nonionic, zwitterionic, and amphoteric surfactants and their mixtures, which are more typical of biological membranes and commercial applications.

Ion–Neutral Complexes

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An ion–neutral complex (INC) consists of an incipient ion coordinated to a putative neutral. The two components of the INC are not connected by a normal covalent bond, but they remain bound together by ionic forces such as ion–dipole attraction. INCs are significant because their charged and neutral components are sufficiently separated that they show reactivities similar to those expected for the isolated species. In particular, the components are able to rotate with respect to one another, thus permitting the occurrence of reactions which would be geometrically impossible if the partners were joined by a covalent bond. Consequently, the chemistry of the species within the INC becomes manifest at energies below those needed to cause complete separation to products. One component of the INC may react individually (e.g., an incipient cation may isomerize); alternatively, the ionic and neutral species may react with each other (e.g., by hydrogen transfer).

INCs are potentially relevant in all forms of science in which ions react in dynamic environments. For instance, the behavior of charged species, especially the rearrangement of carbocations, is a central theme of organic chemistry. The ion in an INC occupies a position intermediate between that of the "bare" (unsolvated) ion and that of the corresponding species in solution. Therefore, analysis of the reactions of INCs should reveal the effects induced by a single solvent molecule (the coordinated neutral) on the intrinsic chemistry of the ion. Thus, the archetypal cation isomerization, $CH_3CH_2CH_2^+ \rightarrow (CH_3)_2CH^+$, can be investigated. Furthermore, the influence of the solvent molecule on the rearrangement may be studied by generating INCs containing a variety of different neutral components attached to the $C_3H_7^+$ cation.

The idea that INCs might be important in the unimolecular reactions of ions was developed independently in several laboratories.[1-4] We first postulated INCs to understand the unusual reactivity of certain metastable ions. Metastable ions dissociate after being partly transmitted through the mass spectrometer. Consequently, they are long-lived species, having lifetimes of typically 10–100 μs, and their reactions usually take place with excess energies in the transition states that are small and comparable to those found in solution experiments.[5] Analysis of the fragmentation of metastable ions offers an almost ideal method of investigating the chemistry of ions.[6] Thus, the $C_4H_9O^+$ oxonium ions **1** and **2** (Scheme I) undergo the same reactions (~85% H_2O loss and ~15% CH_2O expulsion) with the same kinetic energy releases. It is not possible to explain this phenomenon by mechanisms involving only "conventional" intermediates (i.e., those in which the connectivity of atoms is adequately described solely in terms of covalent bonds and the normal rules of valency apply). However, the identical behavior of **1** and **2** was logically explained by supposing that these ions interconvert via the INCs **1a** and **2a**, prior to fragmentation.[1,2,7] Equilibration of **1a** and **2a** corresponds to a 1,2-hydride shift in the incipient propyl cation. Since such shifts are known to be extremely facile, both in solution and in the absence of solvent, we considered that interconversion of **1a** and **2a** via this route was a reasonable hypothesis. Subsequent elaboration of the mechanism rationalized the chemistry of **1** and **2** in detail.[2a] Moreover, parallel mechanisms could be used to explain the reactivity of many other ions of diverse structure and functionality.[2b,6]

A further refinement of this general mechanism is the suggestion that **1a** represents the transition state for

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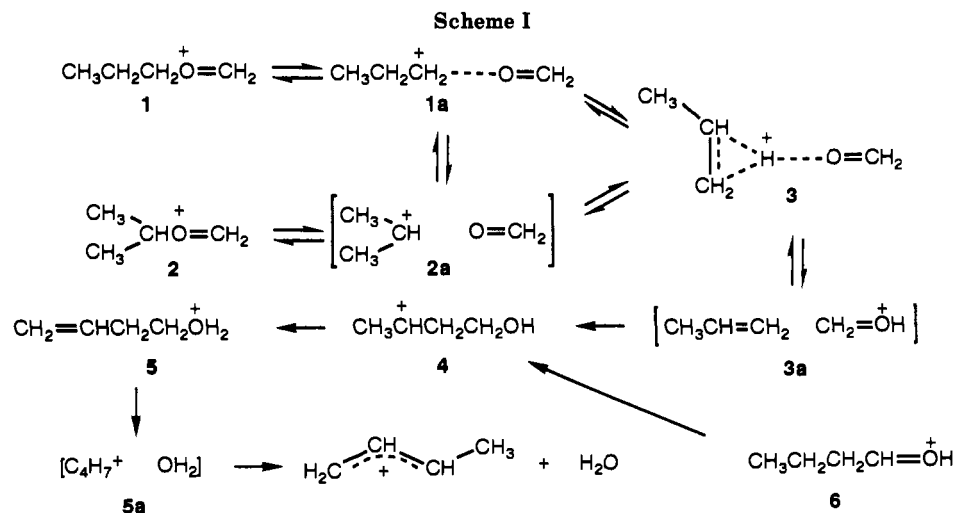(4) Longevialle, P.; Botter, R. *J. Chem. Soc., Chem. Commun.* **1980,** 823.
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Scheme I

$$CH_3CH_2CH_2\overset{+}{O}=CH_2 \rightleftharpoons CH_3CH_2\overset{+}{C}H_2\cdots O=CH_2$$

