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REVIEW COMMENTARY

QUANTITIVE APPROACHES TO REACTION MECHANISMS AND CATALYSIS. SUBSTITUTION AT CARBON*

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I have been interested for a long time in reaction mechanisms and, particularly, in the extent to which these mechanisms can be diagnosed and predicted. I was trained as a physician, but later became interested in biochemistry, and then chemistry. Although medicine may not seem close to chemistry, my training in medicine has frequently been useful in dealing with problems of biochemistry, and even chemistry. I want to describe here something of what I and my co-workers have learned about the chemical reaction of substitution at carbon. This would seem to be one of the simplest reactions in chemistry. It is certainly one of the most studied reactions. In fact, it has turned out to be one of the most complex reactions in chemistry, perhaps because it has been studied so thoroughly by so many different investigators.

How is a medical background useful in chemistry? If one studies reaction mechanisms, one must first make a *diagnosis* of the various reaction mechanisms that have been proposed for a reaction. Next, we would like to know the *etiology* of the mechanism—why does a reaction follow one mechanism rather than another? Then we would like to be able to *predict* what mechanism will be followed when the structure of the reactants or the reaction conditions are changed. This corresponds to issues of public health. Finally, we have triage—one has to identify and define reaction mechanisms that make good sense and characterize the reaction effectively, and discard those that are not clearly defined. In fact, a certain number of the mechanisms that have been proposed should be treated by euthanasia.

Korzybski wrote an extraordinary book, *Science and Sanity*, in 1958 that had a wide influence.[1] Korzybski was a semanticist. The theme put forth in his book basically says that all of the problems of this world arise through semantics—one group of people does not understand what another group is talking about and proceeds to go to war over the issue. This may lead to disastrous consequences. Korzybski emphasized that it is essential to have a clear-cut, unambiguous description of what one is talking about in order to do good *science* and retain *sanity*. Some of the terms that have been used to characterize reaction mechanisms do not follow this criterion. In addition, it is often very difficult to distinguish some of these proposed mechanisms from each other.

The problem is particularly difficult for solvolysis reactions because it is often difficult to distinguish between first- and second-order reactions with the solvent. The concentration of solvent cannot be varied without changing the reaction conditions.

Perhaps the most important distinction is to draw a sharp line between *appearance* and *reality*. Structure–reactivity correlations, solvent effects and other techniques can characterize the nature of the rate-limiting transition state, but they frequently do not give a clear diagnosis of the *mechanism* of the reaction. The semantic problem comes up in the use of terms such as a 'spectrum' of mechanisms, 'merging' mechanisms, 'borderline' mechanisms and 'ion sandwiches.' Terms of this kind do not provide a useful description of reaction mechanisms. A mechanism can have one step or two steps, but it cannot have 1·5 steps.

Some of these terms would be meaningful if 'transition-state structure' were substituted for the word 'mechanism.' Quantitative structure–reactivity correlations and solvent effects provide information about the structure of the rate-determining transition state of a reaction. These include structure–reactivity correlations such as $\sigma\rho$, Brønsted coefficients for general acid and base catalysis and isotope effects on the reaction rate. These parameters can give hints as to the reaction mechanism, but in general they only describe the appearance of the rate-limiting transition state, not the number, nature and sequence of the individual steps that define the mechanism of the reaction.

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The Ingold nomenclature for *reactions* has been extremely useful and is widely utilized.[2] However, it is not always recognized that naming a reaction is not the same as describing the *mechanism* of a reaction. Furthermore, additional terms are sometimes added to the Ingold nomenclature that are hard to interpret. For example, an 'S_N2 intermediate' mechanism has been proposed. It is not clear whether this means that there is an intermediate species formed in the reaction, or whether the structure of the transition state is intermediate between that expected for a monomolecular and a bimolecular reaction. Ingold described the S_N2 reaction very clearly as a reaction that 'contains only one stage, in which two molecules simultaneously undergo covalency change.' Then we have a large collection of elimination reactions: E_1, E_2, $E1cB$, $E1cB_{ip}$ and $E1cB_{ssip}$.

