in n^\ddagger .²⁵ Furthermore, electron-rich substituents can increase n^\ddagger , so it is tempting to assign the increase observed for cyanoacetamide and trifluoroacetamide to such effects. However, the slight curvature of η [$\eta = d/(l_r + l_p)$] versus $(\Delta G^0)^2$ plot advises the testing of other hypotheses before a conclusion is reached, namely a possible change in reaction site.

The assignment of a higher basicity to the N-atom (ca. -2 in pK) for methacrylamide and benzamide, leads to a lower n^\ddagger ($n^\ddagger = 0.65$). This value is more characteristic of a carbon acid than a nitrogen acid. Although the amine electron pair is fairly extensively delocalized in the molecule, probably this factor alone cannot overcome the differences between nitrogen and carbon acids.²⁶

In order to study the imidic acid mechanism, we take imidates as models for the imidic acid behaviour. Their pK_a^1 range from 7.6 for ethylacetimidate to 0.1 for trichloroacetimidate.²⁷ With these pK values, ISM leads to n^\ddagger values between 1.1 and 0.58. Although these extreme values may be unreasonable, amides with substituents having lone pairs of electrons are in the n^\ddagger range where one expects to find nitrogen acids. Consequently, for these amides proton exchange *via* the imidic acid may compete with direct proton exchanges with the solvent, in agreement with the conclusions of Perrin.¹⁸

Finally, the application of ISM to the *O*-protonation and *O*-proton exchange mechanisms shows that this is not a reasonable mechanism. *O*-Protonation involves significant changes in three bonds. The effective force constant may be calculated as $f_{\text{eff}} = [\sum f_i^2]^{1/2}$, where f_i is the force constant of each bond involved in the reaction co-ordinate and the effective bond length is the arithmetic average of the corresponding bond lengths. This leads to very high force constants for reactants and products, which require small d values to reproduce the observed proton exchange rate constants. Although energetically more favourable, these reactions imply n^\ddagger higher than 1, which is not reasonable for these systems.

Our model has shown that proton exchange with the solvent occurs *via* the N-atom, which has pK_a ca. -7 , but electron-rich substituents may trigger alternative mechanisms involving an imidic acid as intermediate. The thermodynamically more favoured *O*-protonation does not seem to compete with the N-atom proton exchange in aqueous solutions, due to a high effective force constant along the reaction co-ordinate.

Table 5. Proton-exchange of amides in aqueous solutions.^a

	$k_p^b/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	Mechanism	pK_a	$\Delta G^0/\text{kJ mol}^{-1}$	$d/\text{\AA}$	η	n^\ddagger
Acetamide	9.2×10^3	(a)	-6.8 ^c	38.5	0.274	0.141	
		(b)	7.6 ^d	43.1	0.220	0.113	~1.1 ^e
		(c)	-0.9 ^f	5.1	0.232	0.096	>1.1
Acrylamide	6.5×10^3	(a)	-7.0 ^c	39.7	0.275	0.141	
		(c)	-0.3 ^f	1.7	0.237	0.098	>1.1
Methacrylamide	3.3×10^4	(a)	-6.26 ^c	35.4	0.269	0.138	
		(a)	-1.8 ^g	10.2	0.320	0.164	<0.66
Benzamide	2.4×10^3	(a)	-7.4 ^c	41.9	0.270	0.139	
		(a)	-2.0 ^h	11.3	0.332	0.170	<0.64
		(b)	6.2 ^d	35.1	0.261	0.134	~0.75 ^e
Cyanoacetamide	3.9×10^1	(a)	-9.2 ^c	52.1	0.292	0.150	
		(c)	-3.7 ^f	21.0	0.242	0.100	>1.1
Trichloroacetamide	1.7×10^{1i}	(b)	0.1 ^d	0.6	0.355	0.186	~0.58
Trifluoroacetamide	8.3	(a)	-9.9 ^c	56.1	0.297	0.152	

^a $f_r = 4.2 \times 10^3$ and $f_p = 3.8 \times 10^3 \text{ kJ mol}^{-1} \text{ \AA}^{-2}$ for mechanism (a), $f_r = 3.8 \times 10^3$ and $f_p = 4.2 \times 10^3 \text{ kJ mol}^{-1} \text{ \AA}^{-2}$ for mechanism (b), $l = 1.95 \text{ \AA}$ for mechanisms (a) and (b), $f_r = 8.9 \times 10^3$, $f_p = 8.2 \times 10^3 \text{ kJ mol}^{-1} \text{ \AA}^{-2}$ and $l = 2.42 \text{ \AA}$ for mechanism (c). $T = 296 \text{ K}$ for all cases, but the frequency factor of the reactions with H_3O^+ in water was multiplied by 55M, to account for the Grothuss mechanism.⁹ ^b Reference 18. ^c From kinetic data, assuming $k_d = 6 \times 10^{10} \text{ s}^{-1}$ for all *N*-protonated amide cations (ref. 22). ^d Taking imidates as analogues of the corresponding imidic acids [C. A. Strenli, *Anal. Chem.*, 1959, **31**, 1652]. ^e Assuming $\lambda = 100 \text{ kJ mol}^{-1}$. ^f Reference 19. ^g Reference 20. ^h Reference 16. ⁱ In ethylene glycol.

Conclusions

We have illustrated that the ambident behaviour of some reagents can be quantitatively interpreted in kinetic terms within the intersecting-state model. The classification of reactions in terms of n^\ddagger - and ΔG^0 -control is a simplistic view, because it has been shown that other factors, such as λ , f , and l , can affect chemical reactivity. Nevertheless the classification into n^\ddagger and ΔG^0 control has useful qualitative insights. When one views a chemical reaction in the absence of solvent two important qualitative features emerge:²⁸

(i) a gain in polarity of the reactive bonds, during the course of the reaction, leads to more negative ΔG^0 ;

(ii) a gain in polarity of the reactive bonds leads to a decrease in n^\ddagger .

Therefore when one compares two reactions where the bonds broken are the same and the bonds formed are, for example, C-N and C-O, it may be concluded that the reaction involving bond formation with the less electronegative atom (nitrogen) is more n^\ddagger -controlled than the one with the more electronegative atom (O), which is more ΔG^0 -controlled. Such rules can be useful sometimes for qualitative interpretations of ambident reactivity.

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