1   **1a**

$$\begin{matrix}CH_3 \\ \ \ \ \ \ CH \\ CH_2\end{matrix}\overset{+}{\cdots}H\cdots O=CH_2$$ **3**

$$\overset{CH_3}{\underset{CH_3}{\diagdown}}\overset{+}{C}H\overset{+}{O}=CH_2 \rightleftharpoons \left[\overset{CH_3}{\underset{CH_3}{\diagdown}}\overset{+}{C}H \quad O=CH_2\right]$$

2   **2a**

$$CH_2=CHCH_2CH_2\overset{+}{O}H_2 \longleftarrow CH_3\overset{+}{C}HCH_2CH_2OH \longleftarrow \left[CH_3CH=CH_2 \quad CH_2=\overset{+}{O}H\right]$$

5   **4**   **3a**

$$[C_4H_7^+ \quad OH_2] \longrightarrow H_2C\overset{CH}{\underset{+}{\cdots}}\overset{CH}{\cdots}CH\diagup CH_3 + H_2O \qquad CH_3CH_2CH_2CH=\overset{+}{O}H$$

5a   **6**

concerted stretching of the C–X bond and the 1,2-H shift that converts the incipient n-$C_3H_7^+$ into i-$C_3H_7^+$. According to this more rigorous view, **1a** is not really an INC because it does not occupy a tangible energy well, and there is little or no opportunity for the components to rotate around each other. Nevertheless, the behavior of transitional species like **1a** is so closely related both historically and chemically to that of true INCs such as **2a** that it must be considered in this Account.[8]
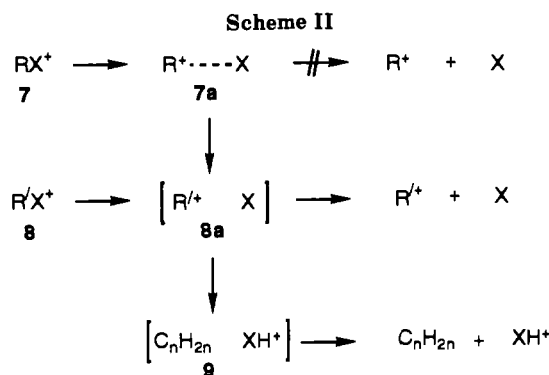
A. The Nature of INCs

1. **Structure and Bonding.** Formation of an INC from the appropriate conventionally bound species involves elongation of the bond between the incipient components. Therefore, the INC is a high-energy species, compared to its precursor ion, because a covalent bond has been broken. However, the disruption of this bond gives freedom to the developing products to react with each other. Rotation of the components around one another becomes feasible; these "orbiting" interactions permit interesting reactions between the putative products to occur. Indeed, it is now generally accepted that this facility for the partners to undergo mutual rotation (the so-called "Longevialle criterion") is an essential feature of a true INC. True INCs (existing in energy wells and to which the Longevialle criterion should apply) are represented in the schemes of this Account by ionic and neutral partners enclosed in square brackets. In contrast, transitional species are depicted with the partners joined by a broken line and without square brackets.

Early work on INCs concentrated on the importance of ion–dipole attractions in binding the components together. In particular, the behavior of the INCs showed a strong dependence on the size of the permanent electric dipole moment (μ) of the coordinated neutral. Equation 1 was found to give a semiquantitative estimate of the stabilization energy, E_s.[7] In this

$$E_s = -\frac{q\mu\cos\theta}{r^2} \qquad (1)$$

simple approximation, q is the charge on the ion, r is the distance between the point charge and point dipole,

Scheme II

$$RX^+ \longrightarrow R^+\cdots X \quad \xslashedrightarrow{} \quad R^+ + X$$

7   **7a**

$$R'X^+ \longrightarrow \left[R'^+ \quad X\right] \longrightarrow R'^+ + X$$

8   **8a**

$$\left[C_nH_{2n} \quad XH^+\right] \longrightarrow C_nH_{2n} + XH^+$$

9

and θ is the angle between the dipole and the charge to dipole axis. In systems such as **1a** and **2a**, in which the coordinated neutral has a large dipole [$\mu(CH_2O) = 2.3\ D^9$], substantial stabilization ($\sim70\ kJ\ mol^{-1}$), relative to the separated products, is possible. This permits **1a** and **2a** to interconvert at lower energies than those needed to promote elimination of CH_2O or H_2O.

Later research revealed that ion-induced dipole attractions, though usually of lesser importance, were also significant, especially for neutral species with a small permanent dipole moment but a large polarizability.[10–12] In addition, other long-range forces play their part in stabilizing INCs. Although quite detailed equations have been adapted from average dipole orientation theory to account for the total binding energies of INCs,[18] a quantitative treatment is unnecessary in this context. The actual values for $-E_s$ can be as large as 100–125 kJ mol^{-1},[7] but stabilizations in the range 50–80 kJ mol^{-1} are more common in INCs containing a neutral having $\mu = 1.5$–2.5 D.