However, this nomenclature can lead to confusion in some cases. It is clear that S_N2 is a second-order nucleophilic substitution and is concerted, whereas S_N1 is a monomolecular nucleophilic substitution. Unfortunately, additional terms have been added to this nomenclature, such as 'S_N2_{ip} (ion pair),' and 'S_N2 intermediate.' The meaning of these terms is not clear. If the substitution proceeds through an ion pair or some other intermediate, it is not concerted.

Several years ago, IUPAC proposed a nomenclature that was designed specifically to describe *reaction mechanisms*. The system describes the mechanism by the number and sequence of steps in the reaction and provides a simple way of identifying the number of individual species along the reaction path.[3] I will not describe the complete system here, but will give a few examples:

A_N is an association reaction in which the primary reactant is a nucleophilic reagent.

D_N is a dissociation in which the leaving group departs with its electron pair.

A_E is an association reaction that is electrophilic.

Thus, A_ND_N is a concerted, one-step reaction with no intermediate.

$D_N + A_N$ has two distinct steps. It involves dissociation of the leaving group with its electron pair followed by association with a nucleophilic reagent, which may be the solvent with its electron pair.

$D_N{}^*A_N$ is a two-step reaction that does not have a 'free' intermediate. This usually represents an ion pair and can be amplified to describe $D_N{}^*A_{Nip}$, and $D_N{}^*A_{Nssip}$ for a solvent-separated ion pair.

General usage of this IUPAC nomenclature would simplify and clarify the description of reaction mechanisms, and might well prevent some of the confusion and controversies that have come about in attempts to characterize these reactions.

HOW DOES A MECHANISM CHANGE?

The mechanism of a reaction obviously depends upon the structure and properties of the reactants, in addition to the reaction conditions. When the structure or reaction conditions are changed, there may well be a change in the mechanism. This could come about because there are two co-existing mechanisms and one is faster than the other under a particular set of conditions. However, many changes in mechanism are 'enforced' because of changes in the reaction conditions or the structure of the reacting molecules.

Some reaction mechanisms can be characterized quantitatively by measuring the lifetimes of intermediate species. For example, the lifetimes of carbocations can be determined by the 'azide clock',[4-6] as shown in equation (1). We had developed a similar procedure previously, with sulfite instead of azide ion as the nucleophilic reagent.[7]

$$\mathrm{R{-}N_3} \underset{k_a}{\overset{k_d}{\rightleftharpoons}} \mathrm{R^+ + N_3^-} \qquad \mathrm{R^+} \xrightarrow{k_{H_2O}} \mathrm{ROH + H^+} \tag{1}$$

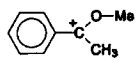
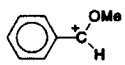
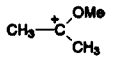
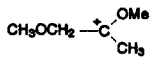
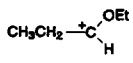
If a carbocation, R^+, is generated from its azide derivative, RN_3, it will be formed with a certain rate constant, k_d, when the azide anion departs to generate the carbocation; an oxocarbenium ion. The carbocation will then react rapidly with water. However, if the reaction is carried out in the presence of added azide, the azide ion will compete with the water and react with the carbocation to regenerate the starting material. When the azide concentration is sufficient to decrease the solvolysis rate by 50%, half of the carbocations are reacting with water and half with azide. Under these conditions, the first-order constant for reaction with water is equal to the pseudo-first-order rate constant for reaction with a particular concentration of azide that gives 50% inhibition. The reaction with azide is diffusion-controlled, with a rate constant close to 5×10^9 l mol^{-1} s^{-1}.[8] When there is 50% inhibition, $k_{HOH} = k_1[N_3^-]$. Thus, if 0·4 M azide gives 50% inhibition, the rate constant for hydration of the carbocation is $k_{HOH} = 5 \times 10^9$ l mol^{-1} s^{-1} × 0·4M = 2×10^9 s^{-1}.

