PART 1

REACTIVE INTERMEDIATES
CHAPTER 1

Carbocations

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1. HISTORICAL PERSPECTIVE

1.1. Definitions

Carbocations are a class of reactive intermediates that have been studied for 100 years, since the colored solution formed when triphenylmethanol was dissolved in sulfuric acid was characterized as containing the triphenylmethyl cation.\(^1\) In the early literature, cations such as Ph\(_3\)C\(^+\) and the tert-butyl cation were referred to as carbonium ions. Following suggestions of Olah,\(^2\) such cations where the positive carbon has a coordination number of 3 are now termed carbenium ions with carbonium ions reserved for cases such as nonclassical ions where the coordination number is 5 or greater. Carbocation is the generic name for an ion with a positive charge on carbon.

1.2. Early Studies

Examples of highly stabilized carbocations as persistent ions in solution have been known for some time. Triarylmethyl halides readily ionize to triarylmethyl cations in weakly nucleophilic solvents such as sulfur dioxide.\(^3\) Tri- and diarylmethyl alcohols undergo equilibrium ionization to cations in aqueous solutions of sulfuric acid and other strong acids (Eq. 1). Equilibrium constants \(K_R\) for this pseudo-acid–base equilibrium (Eq. 2), were determined by acidity function techniques.\(^4\)\(^5\) Values of \(pK_R\) depend strongly on structure and substituents.\(^6\) The parent triphenylmethyl cation has a \(pK_R\) of \(-6.6\) and forms only in solutions with 50% or greater H\(_2\)SO\(_4\). Derivatives with three \(p\)-MeO and \(p\)-Me\(_2\)N groups have \(pK_R\) values of \(-0.8\) and \(9.4\), respectively. The latter cation, crystal violet, is stable in neutral aqueous solution. The aromatic tropylionion C\(_7\)H\(_7\)\(^+\) has a \(pK_R\) of \(4.8\), and forms from the alcohol in weakly acidic aqueous solutions.

\[
\begin{align*}
R^+ + H_2O & \rightleftharpoons ROH + H^+ \quad (1) \\
K_R & = \frac{[ROH][H^+]}{[R^+]} \quad (2)
\end{align*}
\]

1.3. Carbocations as Reactive Intermediates

Simple carbocations are initially encountered in the chemical literature of the 1920s and 1930s, through proposals of their occurrence as short-lived intermediates of organic reactions such as S\(_N\)1 solvolysis, electrophilic alkene addition, and electrophilic aromatic substitution. Three chemists, Hans Meerwein of Germany, Sir Christopher Ingold of England, and Frank Whitmore of the United States, were the pioneers in this field. A number of experimental observations led to the proposals of the intermediate cations. These included substituent effects, orientation in electrophilic addition and substitution reactions, solvent effects especially on the rates of solvolysis, rearrangements, and common ion inhibition. Such criteria are discussed in standard textbooks\(^7\)\(^8\) and the reader is referred to these for a detailed discussion. It was also recognized that in many of these reactions the carbocation
intermediate formed and reacted at the stage of an ion pair. Winstein proposed the involvement of two ion pairs, a contact or intimate ion pair and a solvent separated ion pair.\textsuperscript{8,9} The reader is referred to Chapter 19 in this volume for a discussion of recent studies of such ion pairs involving modern laser methods.\textsuperscript{10} Reactions that are on the borderline of $S_N1$ and $S_N2$ solvolysis are discussed in Chapter 2 in this volume.\textsuperscript{11}

2. PERSISTENT CARBOCATIONS UNDER STABLE ION CONDITIONS

2.1. Superacids

The modern era of carbocation chemistry began in the 1960s with the discovery by George Olah that simple alkyl carbenium ions could be observed at low temperatures in solutions now termed superacids. While a number of these superacids now exist, the most common are mixtures of a strong protic acid such as HSO$_3$F or HF to which has been added SbF$_5$. Substances of low basicity such as SO$_2$ and SO$_2$F$_2$ are often added as a diluent. The initial investigations of Olah employed SbF$_5$/SO$_2$. In addition to being sufficiently polar to support the formation of charged species, superacids are very strongly acidic, being orders of magnitude more acidic than sulfuric acid and perchloric acid. Thus, they are capable of protonating very weakly basic carbon bases to form carbocations. They are also very weakly basic and nucleophilic, so that the carbocations, once formed do not react. The combination of high acidity and weak basicity also means that equilibria such as

$$R_2C^+/C_0/C_0/C_0/C_0\text{CH}_2^+H^+ \rightleftharpoons R_2C^+/C_0/C_0\text{Me}$$

lie far to the right. This finding suppresses a problem common to less acidic solutions, a reaction of the carbocation with the olefin resulting in complex oligomeric mixtures.

2.2. Stable Ion Chemistry

Olah’s initial studies focused on the tert-butyl cation and related simple alkyl systems, as obtained, for example, by dissolving tert-butyl fluoride in SbF$_5$/SO$_2$.\textsuperscript{12} The hydrogen nuclear magnetic resonance (\textsuperscript{1}H NMR) spectrum of this solution showed considerable deshielding of the methyl protons, from $\sim$1.5 to 4.3 ppm. These protons also appeared as a singlet, in contrast to the doublet seen in the starting fluoride associated with H–F coupling. While this result was consistent with the formation of the tert-butyl cation, also possible was a polarized donor–acceptor complex that undergoes rapid fluoride exchange.

Evidence that the cation was the product accumulated quickly.\textsuperscript{1} A $^{13}$C NMR spectrum, only obtained with difficulty in 1960, revealed that the chemical shift
of the tertiary carbon was 335.2 ppm, which was at that time the record for the most deshielded $^{13}$C signal. The $^1$H NMR of the isopropyl cation obtained with Me$_2$CHF and SbF$_5$ showed 13.0 ppm for the CH proton, as well as a $^{13}$C chemical shift for the central carbon at 320.6 ppm. Such highly deshielded chemical shifts can only reasonably be explained by the formation of a full cation. In addition, the $^1$H NMR of the cation EtC$^+$/Me$_2$ showed a large coupling between the methyl protons next to the C$^+$ center and the CH$_2$ protons. This coupling is consistent with transmission through an sp$^2$ carbon, but not through an sp$^3$ carbon, as would be the case for the donor–acceptor complex. Finally, the planar nature of the cation was firmly established by comparing the infrared (IR) and Raman spectra with those obtained for neutral, isoelectronic boron derivatives, trimethylboron, for example, being the model for the tert-butyl cation.

In the ~40 years since Olah’s original publications, an impressive body of work has appeared studying carbocations under what are frequently termed “stable ion conditions.” Problems such as local overheating and polymerization that were encountered in some of the initial studies were eliminated by improvements introduced by Ahlberg and Ek$^{13}$ and Saunders et al.$^{14}$ In addition to the solution-phase studies in superacids, Myhre and Yannoni$^{15}$ have been able to obtain $^{13}$C NMR spectra of carbocations at very low temperatures (down to 5 K) in solid-state matrices of antimony pentafluoride. Sunko et al.$^{16}$ employed a similar matrix deposition technique to obtain low-temperature IR spectra. It is probably fair to say that nowadays most common carbocations that one could imagine have been studied. The structures shown below are a limited set of examples. Included are aromaticly stabilized cations, vinyl cations, acylium ions, halonium ions, and dication. There is even a recent report of the very unstable phenyl cation (C$_6$H$_5^+$) generated in an argon matrix at 8 K.$^{17}$

![Carbocation Structures](image)

### 2.3. Theory

In the early days of stable ion chemistry, the experimental measurements of parameters such as NMR chemical shifts and IR frequencies were mainly descriptive, with the structures of the carbocations being inferred from such measurements. While in cases such as the tert-butyl cation there could be no doubt of the nature of the intermediate, in many cases, such as the 2-butyl cation and the nonclassical ions, ambiguity existed. A major advance in reliably resolving such uncertainties
has been the application of theory. The high-speed computers and sophisticated ab initio programs now available allow properties such as relative energies, geometries, IR frequencies, and NMR chemical shifts to be computed within experimental accuracy. Theoretical methods distinguish transition states, that is, saddle points on a potential energy surface from true ground-state structures that represent real reaction intermediates. Experimental observations such as IR frequencies and NMR chemical shifts can be compared with values computed for the ground-state structures. Where these match, there is reasonable confidence that the structure being observed in the experiment corresponds to the computed structure.

An example of this approach is the 2-butyl cation, an ion that was first observed in 1968. After some debate as to the structure of the ion being observed, a high-level computational search of the C₄H₉⁺ potential energy surface revealed only two minima corresponding to the 2-butyl derivative, a partially bridged 2-butyl cation (1) and the hydrogen-bridged structure (2), with the hydrogen-bridged structure more stable by 0.4 kcal/mol. Comparison of the IR frequencies computed for the two structures with an experimental spectrum obtained for the cation in a low-temperature matrix, lead to the conclusion that the experimental cation was principally the hydrogen-bridged ion (2).