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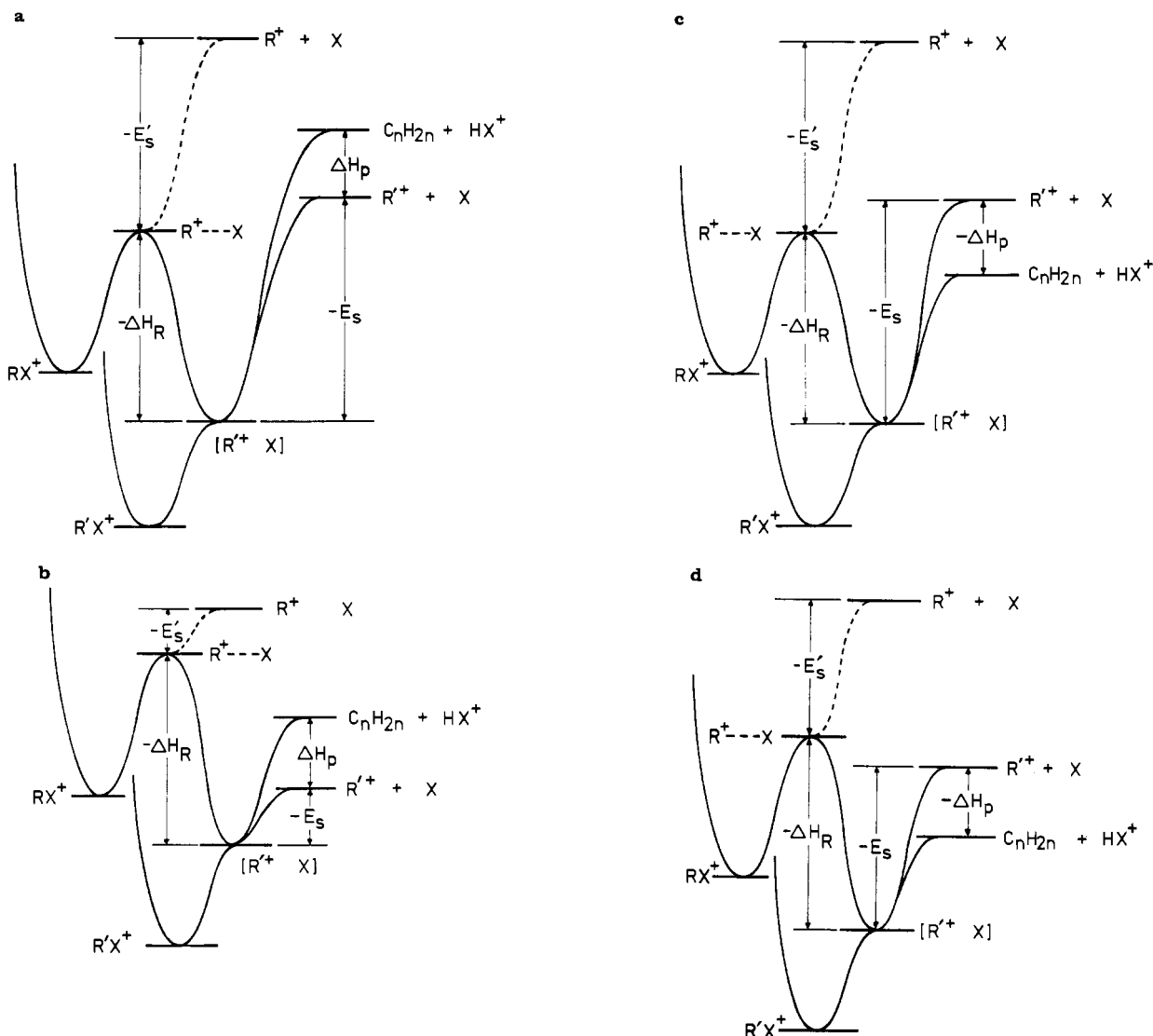
Figure 1. Schematic potential energy profiles corresponding to the situations described in sections A2a–d, respectively.

2. Lifetimes and Reactivities of INCs. Most of the seminal research on INCs was performed on cationic systems.[1–4] An analysis is given below for a generalized case in which the INC contains a developing cation, Scheme II and Figure 1. A parallel analysis can be made for anionic systems, and it is becoming increasingly evident that INCs are relevant in the reactions of anions.[13] Three factors exert a profound influence on the lifetimes, internal energies, and therefore, the reactivities of INCs. The first is the magnitude of $-E_s$, which normally corresponds to the critical energy, E_c, for elimination of X from the INC **8a**. In early work, the stabilization energy, E_s', of **7a** was assumed to be the same as E_s. This supposition is probably an oversimplification, but it is unlikely that E_s and E_s' are markedly different, at least in simple systems. The second factor is the amount of energy $(\Delta H_{R^+ \to R'^+}$, hereafter abbreviated to $\Delta H_R)$ that is released on isomerization of the cation $(R^+ \to R'^+)$ in **7a**. ΔH_R is usually sizably negative (e.g., **1a** → **2a** is exothermic by ~75 kJ mol⁻¹). The third factor is the enthalpy change, ΔH_p, for proton transfer between R'^+ and X. This parameter corresponds to the difference in the proton affinities (PAs) of X and the hydrocarbon (C_nH_{2n}, if R^+ is a saturated carbonium ion $C_nH_{2n+1}^+$) derived by hydride abstraction from R^+.