Some of these rate constants and lifetimes for a series of oxocarbenium ions are shown in Table 1. A plot of these rate constants against the equilibrium constants for formation of the carbocations has a slope of −0·4 and covers a range of rate constants up to *ca* 10^{10} s^{-1}.[9]

Extrapolating these rate constants, by allowing for the known effects of substituents on the lifetimes of oxocarbenium ions, gives rate constants in the range $4 \times 10^{11} - 1 \times 10^{12}$ s^{-1} for hydration of the oxocarbenium ion of a six-carbon sugar.[9] This is consistent with the known properties of such carbocations, which do not exist long enough to be trapped by azide ion or other nucleo-philic reagents in water, but react with alcohols in the solvent to give both retention and inversion of configuration.

If these carbocations have a very short lifetime in

Table 1. Lifetimes of some oxocarbenium ions in water at 25 °C

Compound	$k_{HOH}(s^{-1})$	Lifetime (s)
	5×10^{7}	$1{\cdot}4\times10^{-8}$
	2×10^{9}	$3{\cdot}5\times10^{-10}$
	1×10^{9}	$6{\cdot}9\times10^{-10}$
	4×10^{9}	$1{\cdot}7\times10^{-10}$
	2×10^{10}	$2{\cdot}9\times10^{-11}$

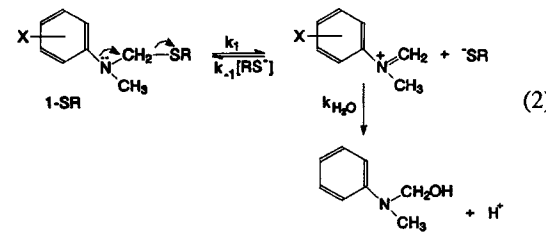
water, they will have no lifetime if they are in contact with a stronger nucleophilic reagent, so that it can be predicted that a concerted substitution reaction will occur. This is observed when electron-withdrawing substituents are added to compounds that generate carbocations with lifetimes of the order of 10^{-10} s or less.[9]

These considerations lead to a biphasic reactivity ratio for the reactions with water and other nucleophilic reagents of carbocations or carbocation-generating species when the structure of the reactants is changed. The lifetimes of the carbocations decrease rapidly when electron-withdrawing substituents are added, as measured by the azide trapping procedure. However, a point is eventually reached at which the mechanism changes, as electron-withdrawing substituents destabilize the carbocation. The reaction of the substrate with azide then proceeds through a concerted bimolecular mechanism because the azide–carbocation pair has no significant lifetime, and the azide/water reaction ratio increases with electron-withdrawing substituents on the substrate.

The conclusion—or notion—is that a reaction *will* be stepwise if it *can* be. However, if the carbocation has no lifetime when it is in contact with a nucleophile, the reaction *must* be concerted and will generally show assistance, i.e. it becomes a simple bimolecular nucleophilic displacement reaction, A_ND_N, in the IUPAC nomenclature.

IMINIUM IONS AND THYMIDYLATE SYNTHETASE

We were interested in the properties of iminium ions, which are intermediate species in the synthesis of thymidine. The biological reaction proceeds through an iminium ion derived from tetrahydrofolate. Eldin[10] examined the properties of iminium ions derived from a series of anilinothioethers. The iminium ion was derived from an *N*,*N*-dimethylaniline with a thiol on one of the methyl groups, 1-SR [equation (2)]



(2)

Eldin measured the rate constants for solvolysis of this compound. The solvolysis occurs by expulsion of the thiolate leaving group to form an iminium ion, which in turn reacts rapidly with water. However, if the reaction is carried out in the presence of added thiolate anion, the thiolate would be expected to react with the iminium ion and regenerate the starting material, which would inhibit the solvolysis [k_1, equation (2)].