A second example is the 1-methyl-1-cyclohexyl cation, a tertiary ion where experimental studies had led to the suggestion that there was actually a pair of structures undergoing rapid equilibration even at very low temperatures. These two structures were conformational isomers: 3, where the ring is distorted to maximize Cβ—Cγ hyperconjugation, and 4 with Cβ—Haxial hyperconjugation. The molecular orbital (MO) calculations performed at the time of the initial experimental observations could only be done using semiempirical methods and were not consistent with this idea. More recent high level ab initio calculations, however, provide full support. The two structures, termed hyperconjomers, are ground states. Moreover, theory provides a close match with three different experimental observations—energy differences between the two, α-deuterium isotope effects, and 13C NMR spectra.
High-level computations are now routine, and failure to match computed and experimental parameters is more likely due to a flaw in the experiment (except for very large structures). The ab initio methods of course provide the full geometry of the ground state. Thus, correspondence of the experimental observations with those computed for a particular ground state means that, within a reasonable confidence level, the detailed geometry of the cation being observed experimentally is known.

2.4. Carbocation Rearrangements

A long-established feature of the carbocation intermediates of reactions, such as S_N1 solvolysis and electrophilic aromatic alkylation, is a skeletal rearrangement involving a 1,2-shift of a hydrogen atom, or an alkyl, or aryl group. The stable ion studies revealed just how facile these rearrangements were. Systems where a more stable cation could form by a simple 1,2-shift did indeed produce only that more stable ion even at very low temperatures (see, e.g., Eq. 3).

$$\begin{align*}
\text{Cl} & \quad \text{CH}_2\text{Cl} \\
\text{or} & \quad \text{SbF}_5\text{SO}_2
\end{align*}$$

Exceptions to this rule were cations such as the secondary 2-adamantyl cation 5, which does not rearrange to the more stable tertiary 1-adamantyl cation 6 by an intramolecular 1,2-hydride shift (Eq. 4).^{22} The migrating group in a 1,2-shift migrates to the adjacent empty \( p \) orbital, so that there is a stereochemical requirement that the migrating group and the \( p \) orbital have a dihedral angle close to zero degrees. The 2-adamantyl cation, where the angle is 90°, is the worst possible case.

$$\begin{align*}
5 & \quad \rightarrow \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H}
\end{align*}$$

For ions of similar or identical stability, 1,2-shifts are also extremely rapid.^{15} Even at very low temperatures, the \(^1\text{H} \) NMR spectrum of the 2,3,3-trimethyl-2-butyl cation 7 has only one signal, while the \(^{13}\text{C} \) NMR shows two signals, one for the methyl carbons and one for the quaternary carbons. As shown in Scheme 1.1, these lie almost exactly midway between those calculated for the static ion. A similar result is obtained for the 1,2-dimethylcyclopentyl cation 8, and other tertiary cations related by 1,2-shifts. Thus, even at very low temperatures, 1,2-shifts
between equilibrating degenerate ions are extremely rapid. The activation barriers associated with these rearrangements are < 5 kcal/mol. (In some cases these have been measured.)

Static forms of cations such as 7 and 8 have been observed by $^{13}$C NMR in solid SbF$_5$ matrices, with chemical shifts for the static ions matching computed values. The signals for the static ions could be observed even at temperatures above the solution-phase limits, which suggests there is a variation in the lattice sites in the solid, and the cations find themselves in different environments. A broad distribution of rearrangement barriers results.

Some systems show NMR coalescence consistent with a rearrangement to an intermediate cation that is less stable. The $^1$H NMR of the isopropyl cation 9, for example, shows a coalescence of the two proton signals between 0 and 40 °C. The activation barrier is 16 kcal/mol, close to the difference between a secondary and a primary cation. Calculations show that a corner protonated cyclopropane (11) is the only other minimum on the C$_3$H$_7^+$ energy surface. The 1-propyl cation 10 is a transition state.

$$\text{H}_3\text{C}±\text{CH}_3 \rightleftharpoons \left[\text{H}_3\text{C}+\text{CH}_2\right] \rightleftharpoons \text{Me} $$

(5)

2.5. Nonclassical Ions

Nonclassical carbocations (or carbonium ions employing Olah’s terminology) are cations in which there is delocalization of $\sigma$ electrons. These are distinguished from carbenium ions in terms of the following definitions. Carbenium ions (or classical carbonium ions) “can be represented by a single Lewis structure involving only two-electron, two-center bonds. Traditionally, $\pi$-conjugated cations such as allyl are included in the category.” A carbonium ion “cannot be represented adequately by a single Lewis structure. Such a cation contains one or more carbon or
hydrogen bridges joining two-electron deficient centers. The bridging atoms have coordination numbers higher than usual, typically five or more for carbon and two or more for hydrogen. Such ions contain two-electron, three center bonds.

The most extensively studied, and at one time highly controversial, system is the 2-norbornyl cation. Initial suggestions of a nonclassical structure came out of studies of solvolysis reactions, principally by the group of Winstein et al. Observations included: (a) exo derivatives (e.g., 12) solvolyzed over two orders of magnitude more rapidly than endo derivatives 13; (b) the product from both was exclusively exo (16); (c) 16 was 100% racemized from chiral 12, while their was some retention of chirality from endo 13; (d) isotopic tracer studies with an exo reagent showed that 50% of the product was derived from solvent addition at C2 where the leaving group was originally attached, but 50% derived from addition at C1. These observations (and others) led to the proposal that the exo substrate ionizes with anchimeric assistance from the C1–C6 bond forming the symmetrically bridged 14 with a plane of symmetry. The carbons that were C1 and C2 in the starting material are equivalent in this cation. Solvent (Sol) adds equally to these two carbons, from the exo face as shown in Scheme 1.2. This results in 100% racemic exo product. The C1–C6 bond in 13 is not aligned correctly to participate in the ionization. Thus, the endo reagent ionizes initially (and more slowly) to a classical structure (15), probably as an ion pair. This cation rearranges to the nonclassical 14, but, especially in nucleophilic solvents, is partly trapped by solvent from the exo face before rearrangement. The latter reaction accounts for the observation that racemization is not complete in the endo system.

For a number of years, a storm of controversy raged over this proposal, with H. C. Brown as the chief opponent. Brown ruled out anchimeric assistance as an explanation for the rate acceleration of the exo derivative, arguing that exo was normal, but that endo was unusually slow because of a steric effect. The racemization and isotopic tracer results, he proposed, could be explained by a rapid equilibrium between the classical ions 15 and 17 (see Scheme 1.3), with a steric effect responsible for the exo addition of nucleophiles. In terms of the cation, the question revolves around the issue whether the classical ions 15 and 17 should be joined by the equilibrium depiction (the rapidly rearranging scenario) or with a
resonance depiction (the nonclassical scenario). The former, which is supported by the rapid migrations in cations such as 7, has the bridged structure 14 (depicted in two ways in Scheme 1.3) as the transition state in the rearrangement. In the latter interpretation, 14 is the ground state, with the classical structures representing resonance contributors according to the resonance convention.

The 2-norbornyl cation has nowadays been extensively studied under stable ion conditions, and there can be no doubt that this ion is the symmetrically bridged 14. At low temperatures (where hydride shifts are frozen out), both the $^{13}$C and $^1$H NMR point to a symmetrical structure, with, for example, two equivalent strongly deshielded protons or carbons for H–Cl and H–C2. Moreover, the solid-state $^{13}$C NMR spectrum obtained in amorphous SbF$_5$ is unchanged from $-144 \, ^\circ\text{C}$ down to $-268 \, ^\circ\text{C}$ (5 K!).$^{29}$ The result at 5 K means that if the symmetry is due to rapidly equilibrating classical ions, the activation barrier for the rearrangement is $<0.2 \, \text{kcal/mol}$. It has been argued that such a barrier is too low for the extensive bonding and geometrical reorganization that would have to occur. Although initial computations were equivocal because of the limitations of the low level of theory, more recent high-level calculations provide full support for the single minimum potential of 14.$^{30}$ The classical structure is not even a minimum. Moreover there is good agreement in both $^{13}$C NMR chemical shifts$^{30}$ and IR frequencies$^{31}$ for values calculated for the bridged structure and for those observed experimentally. A comparison of the carbon 1$s$ photoelectron spectrum of the tert-butyl cation and the norbornyl cation shows the expected difference between classical and nonclassical structures.$^{32}$

Using methods such as those discussed for the norbornyl cation, nonclassical structures have now been established for a number of carbocations.$^{15,16,24,33}$ Representative examples are shown below. The 7-phenyl-7-norbornenyl cation 19 exists as a bridged structure 20, in which the formally empty p orbital at C7 overlaps with the C2–C3 double bond. This example is of a homoallylic cation. The cyclopropylcarbinyl cation 21, historically one of the first systems where nonclassical ions were proposed, has been shown to exist in superacids mainly as the nonclassical bicyclobutonium ion 22, although it appears as if there is a small amount of the classical 21 present in a rapid equilibrium. Cations 23 and 24 are examples of $\mu$-hydridobridged
Solvolysis reactions generating carbocations on medium ring carbocycles often show transannular shifts in the products. Initially, it was proposed that structures such as 23 were transition states in such rearrangements. Stable ion studies accompanied by computations have established that the bridged structures are actually minima in a number of such examples.

2.6. Isotopic Perturbation of Symmetry

The question whether symmetry in the NMR spectrum is due to rapid interconversion of 2 equivalent structures or to a single intermediate structure can be resolved using the tool of isotopic perturbation. Cation 25, with \( L = H \), shows one signal in the \(^{13}\)C NMR for \( C_x \) and \( C_y \) because of the symmetry of the delocalized allylic cation. Substituting \( L = D \) (isotopic perturbation of resonance) has little effect since the \( \pi \) delocalization is not significantly perturbed. The signal for \( C_x \) and \( C_y \) are split in 25, \( L = D \), but only by 0.5 ppm (\( C_x \) downfield).