Unless $-E_s$ is appreciable, **8a** will not be bound with respect to the products of simple cleavage, and no interesting INC-mediated chemistry will be observed. Four important general cases occur in systems in which $-E_s > 0$.

(a) $-E_s > -\Delta H_R$ and ΔH_p is positive (i.e., proton transfer is energetically unfavorable). Interconversion of **7a** and **8a** takes place below the threshold for decomposition of either. This is the situation for **1a** and **2a**, Scheme I. Facile interconversion of **7a** and **8a** in this way is detected by ²H-labeling experiments,[14] which reveal that exchange of the protium and deuterium atoms within the original propyl groups occurs when the n-propyl and isopropyl cations equilibrate. In addition, the quantity of kinetic energy (KE) released when dissociation eventually takes place is abnormally low: These fragmentations are characterized by narrow Gaussian metastable peaks, with $T_{1/2}$ values (KE release estimated from the width at half-height of the corresponding metastable peaks) as low as 0.2–0.5 kJ mol⁻¹.[1,2,7]

(b) $-E_s < -\Delta H_R$ and ΔH_p is positive. In these systems, isomerization of the cation in **7a** is irreversible, and this constitutes the rate-limiting step in decomposition of **7**. Consequently, excess energy is present in the transition state when **8a**, generated by rear-
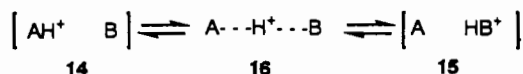
rangement of **7a**, fragments. This excess energy causes a modification in the chemistry of **8a**, which dissociates more rapidly than if it had been formed from **8**.[15] Part of the energy is partitioned as translation, so causing an increase in the KE release for dissociation.[5] Therefore, the $T_{1/2}$ value for loss of X from **7** exceeds that for the same reaction starting from **8**.[15] These conditions are often satisfied when the neutral component of the INCs has only a small dipole moment ($\mu \simeq 0$). Thus, $CH_3CH_2CH_2CO^+$, **10**, and $(CH_3)_2CHCO^+$, **11** (the analogues of **1** and **2**, in which $CH_2{=}O$ is replaced by CO), expel CO, but with different KE releases. A very small $T_{1/2}$ value is found for CO loss from **11**, but that accompanying CO elimination from **10** is ca. 7 times greater.[1,16] The contrast in the behavior of **1** and **2**, compared to that shown by **10** and **11**, is immediately evident from the appearance of the corresponding metastable peaks for expulsion of CH_2O and CO, respectively. Parallel trends in the $T_{1/2}$ values are found in many other $C_3H_7X^+$ systems (X = Br,[16] NH_3,[17] etc.) in which X has a negligible or comparatively small dipole moment.

In these cases, it could be argued that the lifetime of **8a** formed from **7a** is too short to allow rotation of the partners to compete with dissociation; i.e., the Longevialle criterion is no longer satisfied, and **7a** is not, strictly speaking, a true INC. Despite this caveat, however, case b deserves inclusion for the sake of completeness.

(c) $-E_s > -\Delta H_R$ and ΔH_p is negative. This situation occurs when proton transfer between R'^+ and X affords more favorable products than those given by cleavage to R'^+ and X. Dissociation of **8a**, via proton transfer, is usually energetically preferable to reversion to **7a**, even if both **7a** and **8a** are strongly bound. Consequently, isomerization of the incipient cation is the rate-limiting step in dissociation of **7a**, and increased $T_{1/2}$ values accompany this process. Thus, $CH_3CH_2CH_2^+O{=}CHCH_3$, **12**, and $(CH_3)_2CH^+O{=}CHCH_3$, **13**, which are higher homologues of **1** and **2**, both expel C_3H_6, but a larger $T_{1/2}$ value is found for fragmentation of **12**.[7] This phenomenon occurs despite the fact that **12a** and **13a** are more extensively stabilized by ion-dipole attractions than are **1a** and **2a** [μ-$(CH_3CH{=}O) > \mu(CH_2{=}O)$[9]]. It is possible to visualize a situation in which ΔH_p is sufficiently small and negative that $(-E_s)$ still exceeds $(-\Delta H_R + \Delta H_p)$. Rearrangement of R^+ to R'^+ should now be reversible; furthermore, both **7** and **8** would then react via hydrogen transfer ($[C_nH_{2n}]$ elimination). However, few, if any, examples of this behavior are known.

(d) $-E_s < -\Delta H_R$ and ΔH_p is negative. Proton transfer ($[C_nH_{2n}]$ loss, via **8a** and **9**) dominates the chemistry of **8**. In these circumstances, the relative magnitude of ΔH_p and ΔH_R assumes a special significance. If $-\Delta H_R$ is sufficiently great compared to $-\Delta H_p$, isomerization of **7a** to **8a** may release enough energy to allow direct dissociation (X expulsion) to compete with the energetically more favorable H-transfer process ($[C_nH_{2n}]$ loss). In some systems (e.g., X = NH_3[17]), rearrangement of a primary to a secondary cation provides sufficient energy to satisfy this criterion. In others, when $-\Delta H_p$ is bigger (e.g., X = $R^1R^2C{=}NH$[18a,19]), elimination of X

Scheme III

$$\left| \; AH^+ \quad B \; \right| \rightleftharpoons A{\cdots}H^+{\cdots}B \rightleftharpoons \left| A \quad HB^+ \right|$$

$$\text{14} \qquad\qquad\qquad \text{16} \qquad\qquad\qquad \text{15}$$

can occur only after rearrangement of an incipient primary cation to a tertiary isomer has taken place.