This inhibition was observed experimentally. When the concentration of thiolate anion becomes large enough to produce 50% inhibition by regenerating the starting material, the (pseudo)-first-order rate constants for reaction of the iminium ion with water and with the inhibiting thiolate anion are equal. The solvolysis reaction has a very large dependence on the pK_a of the leaving group, with a value of $\beta_{lg} = 0{\cdot}93 \pm 0{\cdot}09$. This is consistent with complete breakage of the carbon–sulfur bond in the transition state, which corresponds to no formation of the carbon–sulfur bond in the transition state for reaction of the thiolate anion with the iminium ion in the reverse direction, as is expected for a diffusion-controlled reaction. Furthermore, the inhibition by thiolate ion decreases with increasing viscosity of the medium with a slope of $-1{\cdot}0 \pm 0{\cdot}1$ for $(k_{-1}/k_{solvent})/(k_{-1}/k_{solvent})_0$, which is consistent with a diffusion-controlled reaction for the recombination of thiolate anion with the iminium ion. Essentially the same slope was obtained with glycerol and with methanol as the viscogen. It is not widely realized that on a volume to volume basis methanol is almost as effective a viscogen as glycerol.[10]

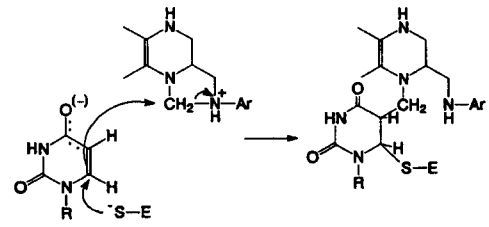
The rate constants for hydration of the iminium ions that are formed from these methylaniline derivatives range from 3×10^{6} to 1×10^{8} s^{-1} and increase with electron-withdrawing substituents on the benzene ring, with a Hammett slope of $\rho^{-} = 1{\cdot}5$. Hence these iminium ions have a high selectivity for their reaction with water, even though their rate constants for hydration are in the range 10^{6}–10^{8} s^{-1}. The dependence of the solvolysis rate on structure is approximately twice as large with a value of $\rho^{-} = 3{\cdot}3$, as might be expected for a transition

state in which bond breaking is essentially complete. The transition state involves diffusion-controlled separation of the ion pair, so that bond breaking is essentially complete in the transition state. There is also a large dependence of the solvolysis rate on the basicity of the aniline with a value of $\beta_{dg} = 0{\cdot}79$, as might be expected for a late transition state involving diffusion-controlled separation of the products. The transition state for hydration of the iminium ion shows a much smaller dependence on substrate structure with a value of $\beta = -0{\cdot}35$, as might be expected for such a reactive intermediate.[10]

If the iminium ion has such a short lifetime in water, it is likely to have an even shorter lifetime, or no lifetime, in the presence of a strong nucleophilic reagent. The rate constant for reaction with water is *ca* 10^8 s^{-1} and a thiolate anion is *ca* 10^8 more reactive than water. This would imply a rate constant of 10^{16} s^{-1} for the thiolate–iminium ion pair, which is much larger than a vibration frequency. Hence we can be certain that there is no chemical barrier for reaction of the iminium ion with the thiolate anion and that the trapping reaction is surely diffusion controlled.

If there is no chemical barrier for reaction of a nucleophile with the iminium ion intermediate, then one might expect that a concerted bimolecular substitution reaction will occur when a nucleophilic reagent is added to the substrate. This was observed. There is a large increase in the rate in the presence of low concentrations of added nucleophilic reagents. The rates increase in the order bromide, iodide, azide, hydrogensulfite, aliphatic thiolate and *p*-carboxybenzenethiolate.[11]

These results suggest that the biological reaction that is catalyzed by thymidylate synthase is likely to occur by an analogous mechanism in which thiolate addition to deoxyuridylate generates an enolate anion that displaces the aniline group in a concerted displacement, as illustrated in equation (3). Furthermore, the *n* values correlate with the rate constants for second-order reactions with a series of nucleophilic reagents with an *s* value of 0·4, indicating that there is a significant amount of bond formation in the rate-limiting transition state for bimolecular nucleophilic substitution.



(3)

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