This situation is quite different in the system of Eq. 7. As discussed previously (see Scheme 1.1) there is only one \(^{13}\)C signal for \( C_x \) and \( C_y \) when \( L = H \) because of a rapid 1,2-hydride shift. Substituting \( L = D \) (isotopic perturbation of equilibrium) now has a large effect. The cation 8a, with a Me group next to the positively charged carbon, is energetically more stable than 8b where there is a CD\(_3\) group. This is a \( \beta \)-deuterium equilibrium isotope effect; \( C-H \) hyperconjugation stabilizes an adjacent positive charge more than \( C-D \) hyperconjugation. The hydride shift is still occurring very rapidly, but the \(^{13}\)C signals are now a weighted average. With \( K < 1 \), \( C_x \) spends more of its time as the cationic carbon than \( C_y \). Thus, compared
to the single chemical shift observed where \( L = H \), \( C_x \) is shifted downfield and \( C_y \), which spends more of its time as an \( sp^3 \) carbon, upfield. The difference between the signals for \( C^+ \) and \( C(sp^3) \) is large, \( \sim 250 \) ppm (see Scheme 1.1). Thus the splitting of the signals for \( C_x \) and \( C_y \) in the deuterated cation is large. For example, \( C_x \) is 81.8 ppm downfield of \( C_y \) at \(-142 \) °C.

\[
\begin{array}{c}
\text{Me} \\
\text{Cl}_3 \\
\text{H} \\
\end{array} \\
\text{C}_x \\
\text{C}_y \\
K \\
\begin{array}{c}
\text{Me} \\
\text{C}_x \\
\text{C}_y \\
\text{Cl}_3 \\
\end{array}
\]

This approach has been applied to the norbornyl cation, where the NMR even at very low temperatures showed equivalent \( ^{13}C \) NMR signals for \( C_1 \) and \( C_2 \). The monodeuterated 26 was prepared, which showed a difference of only 2 ppm in the signals for \( C_1 \) and \( C_2 \).35 This small splitting is inconsistent with rapidly equilibrating ions but is expected for the symmetrical nonclassical cation.

![Norbornyl cation](image)

2.7. Crystal Structures

The first X-ray crystal structure of a carbocation salt was reported in 1965.36 Triphenylmethyl perchlorate (27) has a planar central carbon. The three phenyl rings are each twisted \( \sim 30° \), so that overall the cation has a propellor shape. Disordered perchlorate anions sit above and below the central carbon, with a \( C-Cl \) separation of 4.09 Å.

![Triphenylmethyl perchlorate](image)

Since that time, a number of X-ray structures have been reported, although many of these, especially the earlier ones,37 have represented salts of highly conjugatively stabilized cations. Problems such as the unstable nature of the salts and disordered
crystals have plagued many attempts. No crystal structure of the parent 2-norbornyl cation, for example, has been reported. Through great persistence Laube\textsuperscript{38} has managed to obtain crystals structures of some important cations. Representative examples follow.

The tert-butyl cation, as its Sb\textsubscript{2}F\textsubscript{11} salt, has the expected planar central carbon, with relatively short C\textsuperscript{+}/C\textsubscript{a} bonds (1.44 Å).\textsuperscript{39} The structure is in agreement with the C–H hyperconjugation model of Eq. 8.

\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{Me} \quad \text{Me}
\]

The remarkable effect of hyperconjugation is seen in the structure of the 3,5,7-trimethyl-1-adamantyl cation (28), also obtained as its Sb\textsubscript{2}F\textsubscript{11} salt.\textsuperscript{40} The cation shows a significant flattening at C1, with short C\textsuperscript{+}/C\textsubscript{a} bonds (1.44 Å) and relatively long C\textsubscript{a}/C\textsubscript{b} bonds (1.61 Å). These point to significant C–C hyperconjugation, as shown in Eq. 9.

\[
\begin{align*}
\text{28} & \quad \text{28} \\
\text{Me} & \quad \text{Me} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

As shown below, the 2,3-dimethyl-7-phenyl-7-norbornenyl cation (29) shows significant distortion of the bridging C7 toward the C2–C3 double bond.\textsuperscript{41} The C7–C3 distance is only 1.87 Å, and the C2–C3 bond has elongated to 1.41 Å. This structure is in agreement with the nonclassical (bis-homoaromatic) character of the non-methylated analogue 20.

\[
\begin{align*}
\text{29} & \quad \text{29} \\
\text{Me} & \quad \text{Me} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

As a further comment, the structure (i.e., bond lengths, bond angles) computed by high-level methods generally shows good agreement with the X-ray structure. Thus, the counterions in the crystal do not distort the structure to a significant extent. Laube has in fact suggested that the locations of the anions approximate the position of a leaving group or nucleophile in the transition state for the ionization or cation–anion combination. As a final comment, the Reed group at Riverside has recently reported some interesting solid superacids with very weakly
nucleophilic carborane anions. The crystal structure of the parent benzenium ion (protonated benzene) has been obtained from such a superacid.

3. REACTIVITY OF CARBOCATIONS

3.1. Introduction

While providing structural details and rates of intramolecular rearrangements–fragmentations, stable ion studies do not address questions relating to the reactivity of a carboxation with a second reagent, either with a solvent such as water or with some added nucleophile (Nu). Shown in Scheme 1.4 is the kinetic scheme for a limiting S_N1 solvolysis, that is, for a solvolysis that proceeds by way of a free carboxation. As is true for any reaction in which a reactive intermediate is formed as a stationary-state species, studies of this system cannot provide absolute rate constants. However, as recognized in early studies, relative rate constants or selectivities can be obtained.

\[
\text{Rate} = -\frac{d[RX]}{dt} = k_{\text{obs}}[RX] = \left(\frac{k_{\text{ion}}k_s}{k_x[X^-] + k_s}\right)[RX]
\]

(10)

where, as will be the case throughout this chapter, the rate constant \(k_s\) is defined as the first-order rate constant for the decay of the cation in solvent. Rearranging Eq. 10,

\[
\frac{1}{k_{\text{obs}}} = \left(\frac{1}{k_{\text{ion}}}\right)\left(\frac{k_x}{k_s}\right)[X^-] + \left(\frac{1}{k_{\text{ion}}}\right)
\]

(11)

and the relative rate constants for return to starting material \((k_x)\) and capture by solvent \((k_s)\) are obtained as the ratio of the slope to the intercept of a plot of \(1/k_{\text{obs}}\) versus \([X^-]\).
In the method of competition kinetics, the intermediate cation is partitioned between two competing nucleophiles whose concentration is in excess over that of the cation precursor. For Scheme 1.4, where one of the nucleophiles is the solvent,

\[
\frac{[\text{RNu}]}{[\text{ROSol}]} = \left( \frac{k_{\text{Nu}}}{k_s} \right) \cdot [\text{Nu}]
\]

and, because the concentration of the nucleophile is known, the product ratio can be converted into a rate constant ratio.

The latter method, with azide ion and water as the competing nucleophiles in 80% acetone, was found to lead to an apparent reactivity–selectivity relation. The latter, in general terms, states that the selectivity of a reactive intermediate toward two competing reagents will decrease as the reactivity of the intermediate increases (or its stability decreases). The argument is that a highly reactive unstable intermediate will have an early transition state in its reactions, and thus show little discrimination. A less reactive and more stable intermediate on the other hand will have a later transition state, and thus show greater selectivity. Raber et al.\(^{45}\) took the rate constant for the solvolysis \(k_{\text{ion}}\) of Scheme 1.4 as a measure of the reactivity of the cation intermediates of a series of solvolysis reactions. Their argument was that \(k_{\text{ion}}\) measures cation stability (and hence reactivity), the more stable ion forming more easily \( (> k_{\text{ion}}) \) but, once formed, reacting more slowly. For 16 systems, a plot of \(\log k_{\text{ion}}\) versus \(\log (k_{\text{az}} : k_w)\) \((\text{az} = \text{azide}, \text{w} = \text{water})\) was found to be approximately linear. In other words, the more easily formed and more stable cations showed a greater selectivity toward azide ion.

### 3.2. Ritchie’s \(N^+\) Scale

Ritchie was the first to directly measure the absolute reactivity of cations toward solvent and added nucleophiles.\(^6\) The cations were highly stabilized examples, triarylmethyl cations bearing stabilizing substituents such as 30 and 31, xanthylum ions (e.g., 32) and tropylium ions (e.g., 33). The feature (and requirement) of these cations was that they had a lifetime in water such that kinetics could be followed by conventional or stopped-flow spectroscopy whereby one solution containing the pre-formed cation was added to a second solution. The time required to mix these solutions was the important factor and limited measurements to cations with lifetimes longer than several milliseconds. The lifetimes in water for 30–33 are provided below. Lifetime is defined as the reciprocal of the first-order rate constant for the decay of the cation in solvent.
One of the surprising features of Ritchie’s studies was a constant selectivity. While the absolute rate constants differed considerably over the series of cations, the selectivities toward pairs of nucleophiles were constant and independent of the reactivities of $R^+$. Rate constants were correlated by a simple two parameter equation

$$\log k_{Nu} (R^+_n) = \log k_0 + N_+$$

where $\log k_{Nu}$ is the rate constant for cation $R^+_n$ reacting with $Nu$, $\log k_0$ is a parameter that depends only on the cation, and $N_+$ is a parameter that depends only on the nucleophile and the solvent. The latter was defined relative to $k_w$, the first-order rate constant for decay in water, as $N_+ = \log (k_{Nu} : k_w)$. Selected values are provided in Table 1.1. According to Eq. 13, plots of $\log k_{Nu}$ versus $N_+$ are parallel, differing only in the reactivity of the cation as defined by $\log k_0$. Figure 1.1 depicts this relationship in schematic terms.