The correlation between the occurrence of the higher energy dissociation route (X loss) and the presence of an unstable cation, prone to ready isomerization, is at first sight surprising. A naive interpretation (preferential elimination of X when R^+ is a more stable cation) predicts the opposite trend. However, the hypothesis involving exothermic rearrangement of R^+ neatly accounts for the experimental trend, since only in these cases is additional energy supplied to **8a**, so permitting X loss to compete with $[C_nH_{2n}]$ expulsion. This explanation is supported by the observation that the low-energy ions (**7**) can be made to lose X if they are energized by collision. For instance, of the isomeric $R^1R^2C{=}NH^+C_4H_9$ immonium ions, those containing an isobutyl group are unique in expelling an imine ($R^1R^2C{=}NH$), because only in these ions is there the possibility of rearranging an incipient isobutyl to a *tert*-butyl cation. Nevertheless, the isomeric species in which the original *N*-alkyl substituent has the *tert*-butyl structure do show elimination of an imine in their collision induced dissociation spectra.[19]

The reactions of metastable $PhOR^{\bullet+}$ species, which were historically important in the development of the concept of INC-mediated chemistry,[3] exhibit a parallel trend. Only $PhOC_4H_9^{\bullet+}$ ions containing an isobutyl group expel $PhO^{\bullet}$; all the rest eliminate solely C_4H_8, via hydrogen transfer.[20]

3. Relationship of INCs to Proton-Bridged Complexes. Interconversion of a pair of INCs, **14** and **15**, via hydrogen transfer between the partners can be envisaged to occur via a structure, **16**, in which two incipient neutrals are attached to a common proton, Scheme III. These proton-bridged complexes (PBCs) are familiar species in bimolecular ion chemistry, but MO calculations[21] and other considerations suggest that they may sometimes be involved in the unimolecular reactions of ions. The PAs[22] of A and B are important in determining the geometries and relative stabilities of **14**, **15**, and **16**.

When A and B have similar PAs, **14** and **15** often have similar energies, especially if the capacities of A and B to stabilize a cation are comparable. These factors facilitate rapid interconversion of **14** and **15**, probably via **16**. This situation can be detected by ^2H-labeling experiments, which reveal that the protium or deuterium atoms on the appropriate sites of labeled analogues of **14** and **15** are exchanged prior to fragmentation.[23] Moreover, eventual dissociation is characterized by an abnormally small KE release in these cases. In contrast, when B has a substantially greater PA than A (by $\sim$50 kJ mol^{-1}, or more), proton transfer (**14** → **16**) is essentially irreversible,[24] and a greater KE

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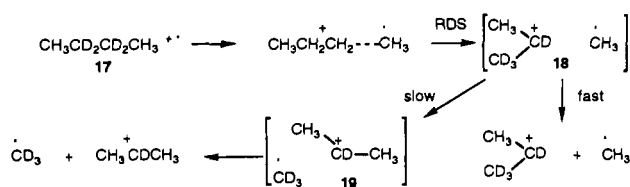(21) Swanton, D. J.; Marsden, D. C. J.; Radom, L. *Org. Mass Spectrom.* **1991**, *26*, 227.
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Scheme IV

release accompanies the final fragmentation.[23]

Although a system in which 14, 15, and 16 each exist in an energy well may be theoretically feasible, such a possibility is rarely, if ever, encountered in practice. Typically, 14 and 15 occupy energy wells, and 16 represents the transition state for their interconversion.

B. Reactions of INCs

A vast range of reactions have been interpreted in terms of mechanisms in which INCs play central roles,[11,12] and an exhaustive treatment is impossible in this Account. However, three main categories of INC-mediated processes can be identified.

1. Cation Rearrangements. This sort of reaction, which has already been illustrated by the behavior of $CH_3CH_2CH_2CO^+$ and $(CH_3)_2CHCO^+$,[1,16] is common. It is often encountered in combination with subsequent H-transfer steps, as exemplified several times in section A2.