### Table 1.1. Selected Values for $N_+$

<table>
<thead>
<tr>
<th>Nuc(solv)</th>
<th>$N_+$</th>
<th>Nuc(solv)</th>
<th>$N_+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_2O(H_2O)$</td>
<td>0.0</td>
<td>$HOO^- (H_2O)$</td>
<td>8.5</td>
</tr>
<tr>
<td>$MeOH(MeOH)$</td>
<td>0.5</td>
<td>$CN^-(DMSO)^a$</td>
<td>8.6</td>
</tr>
<tr>
<td>$CN^- (H_2O)$</td>
<td>3.8</td>
<td>$N_3^-(MeOH)$</td>
<td>8.8</td>
</tr>
<tr>
<td>$NH_3(H_2O)$</td>
<td>3.9</td>
<td>$PhS^-(H_2O)$</td>
<td>9.1</td>
</tr>
<tr>
<td>$OH^- (H_2O)$</td>
<td>4.5</td>
<td>$N_3^-(DMSO)^a$</td>
<td>10.7</td>
</tr>
<tr>
<td>$EtNH_2(H_2O)$</td>
<td>5.3</td>
<td>$PhS^-(MeOH)$</td>
<td>10.4</td>
</tr>
<tr>
<td>$N_3^-(H_2O)$</td>
<td>7.5</td>
<td>$PhS^-(DMSO)^a$</td>
<td>13.1</td>
</tr>
</tbody>
</table>

$^a$ Dimethyl sulfoxide = DMSO.
3.3. Azide Clock

There is a dichotomy between the constant selectivity observed with the very stable cations by Ritchie, and the changing selectivity for the cations studied by Raber et al. The cations in the latter series are, however, much more reactive, and this led Rappoport and Richard and Jencks to provide an explanation. They suggested that for reactive carbocations powerful nucleophiles such as azide reacted on every encounter, that is, at the diffusion-controlled rate. Changes to encounter control had been suggested by Ritchie through the observation of sharp breaks in plots of \( \log k_{\text{Nu}} \) versus \( N^+ \) when \( k_{\text{Nu}} \) surpassed \( \sim 10^9 \text{M}^{-1}\text{s}^{-1} \) (see R\(_4^+\) in Fig. 1.1). According to Rappoport and Richard and Jencks, \( k_{\text{az}} \) was constant with changing cation reactivity since this nucleophile was already reacting as fast as it could. The apparent linear correlation of \( \log k_{\text{ion}} \) and \( \log (k_{\text{az}} : k_{\text{w}}) \) therefore was just a correlation of \( \log k_{\text{ion}} \) and \( -\log k_{\text{w}} \).

Recognizing this, Richard and Jencks, proposed using azide ion as a clock for obtaining absolute reactivities of less stable cations. The basic assumption is that azide ion is reacting at the diffusion limit with the cation. Taking \( 5 \times 10^9 \text{M}^{-1}\text{s}^{-1} \) as the second-order rate constant for this reaction, measurement of the selectivity \( k_{\text{az}} : k_{\text{Nu}} \) for the competition between azide ion and a second nucleophile then provides the absolute rate constant \( k_{\text{Nu}} \), since \( k_{\text{az}} \) is “known.” The “clock” approach has now been applied to a number of cations, with measurements of selectivities by both competition kinetics and common ion inhibition. Other nucleophiles have been employed as the clock. The laser flash photolysis (LFP) experiments to be discussed later have verified the azide clock assumption. Cations with lifetimes in water less than about 100 \( \mu\text{s} \) do react with azide ion with a rate constant in the range \( 5-10 \times 10^9 \text{M}^{-1}\text{s}^{-1} \), which means that rate constants obtained by a “clock” method can be viewed with reasonable confidence.

3.4. Flash Photolytic Generation of Carbocations

Laser flash photolysis provides access to the absolute rate constants for more reactive cations. To apply this technique, a photochemical reaction must be available that generates the desired intermediate. A number of such reactions have now been found, and are briefly summarized below.

The most common and widely studied photochemical reaction is photoheterolysis, the heterolytic cleavage of a C–X bond in the excited state. Like its ground-state analogue, the \( \text{S}_{\text{n}}\text{I} \) reaction, polar solvents such as water, alcohols, and acetonitrile are required. Unlike the ground-state reaction, a competing photohomolysis is usually observed, which can be recognized in the products through the observation of both cation- and radical-derived products (Scheme 1.5). In LFP experiments, the cation and radical transients are easily distinguished by their kinetics. Cations decay exponentially by reacting with the solvent. The decay is not affected by oxygen, but is accelerated by added nucleophiles, azide ion being a particularly good indicator of a carbocation. Radicals decay by second-order kinetics (usually), and are quenched by oxygen but not azide.
A variety of leaving groups can be employed, as illustrated by studies involving diarylmethyl cations. There is a general trend that better leaving groups yield more cation, although there are exceptions. Overall the effect of leaving group is highly attenuated relative to the situation in ground-state solvolysis. With respect to the cationic component there are some fascinating differences between the ground- and excited-state reactions. As one example, observed in one of the early studies of photosolvolysis, methoxy groups promote photoheterolysis of a benzylic–X bond much better than p-methoxy. A second example is shown in Eq. 14. 9-Fluorenol, when irradiated in water and alcohols, cleaves the poor leaving group hydroxide with a high quantum efficiency to give the 9-fluorenyl cation. Under the same conditions, diphenylmethanol yields no cation. Wan and Krogh attributed the remarkable result in the fluorenyl system to the 4nπ cyclic system of the 9-fluorenyl cation, which in the excited state is expected to have aromatic character.

Alkenes, alkynes, and arenes become stronger bases in the singlet excited state. As a result, photoprotonation can occur under much more weakly acidic conditions than required in the ground state. Excited styrenes and phenylacetylenes, for example, are protonated by the solvent in 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), giving rise to phenethyl and α-arylvinylcations that can be observed by LFP (see Eq. 15). In a similar manner, benzenium ions can be observed by photoprotonation of electron-rich aromatics in HFIP. Equation 16 provides an example where the orientation of the protonation is different in the excited state from that of the ground state.
Carbocations have also been obtained by protonation of photochemically generated carbenes (see Eq. 17),\textsuperscript{55,56} by the fragmentation of photochemically generated cation radicals (see Eq. 18),\textsuperscript{57} and by the addition of one photochemically generated cation to an arene (or alkene) to generate a second cation.\textsuperscript{58–60} As illustrated in Eq. 19, the last method has been employed to convert invisible carbocations into visible ones. Short-lived aryl cations\textsuperscript{59} and secondary alkyl cations\textsuperscript{60} are quenched by electron-rich aromatics such as mesitylene and 1,3,5-trimethoxybenzene in HFIP to give benzenium ions that can be observed by LFP in this solvent.

As illustrated in Eq. 17, the last method has been employed to convert invisible carbocations into visible ones. Short-lived aryl cations\textsuperscript{59} and secondary alkyl cations\textsuperscript{60} are quenched by electron-rich aromatics such as mesitylene and 1,3,5-trimethoxybenzene in HFIP to give benzenium ions that can be observed by LFP in this solvent.

As in any LFP experiment the cation must be observable, and it must have a lifetime longer than the pulse of light employed to generate it. Since absorption spectroscopy has been the standard detection method to date, the majority of cations that have been studied are conjugated, usually benzylic-like or benzenium ions. The trick of turning invisible cations into visible ones has thus far seen limited application. With respect to lifetime, protic solvents react with a given cation in the order MeOH > EtOH > H2O > TFE > HFIP (Table 1.2), which can be exploited to increase lifetime into a range where a particular cation becomes detectable. The parent diphenylmethyl cation, for example, requires picosecond LFP to be observed in methanol, ethanol, and water,\textsuperscript{61} but can be studied by nanosecond LFP in TFE and in HFIP. In fact, it is quite long lived in HFIP. The 9-fluorenyl cation requires picosecond LFP even in TFE but is observed with nanosecond LFP in HFIP.
As a final comment there is the question whether the cation observed with LFP is the same as the one produced in a ground-state reaction. With nanosecond LFP, the time interval from excitation to observation is likely sufficient to ensure that this is the case. Two pieces of evidence can be cited. (1) There is a good correspondence of ultraviolet–visible (UV–vis) spectra for the transient cations with ones obtained for solutions of ground-state cations under strongly acidic solutions. (2) Ratios of rate constant obtained directly by LFP agree with selectivities measured for the ground-state reactions. Diffusional separation of ion pairs is complete within 1–10 ns, so that a transient cation observed with nanosecond LFP is a free ion. At shorter times, that is, in picosecond LFP, ion pairs can be observed and their dynamics studied.

3.5. Lifetimes of Carbocations in Protic Solvents

Table 1.3 provides rate constants for the decay of selected carbocations and oxocarbocations in H₂O, TFE, and HFIP. As a general comment, water, methanol, and ethanol are highly reactive solvents where many carbocations that are written as free cations in standard textbooks have very short lifetimes. The diphenylmethyl cation, with two conjugating phenyl groups, has a lifetime in water of only 1 ns. Cations such as the benzyl cation, simple tertiary alkyl cations such as tert-butyl, and oxocarbocations derived from aldehydes and simple glycosides, if they exist at all, have aqueous lifetimes in the picosecond range, and do not form and react in water as free ions. This topic is discussed in more detail in Chapter 2 in this volume.

Lifetimes are longer in the more weakly nucleophilic TFE and HFIP, and cations whose existence is on the borderline in water and simple alkanols can become quite long lived, especially in HFIP. Benzenium ions such as protonated mesitylene can also be observed in HFIP, and there is an estimate for a simple secondary cation 77. There is one estimate of the lifetime of an acylium ion (72), based upon the clock approach. Even with the powerful electron-donor 4-Me₂N on the aromatic ring, this cation appears to be very short lived in water.

The $\sigma^+$ substituent constant scale was developed based upon the solvolysis of substituted cumyl chlorides, where cumyl cations are formed in the rate-determining ionization. For the carbocation-forming reaction of Eq. 20, there is a good correlation of log $k_{H}$ versus the sum of the $\sigma^+$ constants for the substituents directly on the carbon. Such a correlation clearly does not exist for the reaction where the

### Table 1.2. Effect of Solvent on Rate Constants $k_s$ (s⁻¹, 20 °C) for Decay of Cations⁴

<table>
<thead>
<tr>
<th>Cation</th>
<th>MeOH</th>
<th>EtOH</th>
<th>H₂O</th>
<th>TFE</th>
<th>HFIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>(An)₂CH⁺</td>
<td>8.6 × 10⁶</td>
<td>5.5 × 10⁶</td>
<td>1.0 × 10⁵</td>
<td>1.4 × 10¹</td>
<td></td>
</tr>
<tr>
<td>Ph₂CH⁺</td>
<td>2.5 × 10¹⁰</td>
<td>1.4 × 10¹⁰</td>
<td>1.3 × 10⁹</td>
<td>3.2 × 10⁶</td>
<td>~ 1 × 10⁴</td>
</tr>
<tr>
<td>9-Fluorenyl</td>
<td>&gt; 4 × 10¹⁰</td>
<td>8 × 10⁸</td>
<td>2 × 10⁴</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

⁴Rate constants in bold have been measured using nanosecond LFP. Others require picosecond LFP. (An = 4-methoxyphenyl.)
cations react with solvent.\textsuperscript{69} This finding is dramatically demonstrated by comparing the triphenylmethyl cation \textsuperscript{60}, \(\Sigma \sigma^+ = -0.51\), with the dialkoxy carbocation \textsuperscript{55}, which is two orders of magnitude more reactive despite having \(\Sigma \sigma^+ = -1.6\).

\[
\begin{align*}
\text{R} & \text{C}CH_2 + H^+ \rightarrow \text{R}^+ + \text{CH}_3 \quad (20) \\
\end{align*}
\]

Even for a series with varying aromatic substituents, the correlations with \(\sigma^+\) deviate significantly from linearity. Typical behavior is illustrated with data for monosubstituted triarylmethyl cations in Figure 1.2. Significant deviations are observed in the points for the para π donors. Moreover, these deviations are in the direction that indicates that these substituents have kinetic stabilizing effects greater than indicated by \(\sigma^+\). In fact, there are good correlations with \(\sigma^\text{C+}\), a parameter based on \(^{13}\text{C}\) NMR chemical shifts of benzylic-type cations obtained under stable ion conditions.\textsuperscript{70}

**TABLE 1.3. Solvent Reactivities of Selected Carbocations at 20 °C**

<table>
<thead>
<tr>
<th>Cation</th>
<th>(k_w (s^{-1}))</th>
<th>(k_{\text{TFE}} (s^{-1}))</th>
<th>(k_{\text{HFIP}} (s^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(MeO)_3C^+ (52)</td>
<td>(1.4 \times 10^3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhC^+(OMe)_2 (53)</td>
<td>(1.3 \times 10^5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeC^+(OMe)_2 (54)</td>
<td>(1.3 \times 10^5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC^+(OEt)_2 (55)</td>
<td>(2.0 \times 10^7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhC^+(Me)(OMe) (56)</td>
<td>(5 \times 10^7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhCH^+(OMe) (57)</td>
<td>(2 \times 10^9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me_2C^+(OMe) (58)</td>
<td>(1 \times 10^9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EtCH^+(OEt) (59)</td>
<td>(6 \times 10^{10})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph_3C^+ (60)</td>
<td>(1.5 \times 10^5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4-MeOC_6H_4)_2CH^+ (61)</td>
<td>(1.0 \times 10^5)</td>
<td>(1.4 \times 10^4)</td>
<td>(\sim 1 \times 10^1)</td>
</tr>
<tr>
<td>(4-MeOC_6H_4)PhCH^+ (62)</td>
<td>(2.0 \times 10^6)</td>
<td>(1.2 \times 10^3)</td>
<td></td>
</tr>
<tr>
<td>Ph_2CH^+ (63)</td>
<td>(1.3 \times 10^9)</td>
<td>(3.2 \times 10^6)</td>
<td></td>
</tr>
<tr>
<td>9-Xanthylum (64)</td>
<td>(2.3 \times 10^4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-Phenyl-9-fluorenyl (65)</td>
<td>(1.5 \times 10^7)</td>
<td>(1.5 \times 10^4)</td>
<td></td>
</tr>
<tr>
<td>9-Fluorenyl (35)</td>
<td>&gt; (4 \times 10^{10})</td>
<td>(8 \times 10^8)</td>
<td>(2 \times 10^4)</td>
</tr>
<tr>
<td>4-MeOC_6H_4+CMe_2 (66)</td>
<td>(\sim 4 \times 10^7)</td>
<td>(1.6 \times 10^4)</td>
<td></td>
</tr>
<tr>
<td>4-MeOC_6H_4C^+HMe (67)</td>
<td></td>
<td>(3.9 \times 10^5)</td>
<td></td>
</tr>
<tr>
<td>4-MeOC_6H_4CH_2^+ (68)</td>
<td></td>
<td>(4.3 \times 10^6)</td>
<td>(3 \times 10^2)</td>
</tr>
<tr>
<td>4-MeOC_6H_4C^+CH_2 (69)</td>
<td></td>
<td>(1.3 \times 10^6)</td>
<td></td>
</tr>
<tr>
<td>PhC^+Me_2 (70)</td>
<td></td>
<td></td>
<td>(9 \times 10^3)</td>
</tr>
<tr>
<td>PhC^+HMe (71)</td>
<td></td>
<td></td>
<td>(6 \times 10^5)</td>
</tr>
<tr>
<td>4-Me_2NC_6H_4C^+=O (72)</td>
<td>(1 \times 10^{10})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,4,6-Trimethoxybenzenium (73)</td>
<td>(5.8 \times 10^5)</td>
<td>(7 \times 10^2)</td>
<td></td>
</tr>
<tr>
<td>2,4-Dimethoxybenzenium (74)</td>
<td></td>
<td></td>
<td>(2 \times 10^3)</td>
</tr>
<tr>
<td>2-Methoxybenzenium (75)</td>
<td></td>
<td></td>
<td>(7 \times 10^5)</td>
</tr>
<tr>
<td>2,4,6-Trimethylbenzenium (76)</td>
<td></td>
<td></td>
<td>(1 \times 10^5)</td>
</tr>
<tr>
<td>Me_2CH^+ (77)</td>
<td></td>
<td></td>
<td>(7 \times 10^9)</td>
</tr>
</tbody>
</table>
3.6. Rate-Equilibrium Correlation

A plot of log $k_w$ versus $pK_R$ (see Eqs. 1 and 2) represents a linear free energy correlation, where the rate constant and the equilibrium constant refer to the same reaction. With flash photolysis providing $k_w$ for more reactive cations, a plot covering a range of 23 $pK_R$ units can be constructed for carbocation hydration (Fig. 1.3). It can be seen that the data separate into families comprising structurally related ions, with different intrinsic reactivities. For the cations of Figure 1.3, the decreasing order of intrinsic reactivity is 9-xanthyl > C$_{24}$cyclic dialkoxy carbocation > phenyltropylium > diarylmethyl > triarylmethyl > 9-ary1-9-fluorenyl.

Lines in Figure 1.3 have been drawn with the assumption that there is a linear relation. Scatter, however, may mask a gentle downward curvature consistent with the transition state becoming more cation-like as the reactivity of the cation increases. However, if there is curvature, it is slight. The quantity $d(\log k_w)/dpK_R$ is remarkably unchanged ($-0.6 \pm 0.1$). For a very large change in thermodynamic driving force, there is remarkably little change in the position of the transition state. This point has recently been emphasized through the measurement of secondary kinetic and equilibrium isotope effects for the water addition to Ar$_2$CL$^+$ (L = H, D). These also show a transition state 50–60% developed along the reaction coordinate, with no significant change over a wide range of reactivity. This is clearly consistent with the slopes in Figure 1.3.