Simple cleavages of ions frequently lead to energetically unfavorable products. These processes rarely occur, especially at low internal energies, because they are preempted by rearrangement of the developing ion. For example, alkyl radical elimination from ionized n-alkanes does not yield a high-energy primary carbonium ion; instead, formation of a thermodynamically more stable secondary or tertiary isomer occurs.[25] This observation, and the results of ^2H- and ^{13}C-labeling experiments,[26,27] can be understood if isomerization of the incipient primary cation takes place. Thus, $CH_3CD_2CD_2CH_3^{\cdot+}$ expels $CH_3^{\cdot}$ and $CD_3^{\cdot}$, but almost no $CH_2D^{\cdot}$ or $CHD_2^{\cdot}$; this apparently puzzling result is explained by Scheme IV.[10]

2. Hydrogen-Transfer Reactions. (a) Single Hydrogen Transfer (SHT). SHT is perhaps the most common of all INC-mediated processes. An exceedingly large number of ions fragment via cleavage of a single bond with an associated hydrogen transfer; in normal mass spectra, this leads to peaks displaced by one m/z unit from the values expected on the basis of rupture of the relevant bonds. Such processes, which confuse the unwary interpreter, are readily rationalized by supposing that H transfer occurs within an INC.

The hydrogen transferred often comes from a carbon atom immediately adjacent to the site of bond fission. However, hydrogen transfer from more distant positions is found in some cases. Indeed, long-range hydrogen transfers take place between substituents located on opposite ends of conformationally rigid steroid structures.[4,28,29] This phenomenon is one of the most com-

pelling pieces of evidence supporting the hypothesis that INCs play a significant role in ion chemistry.

Onium ions of general structure 20 often show SHT, Scheme V. The observed fragmentation can be predicted by assuming that the component of the pair of INCs, 20a and 20b (or, as originally formulated, the PBC, 21), having the greater PA retains the proton.[1] Thus, $C_2H_5^+O{=}CH_2$ expels C_2H_4 [PA(CH_2O) > PA(C_2H_4)], whereas both isomers of $C_3H_7^+O{=}CH_2$ eliminate CH_2O [PA(C_3H_6) > PA(CH_2O)]. Similarly, immonium ions (Z = NH, NR^7) typically lose alkenes because PA(imines) > PA(alkenes).

Isomerization of the developing cation in 20a frequently takes place. When this step is rate-limiting, the final hydrogen transfer shows unexpected specificity. For example, the immonium ions $RCH{=}NH^+$-$CH_2CH_2CH_3$ do not show exclusive β-hydrogen transfer in propene elimination.[18a,d,30] The contributions from α- and γ-hydrogen transfer are neatly explained by postulating unidirectional isomerization of the n-propyl to an isopropyl cation within an INC, followed by transfer to nitrogen of one of the four protiums or two deuteriums contained in the two methyl groups. Thus, $RCH{=}NH^+CD_2CH_2CH_3$ (R = H, CH_3) ions lose $C_3H_4D_2$ and C_3H_5D in a ratio (68:32) close to 2:1, Scheme VI.[18a,d]

SHT is encountered in many odd-electron systems, in which it sometimes involves hydrogen atom, as opposed to proton, transfer. This modification does not, however, make much difference to the basic energetic arguments presented in section A2.

For instance, alkane loss takes place from numerous ionized alkanes,[10,25,26] small secondary alcohols, and the derived ethers,[23,31-34] Scheme VII. In certain systems, for which 22a and 23 have similar energies, reversible hydrogen transfer is observed, as indicated by labeling experiments and the abnormally small KE release that accompanies the final dissociation step.[23] Ionized ketones frequently expel alkanes via a parallel mechanism, with production of ionized ketenes.[31,34]

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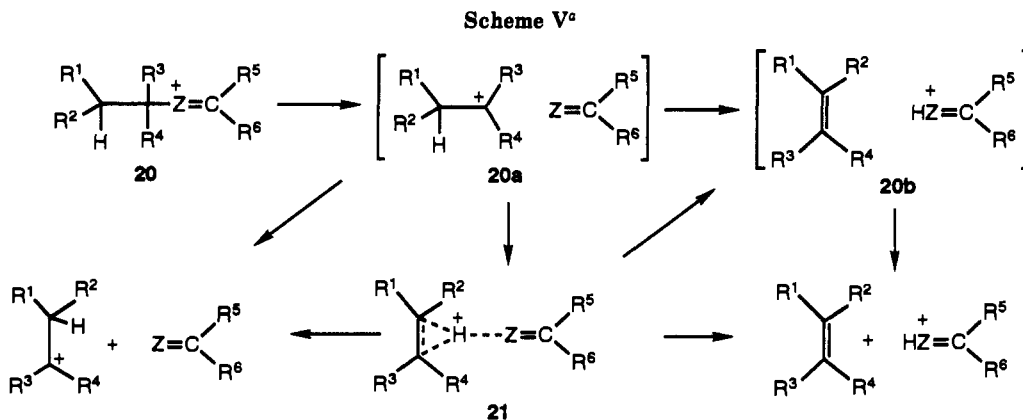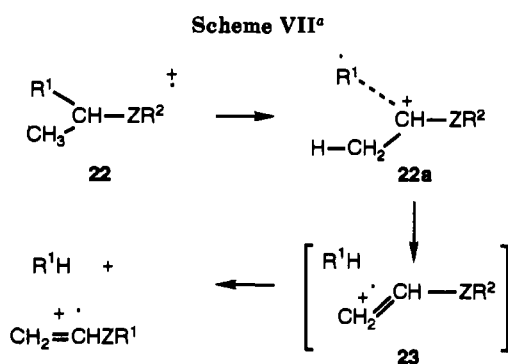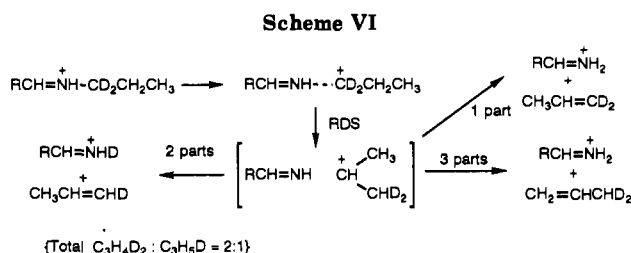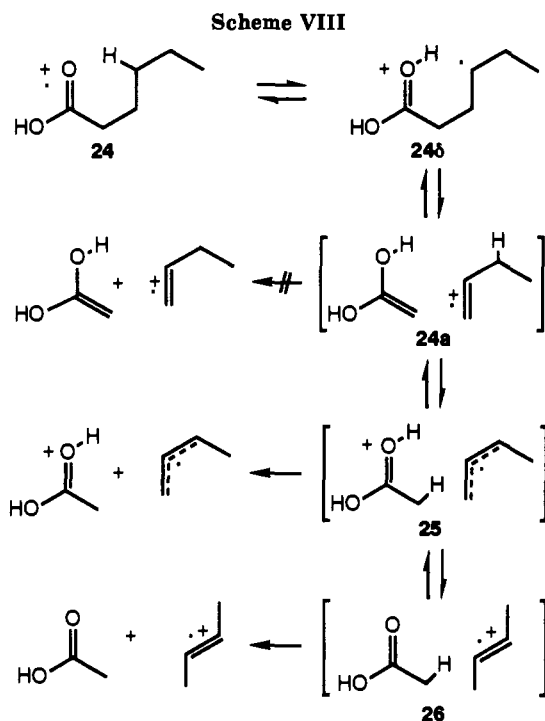
Scheme V[a]