Further insight into the nature of the transition state for carbocation hydration comes from application of the two parameter Yukawa-Tsuno equation (Eq. 21).
This equation was originally introduced for systems where the interactions lie between those of the two reactions that define the $\sigma$ and the $\sigma^+$ scales with the parameter $r^+$ intended to lie between 0 and 1. However, $\log k_w$ (and $pK_R$) require $r^+$ values significantly $>1$ (Table 1.4), which is consistent with the idea that $\sigma^+$ underestimates the effect of para $\pi$ donors on reactions of fully formed cations. The rate constants for the cation-forming reaction of Eq. 1 ($\log k_H$) on the other hand correlate with $r^+$ slightly $<1$. In other words, these show a reasonable correlation with $\sigma^+$, which is not surprising since both $k_H$ and $\sigma^+$ refer to rate constants of reactions forming carbocations.

$$\log(\frac{k}{k_0}) = \rho\{\sigma + r^+(\sigma^+ - \sigma)\}$$ \hspace{1cm} (21)

**Figure 1.3.** Rate-equilibrium correlation for hydration of carbocations: triarylmethyl and 9-aryl-9-fluorenyl (■ and □, respectively, slope = −0.60); diarylmethyl (△, −0.54); aryltropylium (○, −0.68); 9-xanthylium and cyclic phenyldialkoxycarbocations (● and ▲, respectively, slope = −0.63).

<table>
<thead>
<tr>
<th>Parameter $r^+$ Parameter</th>
<th>Ar–$^+$CHMe</th>
<th>Ph$_2$C–Ar</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r^+(k_w)$</td>
<td>2.3</td>
<td>3.6</td>
</tr>
<tr>
<td>$r^+(k_H)$</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>$r^+(K_R)$</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>$\rho_n(norm)$</td>
<td>$\rho_n(k_w)/\rho_n(K_R)$</td>
<td>0.36</td>
</tr>
<tr>
<td>$\rho_r(norm)$</td>
<td>$\rho_r(k_w)/\rho_r(K_R)$</td>
<td>0.61</td>
</tr>
</tbody>
</table>
The two-parameter equation suggested by Jencks and co-workers\textsuperscript{47b} (Eq. 22) separates substituent effects into a polar or inductive contribution described by $\rho_n$ and a resonance contribution described by $\rho_r$. 

$$\log(k/k_0) = \rho_n\sigma + \rho_r(\sigma^+ - \sigma)$$ (22)

Where both rate and equilibrium constants are known, “normalized” $\rho$ values ($\rho_{\text{norm}}$) are defined as the ratios $\rho_n(k_w)/\rho_n(K_R)$ and $\rho_r(k_w)/\rho_r(K_R)$. Since the value of $\rho(K_R)$ measures the overall substituent effect on proceeding from reagent to product, $\rho_{\text{norm}}$ measures the fraction that has occurred at the transition state. As seen in Table 1.4, $\rho_n(\text{norm})$ in the direction of cation hydration, is significantly $<0.5$, whereas $\rho_r(\text{norm})$ is $>0.5$. The inequality means that there is imbalance in the transition state. When comparing the transition state to starting carbocation, the substituent “sees” a much larger fractional decrease in positive charge in its resonance interaction as compared to the decrease that it “sees” through the polar interaction. This imbalance is shown schematically in Scheme 1.6 where the numbers represent the charges experienced by the substituent normalized to $+1$ in the cation and $0$ in the alcohol. A simple explanation is that the incoming water nucleophile has pyramidalized the alpha carbon, so that the resonance interaction has considerably diminished by the time the transition state is reached. There is still substantial positive charge at the alpha carbon, however, so that the polar interaction is still quite strong. For the reverse direction where the cation is forming, the transition state is well developed with respect to the polar interaction, but now the resonance interaction lags behind. For the latter reason, it is not surprising that the $\sigma^+$ substituent scale based upon rate constants for carbocation formation considerably underestimate the full conjugative effect of the aryl substituents.

3.7. Reactivity with Added Nucleophiles

Rate constants for the reactions of carbocations with added nucleophiles are obtained in LFP experiments as the slopes of linear plots of first-order rate constants for cation decay against the concentrations of added nucleophile. One of the first detailed studies using LFP showed that rate constants for the parent triphenylmethyl cation did not adhere to the simple Ritchie $N_+$ relation of Eq. 13, but that the slope of a plot of $\log k_{\text{Nu}}$ versus $N_+$ was significantly $<1$.\textsuperscript{73} This finding has been verified.
with other cations. It is now clear that the stable cations with lifetimes of the orders of magnitude of that employed by Ritchie do show an approximately constant selectivity as expressed by Eq. 13, but as the cations become more reactive there is a changeover. The more reactive cations seem to show a decreasing selectivity with increasing reactivity, in accordance with the reactivity–selectivity principle.

The extent to which the latter conclusion is influenced by reactions occurring at close to the diffusion limit is still not clear. It has also been established that nucleophiles can reach a reactivity limit well below diffusion because of a requirement for desolvation, which is seen, for example, in a LFP study of the reaction of primary amines and diarylmethyl cations. In 100% acetonitrile, these reactions are fast, with \( k(\text{RNH}_2) \) approaching the encounter limit. There is a small dependence on amine structure, in the expected direction of \( k(\text{RNH}_2) \) increasing with increasing amine basicity. As water is added to the solvent, \( k(\text{RNH}_2) \) decreases regardless of the nature of \( \text{RNH}_2 \), but the effect is more pronounced the more basic the amine. By the time highly aqueous solvents are reached, reactivity no longer parallels basicity. For example, for some cations \( k(n\text{-propylamine}) \) is smaller than \( k(2\text{-cyanoethylamine}) \) despite the weaker basicity of the cyano-substituted amine. Scheme 1.7 provides an explanation. For an amine (or indeed any nucleophile) to react with a carbocation in water, the hydrogen bond to the nucleophile must be broken. One can envisage two ways that this occurs. One involves forming the reactive complex from the small concentration of free, non-hydrogen-bonded amine in equilibrium with the hydrogen-bonded amine. The second involves the sequence, in which the hydrated amine encounters the cation, and the water molecule is then moved out of the way. Either model explains the inversion of nucleophilic reactivity and basicity for the more reactive cations. For such cations, the actual barrier to formation of the nitrogen–carbon bond is low. What determines the reactivity is the ease of forming the reactive complex, which depends inversely on the strength of the hydrogen bond. Because this hydrogen bond is stronger for more basic amines, these react more slowly.

Rate constants for cations reacting with carbon nucleophiles have also been obtained by LFP. HFIP is a good solvent for such studies, because cations can be generated photochemically in this solvent, but it is quite weakly nucleophilic, allowing
the carbon nucleophile to compete. Equation 23 (Fl = 9-fluorenyl) describes one study in which the fast electrophilic addition step of a Friedel–Crafts alkylation was directly studied.\textsuperscript{78,79} In fact, with electron-rich aromatics the cyclohexadienyl cation could be seen to grow as the fluorenyl cation decayed, so that both cationic intermediates of the alkylation were observed in the same experiment. The second-order rate constants for the addition of \( \text{Fl}^+ \) shows a strong dependence on the substituent for the less electron-rich aromatics, with \( \log k_2 \) correlating with \( \sigma^+ \) with a slope \( \rho^+ \) of \(-8\). This result is obviously indicative of a transition state with considerable cyclohexadienyl cation character. Anisole shows a negative deviation from the correlation line. In fact, anisole and other electron-rich aromatics all react with very similar rate constants in the range \( 1 \text{–} 2 \times 10^9 \text{ M}^{-1} \text{s}^{-1} \), indicating that these reactions have become diffusion controlled. The same rate constants mean that there is no intermolecular selectivity in a competition involving two electron-rich systems. Interestingly, the products still display large positional preferences, that is, intramolecular selectivity. Thus, although the encounter complex reacts to form products rather than separate them (to account for diffusion control), it still determines the carbon to which it attaches the fluorenyl group based upon the stabilities of the cyclohexadienyl cations.

![Equation 23](image)

The 9-fluorenyl cation also reacts at the diffusion limit with substituted styrenes, as indicated by the observation that the rate constants are \( 3 \times 10^9 \text{ M}^{-1} \text{s}^{-1} \) independent of the styrene substituent. The reaction of styrene with the phenethyl cation (71), the first step in the polymerization of styrene (Sty) catalyzed by Brønsted acids, has also been directly observed (Scheme 1.8).\textsuperscript{53} Photoprotonation of styrene

![Scheme 1.8](image)
in HFIP generates 71, observed with LFP at $\lambda_{\text{max}} = 325$ nm. The cation reacts with the styrene not consumed in the photolysis with $k_{\text{init}} = 1 \times 10^9 M^{-1}s^{-1}$. As the absorbance due to 71 decreases at 325 nm, the absorbance of the dimer cation 83, $\lambda_{\text{max}} = 345$ nm, is observed to grow in at higher wavelengths. This absorbance is considerably more stable, decaying only on the milliseconds time scale. In both reactivity and $\lambda_{\text{max}}$, the dimer 83 is very similar to the propagating cation 84 observed in stopped-flow experiments, where $k_{\text{prop}}$ has been measured as $1 \times 10^5 M^{-1}s^{-1}$. Thus, the monomer 71 has a lower $\lambda_{\text{max}}$ and reacts four orders of magnitude more quickly than the dimer and oligomer cations 83 and 84. One possible explanation is that the latter cations are stabilized by a charge-transfer interaction with the nearby phenyl ring, as depicted in Scheme 1.8.

### TABLE 1.5. Electrophilicity and Nucleophilicity Parameters$^a$

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>$E$</th>
<th>Nucleophile</th>
<th>$N(s)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph$_2$CH$^+$</td>
<td>5.90</td>
<td>-4.47 (1.32)</td>
<td></td>
</tr>
<tr>
<td>4-MeC$_6$H$_4$CH$^+$ (Ph)</td>
<td>4.59</td>
<td>-2.44 (1.09)</td>
<td></td>
</tr>
<tr>
<td>(4-MeC$_6$H$_4$)$_2$CH$^+$</td>
<td>3.63</td>
<td>-0.13 (1.21)</td>
<td></td>
</tr>
<tr>
<td>4-MeOC$_6$H$_4$CH$^+$ (Ph)</td>
<td>2.11</td>
<td>0.13 (1.27)</td>
<td></td>
</tr>
<tr>
<td>4-MeC$_6$H$_4$CH$^+$ (OMe)</td>
<td>1.95</td>
<td>0.34 (0.68)</td>
<td></td>
</tr>
<tr>
<td>4-MeOC$_6$H$_4$CH$^+$ (OMe)</td>
<td>0.14</td>
<td>0.78 (0.95)</td>
<td></td>
</tr>
<tr>
<td>(4-MeOC$_6$H$_4$)$_2$CH$^+$</td>
<td>0.00</td>
<td>0.96 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Co$_2$(CO)$_6$</td>
<td>-0.83</td>
<td>1.79 (0.96)</td>
<td></td>
</tr>
<tr>
<td>S$^+$</td>
<td>-2.14</td>
<td>2.06 (0.68)</td>
<td></td>
</tr>
<tr>
<td>S$^+$</td>
<td>-3.72</td>
<td>2.48 (1.09)</td>
<td></td>
</tr>
<tr>
<td>S$^+$Ph</td>
<td>-5.88</td>
<td>3.09 (0.90)</td>
<td></td>
</tr>
<tr>
<td>(4-MeC$_6$H$_4$)$_2$CH$^+$</td>
<td>-7.02</td>
<td>3.64 (0.65)</td>
<td></td>
</tr>
<tr>
<td>Fe(CO)$_3$</td>
<td>-7.78</td>
<td>3.99 (0.62)</td>
<td></td>
</tr>
<tr>
<td>(Ferrocenyl)$_2$CH$^+$</td>
<td>-8.54</td>
<td>5.41 (0.91)</td>
<td></td>
</tr>
<tr>
<td>Pd[P(OPh)$_3$]$_2$</td>
<td>-10.33</td>
<td>5.46 (0.89)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.64 (0.59)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.23 (0.96)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.40 (0.83)X = O</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.36 (0.81)X = CH$_2$</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Data from Ref. 81c.

$^b$ Reacts by hydride transfer.
3.8. Mayr’s Scales of Electrophilicity and Nucleophilicity

In a series of reports published over the last 10–15 years, Mayr and co-workers\textsuperscript{81} obtained second-order rate constants for reactions of carbocations and other electrophiles such as metal–π complexes with a series of nucleophiles, especially π-nucleophiles where a C–C bond is formed. An impressive body of reactivity data has been accumulated, and, including data from other groups, correlated by the following equation,

\[
\log k(20 ^\circ C) = s(N + E)
\]  

(24)

where \( k \) is the second-order rate constant for the electrophile–nucleophile combination, \( E \) is the electrophilicity parameter, \( N \) is the nucleophilicity parameter, and \( s \) is the nucleophile-dependent slope parameter. Values of these parameters for selected electrophiles and nucleophiles are provided in Table 1.5. Equation 24 takes the same form as the Ritchie equation, Eq. 13, with the addition of the \( s \) parameter. It can be seen that \( s \) lies in a narrow range around unity; a value of 1 converts Eq. 24 into Eq. 13, and indeed many of the systems investigated by the Mayr group display a constant selectivity with changing reactivity. The Mayr correlation now covers a reactivity range of 30 orders of magnitude in both electrophiles and nucleophiles. The equation reproduces rate constants within a factor of 10–100, excluding reagents of steric bulk such as trityl cations. It has the power of predicting with reasonable precision the rate constant for a particular combination of cation and electrophile, and thus is of value in organic synthesis.

4. MISCELLANEOUS TOPICS

4.1. Carbocations with Electron-Withdrawing Substituents

There has been considerable interest in benzylic cations in which the α-carbon bears an electron-withdrawing group such as CN, CF\(_3\), or COR. Originally, these cations were investigated in the context of solvolysis reactions. Despite large rate decreases associated with the substitution of the electron-withdrawing group, a cationic intermediate was still proposed.\textsuperscript{82} This result has been verified by azide-clock experiments, which have suggested that the cation has a similar lifetime to analogues without the electron-withdrawing group.\textsuperscript{83} The LFP studies have provided absolute rate constants.\textsuperscript{84} Representative values are given in Table 1.6.

Taking the comparison of 67 and its α-CF\(_3\) analogue 85 as the example (Eq. 25), a \( 10^7–10^9 \) difference is observed in the rate constants \( k_{for} \) for formation of the cations, but there is virtually no difference in the rate constants \( k_{rev} \) for their reactions with nucleophiles. In other words, the α-CF\(_3\) cation is considerably less stable in the thermodynamic sense but of comparable stability in the kinetic sense. This finding has been explained\textsuperscript{83b,85} by a model separating the substituent effects into polar and resonance contributions. The polar effect, which substantially destabilizes
the CF₃-substituted cation, dominates the equilibrium and is responsible for the thermodynamic destabilization. The polar effect, however, is partially compensated by a increased resonance stabilization in the CF₃-substituted cation due to the greater importance of the quinonoid resonance contributor 85b as the positive charge is moved away from the electron-withdrawing CF₃ group. Evidence for the importance of this resonance contributor is the observation that α-CF₃-substituted cations show the highly unusual feature of reacting with nucleophiles at the para position of the benzene ring. As has been discussed in Section 3.6, there is an imbalance in the transition state for a cation–nucleophile combination, with a substantial loss of the resonance interaction at the transition state, but less of a change in the polar interaction. With the greater importance of the latter on the overall equilibrium, it is argued that the opposing changes in resonance and polar effects almost cancel, with the result that the effects on k_rev are small.

In Table 1.6, it can be seen that the relative kinetic stability of the cation substituted with an electron-withdrawing group is also found in comparing cations 89 and 90 where the para position is substituted by a methyl group. Other cations of interest are those substituted with an α-thioamido group such as 88. These exhibit a substantial kinetic stabilization. The reasons for this are not entirely clear at this time. One suggestion is that there is stabilization by a bridging interaction with the C=S group.

### 4.2 Silyl Cations

This section provides a discussion of R₃Si⁺, the silicon analogue of the carbenium ion. While such species do exist in the gas phase, their existence in condensed
phases has proved controversial. The high bond dissociation energy of silicon–halogen and silicon–oxygen bonds has ruled out traditional $S_N1$ solvolyses as a route to these intermediates. The reactive intermediates $92$ and $93$ decay by heterolytic cleavage of a silicon–carbon bond. The LFP studies of these reactions, however, have shown that even in the weakly nucleophilic solvents acetonitrile ($92^{86}$) and HFIP ($93^{87}$) the C–Si cleavage occurs with solvent participation at the silicon so that no free silyl cation is formed. Mayr et al. $^{88}$, on the other hand, have concluded that hydride transfer from $R_3SiH$ to diarylcarbenium ions in $CH_2Cl_2$ does proceed to give $R_3Si^+$ as an intermediate.

Lambert et al. $^{89}$ summarized the history of the attempts by his group and others to observe $R_3Si^+$ under stable ion conditions. Hydride transfer from $R_3SiH$ to salts of carbocations such as the trityl cation does occur and has been used extensively. Initial studies involved silanes such as $Ph_2MeSiH$ and the perchlorate salt of the trityl cation. The products were found to be covalent, that is, $R_3Si/C\equiv C/O\text{ClO}_3$. Switching to alkylthiosilanes such as ($i$-PrS)$_3SiH$ to take advantage of stabilization by the sulfur led to conducting solutions, but the products were complexes with the solvent. This conclusion was based upon $^{29}Si$ NMR chemical shifts that were typically in the range of 30–50 ppm, far upfield from a value $\sim 300$ ppm calculated for the free silyl cation. The trityl counterion was then changed to $(C_6F_5)_4B^-$ and the hydride transfer performed in aromatic solvents such as benzene and toluene. Once again, the value of the $^{29}Si$ resonance, 80–100 ppm, led to the conclusion that there was coordination with the solvent, which was verified by a crystal structure of the toluene complex of the Et$_3Si^+\cdot(C_6F_5)_4B^-$ salt $94$. This revealed a toluene ring geometry that was essentially unperturbed and a C–Si bond distance of 2.18 Å, considerably lengthened from the normal distance of 1.85 Å. The silicon portion, however, was not planar, which is consistent with tetracoordination. Thus, while the borate counterion was well removed, there was loose coordination to the toluene. Studies by the Reed $^{90}$ group with halocarboranes as the anion produced similar materials described as “closely approaching a silyl cation.” Here there was coordination between the silicon and halogen atom of the counteranion. Although the silicon–halogen distance was long, the geometry around the silicon was still not planar, as required for the free cation.
In addition to its interesting structure, the triethylsilylium–aromatic complex has proved useful in preparing other cations. Reaction with 1,1-diphenylethylene, for example, provided the cation 95, the first example of a persistent β-silyl substituted carbocation (i.e., where decomposition by loss of the silyl group did not occur).91

$$\text{[Et}_3\text{Si}^+ \cdot (C_6F_5)_4\text{B}^-]_{\text{ArH}} + \text{CH}_2=\text{CPh}_2 \rightarrow \text{Et}_3\text{SiCH}_2\text{CPh}_2^+ \cdot (C_6F_5)_4\text{B}^-$$