$^aR^1-R^7$ = H, alkyl; Z = O, NH, NR^7.

Scheme VI

{Total $C_3H_4D_2$: C_3H_5D = 2:1}

Scheme VII[a]

^aZ = O, CH$_2$; R^1 = alkyl; R^2 = H, alkyl.

Scheme VIII

(b) Reciprocal Hydrogen Transfer (RHT). When approximately thermoneutral hydrogen transfers can occur between the cation and more than one site in the neutral, reversible hydrogen exchange opens a route for isomerization of the neutral. These RHTs are exemplified by the CH$_3$CH=O$^+$CH$_2$CH$_2$CH$_2$CH$_3$ system, in which butene loss involves a contribution from hydrogen transfer from each of the four sites in the butyl chain. This phenomenon has been rationalized by proposing that hydrogen exchange occurs via equilibration of the INCs [CH$_3$CH=O   C$_4$H$_9$$^+$] and [CH$_3$CH=OH$^+$ C$_4$H$_8$].[26]

RHT provides a route for eventual formation of the most stable ion and neutral structures accessible by hydrogen (as opposed to skeletal) rearrangement. Thus, at low energies, fragmentation of n-C$_5$H$_{11}$CO$_2$H$^{•+}$, via the McLafferty rearrangement, affords CH$_3$CH=

CHCH$_3$$^{•+}$ and CH$_3$CO$_2$H.[35] Production of only the less stable isomers, CH$_3$CH$_2$CH=CH$_2$$^{•+}$ and CH$_2$=C(OH)$_2$, would be expected on the basis of the conventional mechanism.

(c) Double Hydrogen Transfer (DHT). Occasionally, a second hydrogen transfer is energetically favorable after SHT has occurred. These DHTs are less common than SHTs, but they are far from rare. DHTs often take place via routes involving both INCs and DIs (distonic ions,[36,37] in which the formal charge and spin sites are localized on separate "heavy" atoms, typically separated by one or more sp^3 carbon atoms). An example is furnished by the process that yields the "McLafferty + 1" peak[38] (so called because it appears at one m/z unit above the peak arising by the McLafferty rearrangement) in the mass spectra of carbonyl compounds.[39] The unified mechanism of Scheme VIII accounts for this fragmentation.
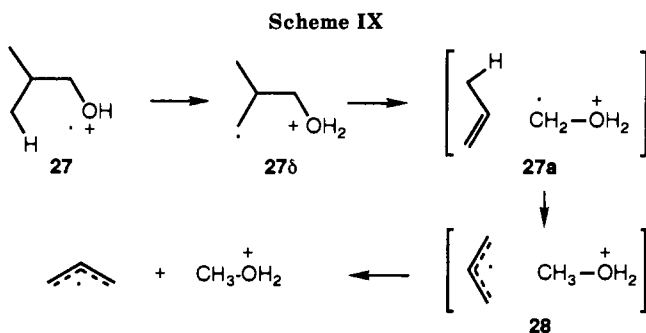
This class of DHT results in elimination of a stabilized allyl radical, so providing part of the thermodynamic driving force for the isomerization steps. Similarly, ionized isobutanol expels C$_3$H$_5$$^•$,[40] and ionized neopentylamine eliminates C$_4$H$_7$$^•$.[41] Some aspects of these DHTs have been the subject of controversy, but