Lambert then turned to the mesityl (2,4,6-trimethylphenyl) group Mes, in which the two ortho methyl groups provide steric hindrance that might prevent coordination. Trimesitylsilane, (Mes)$_3$SiH, did not transfer its hydride, however, presumably because the carbocation could not approach close enough. In what has been termed the “allyl leaving-group approach,” trimesitylallylsilane was prepared. Its reaction in C$_6$D$_6$ with the β-silyl carbenium salt 95 led to the first free silyl cation 96,92 with a chemical shift of 225 ppm in good agreement with the computed value of 230 ppm. This reaction presumably proceeds via electrophilic addition to the terminal end of the allyl group to give an intermediate 97, followed by cleavage of the silyl cation. Other examples of silyl cations have more recently been reported.93 A crystal structure of a carborane salt of (Mes)$_3$Si$^+$ has confirmed that it has a free three-coordinate silyl cation.94

Zeolites are porous aluminosilicate caged structures that can have both Brønsted and Lewis acid sites approaching superacid strengths. These structures play an important role in the petroleum industry because of their ability to catalyze transformations of hydrocarbons in reactions that proceed by way of carbocation intermediates. This has led to a considerable interest in observing such species within the zeolite framework. Relatively stabilized cations such as triarylmethyl, xanthylum, dibenzotropylium, and cyclopentenyl cations can be observed as persistent ions in acidic zeolites, where they have been characterized in similar manners as in superacids, that is, by solid-state NMR, IR, and UV–vis spectroscopy. Less stable cations such as cumyl cations and the 9-fluorenyl cation do not persist. However, such ions have recently been studied as transient intermediates using LFP with diffuse reflectance detection.96 These studies provide information about the reactivity of carbocations generated within the zeolite cavities. There are some interesting differences from reactions in homogeneous solution associated with both the active and passive influences of the zeolite environment. In the former sense, the zeolite
can directly participate in cation decay by direct participation as a nucleophile, leading to framework-bound products. In the latter sense, the zeolite can have significant effects on the reactions with added nucleophiles, slowing down diffusional encounter but enhancing the reactivity once the nucleophile is in the same cage in the zeolite.

### 4.4. Carbocations in Carcinogenesis

Most chemical carcinogens share the property of forming DNA adducts, a lesion, which if not repaired, can lead to mutagens and cancer. While some carcinogens form these adducts via radical chemistry, the more common mechanism is one where DNA reacts as a nucleophile. The carcinogen is either an electrophile or is converted by metabolism into an electrophile. Of these, there are several important systems where the electrophile is a delocalized carbocation. Scheme 1.9 summarizes two of the widely studied examples. The polycyclic aromatic hydrocarbon (PAH) carcinogens, typified by benzo[a]pyrene (98), undergo metabolic activation to a diol epoxide (99), that (possibly in the presence of DNA) undergoes acid-catalyzed ring opening to a delocalized benzylic-type cation (100). Tamoxifen (101) (Ar = −C₆H₄-4-OCH₂CH₂NMe₂), an antiestrogen employed in the treatment of breast cancer, causes a small number of endometrial cancers. A mechanism has been implicated involving allylic hydroxylation, followed by sulphation to the ester 102. This ester is short lived, undergoing S_N1 ionization to the allylic cation 103. As is typical of delocalized carbocations, 103 and the benzylic cations derived from the PAHs alkylate deoxyribonucleic acid (DNA) at the exocyclic amino groups of adenine and guanine to give relatively stable adducts such as 104. This behavior contrasts dramatically with that of S_N2 alkylating agents, which react principally at N₇.

![Scheme 1.9](image)

Benzylic-type cations derived from PAHs have been studied under superacid conditions, where, not surprisingly, they are relatively stable. Lifetimes in water of diastereomeric forms of the benzo[a]pyrene derivative (100) have been determined by the azide clock approach to be 50 ns. The tamoxifen cation 103 has
been studied directly by LFP; this has a lifetime at pH 7 of 25 μs.\textsuperscript{100} As nucleophiles, guanine and adenine in monomeric forms do not compete effectively with water for such cations.\textsuperscript{102} There are indications, however, that when incorporated in DNA they are significantly more nucleophilic.\textsuperscript{97} The reasons for this are a subject of current investigation. It has been suggested that in the double helix the hydrogen-bonded partner functions as a general base catalyst removing one of the NH protons at the same time as the cation reacts.\textsuperscript{103} There are also indications that delocalized cations preassociate in some manner with DNA before reaction occurs.\textsuperscript{104}

4.5. Carbocations in Biosynthesis

The isoprene pathway produces a diverse range of natural products such as terpenes and steroids. A number of complex biochemical transformations are involved, many of which have been proposed to involve short-lived carbocation intermediates. Two recent studies provide a brief introduction.

The enzyme isopentenyl diphosphate: dimethylallyl diphosphate isomerase catalyzes a key early step whereby \textsuperscript{105} isomerized to \textsuperscript{107} (Eq. 28, OPP = diphosphate). A number of studies, including a recent crystal structure,\textsuperscript{105} have led to a mechanism whereby an intermediate tertiary carbocation \textsuperscript{106} is formed by protonation by a cysteine residue C\textsubscript{67}. Deprotonation is proposed to involve a metal bound glutamate E\textsubscript{116} facing the cysteine in the active site. An interesting aspect of the enzyme is the requirement for a tryptophan residue W\textsubscript{161}, which is suggested to stabilize the cationic intermediate through quadrupole-charge interaction with the indole π electrons.

![Diagram](image)

\[ \text{C}_{67}-\text{S}-\text{H} \quad \text{OPP} \quad \text{C}_{67}-\text{S}^- \quad \text{OPP} \quad \text{C}_{67}-\text{S}^- \]

\[ \begin{align*}
\text{CO}_2^- & \quad \text{E}_{116} \\
\text{105} & \\
\text{CO}_2^- & \quad \text{E}_{116} \\
\text{106} & \\
\text{COOH} & \quad \text{E}_{116} \\
\text{107} &
\end{align*} \]

Squalene synthase catalyzes the first committed step in cholesterol biosynthesis, condensation of two farnesyl diphosphates to form presqualene diphosphate (\textsuperscript{108}), with subsequent rearrangement and reduction to squalene (\textsuperscript{112}) (Eq. 29). It has been proposed that \textsuperscript{108} ionizes to the cyclopropylcarbinyl cation \textsuperscript{109}, which rearranges via a cyclobutyl cation \textsuperscript{110} (which may be a transition state) to a second more stable cyclopropylcarbinyl cation \textsuperscript{111}.\textsuperscript{106} Reductive ring opening produces squalene. The enzyme controls both the regio- and stereochemistry of the reaction. Of interest are model studies suggesting that the rearrangement of \textsuperscript{109} to \textsuperscript{111} is a minor reaction channel without the enzyme, with the preferred reaction being rearrangement to the allylic cation \textsuperscript{113}. Within the active site of the enzyme, the
The transition state for the cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement must be stabilized by $>7.9$ kcal/mol relative to that of the competing rearrangement.

As a general comment, the cations that have been implicated in such biosyntheses are of the type for which analogues have been observed in superacids. However, many of these cations, (e.g., 106 and 109) would have a questionable existence as a free cation in an aqueous solution. This finding raises an interesting question whether they do have more than a fleeting existence within the active site of the enzyme. Does the enzyme provide some form of stabilization, such as that suggested when 106 is formed in the active site of isopentenyl diphosphate: dimethylallyl diphosphate isomerase?

5. CONCLUSION AND OUTLOOK

The study of carbocations has now passed its centenary since the observation and assignment of the triphenylmethyl cation. Their existence as reactive intermediates in a number of important organic and biological reactions is well established. In some respects, the field is quite mature. Exhaustive studies of solvolysis and electrophilic addition and substitution reactions have been performed, and the role of carbocations, where they are intermediates, is delineated. The stable ion observations have provided important information about their structure, and the rapid rates of their intramolecular rearrangements. Modern computational methods, often in combination with stable ion experiments, provide details of the structure of the cations with reasonable precision. The controversial issue of nonclassical ions has more or less been resolved. A significant amount of reactivity data also now exists, in particular reactivity data for carbocations obtained using time-resolved methods under conditions where the cation is normally found as a reactive intermediate. Having said this, there is still an enormous amount of activity in the field.
The roles of carbocations in commercially important hydrocarbon transformations are still not perfectly understood. The same can be said for carbocations in biological systems. Significant questions concerning reactivity still need to be explained. Why do so many reactions of carbocations show constant selectivity, in violation of the reactivity–selectivity principle? Is it possible to develop a unified scale of electrophilicity–nucleophilicity, in particular one that incorporates these parameters into the general framework of Lewis acidity and basicity. Finally, quite sophisticated synthetic transformations are being developed that employ carbocations, based upon insights revealed by the mechanistic studies.

**SUGGESTED READING**


**REFERENCES**


69. See Figure 2 of Ref. 48.


104. R. A. McClelland and G. Marji, unpublished work.