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Scheme IX

Scheme X

Scheme XI^a

^{a} R = CH$_3$, C$_2$H$_5$.

a generally accepted mechanism is illustrated in Scheme IX.[42]

DHT is also favored when it yields an ionic product of particularly low energy. Thus, for example, many RCO$_2$C$_n$H$_{2n+1}$ ($n > 2$) esters display prominent [M − C$_n$H$_{2n-1}$]$^+$ signals in their mass spectra.[43] Energy measurements reveal that [M − C$_2$H$_3$]$^+$ and [M − C$_3$H$_5$]$^+$, formed by expulsion of a vinyl and allyl radical, respectively, from ionized ethyl and propyl esters, have the [RC(OH)$_2$]$^+$ structure.[44] Formation of this exceptionally stable carbonyl protonated isomer of the parent acid is thermodynamically so favorable that is occurs even when it involves loss of a relatively unstable vinyl radical. Ionized inorganic esters frequently behave similarly.[45]

(d) Triple Hydrogen Transfer (THT). A further hydrogen transfer, giving overall THT, is sometimes observed. THT is relatively rare, though definite examples of it are known.[46]

3. Rearrangements Involving INC Recombination. This category of processes embraces all those in which the components of an INC recombine to form an isomeric structure in which a new bond connecting "heavy" atoms has been made. This possibility provides an explanation for many previously baffling skeletal rearrangements.

For instance, numerous oxonium ions such as C$_2$H$_5$$^+$O=CH$_2$ and C$_3$H$_7$$^+$O=CH$_2$ eliminate H$_2$O.[2] This extraordinary process, which necessitates rupture of three C−O bonds and formation of two O−H linkages, is logically explained by the route illustrated in Scheme I.[47] Reorganization of the INC **3a**, via nucleophilic addition of CH$_3$CH=CH$_2$ to the polarized π-bond of CH$_2$=OH$^+$, gives the open-chain cation, **4**; a 1,5-H shift leads to protonated homoallyl alcohol, **5**. Cleavage of **5**, with an associated 1,2-H shift (possibly within the INC **5a**), then affords 1-methylallyl cation and H$_2$O. This mechanism is supported by the behavior of **6**, which also expels H$_2$O, and by extensive ^{2}H-labeling data.[2,19]
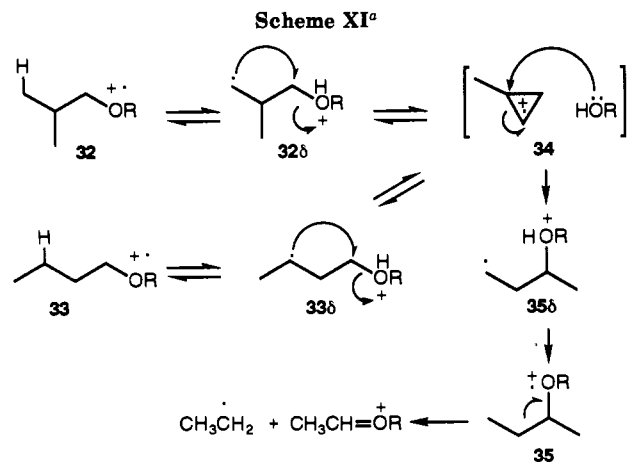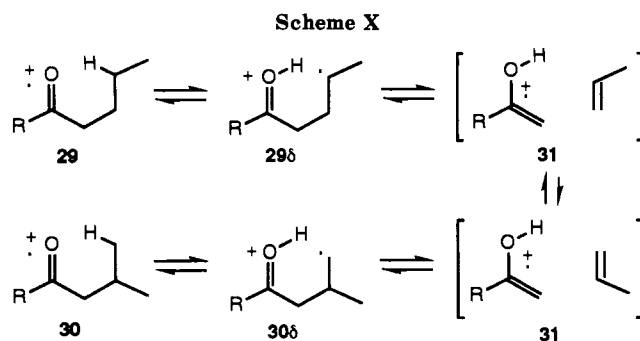
The immonium ion analogues of **1** and **2** do not, however, undergo the corresponding process (NH$_3$ loss). This contrast reflects differences in the underlying energetics: the key recombination step, **3a** → **4**, is favorable in the oxonium ion series, but the analogous step in the case of immonium ions is very unfavorable.

Skeletal rearrangements of ionized carbonyl compounds[48,49] and ethers[50,51] have also been interpreted by

similar mechanisms involving recombination of the components of INCs, Schemes X and XI, respectively.

C. Establishing the Existence of INCs

It is hoped that this Account will convey a clear impression of the range of ionic reactions that can be interpreted by means of INCs. The success of INC-mediated mechanisms in providing logically satisfying explanations for many processes that previously appeared to be bizarre can hardly be disputed. However, neither this success nor the findings of MO calculations which implicate INCs in the fragmentation of certain ions are sufficient to convince the skeptical experimentalist that INCs are genuine intermediates capable of surviving for many bond vibrations. Much of the current interest in INCs is focused on devising experiments which will demonstrate their existence to the satisfaction of skeptics. Since INCs cannot be observed directly by spectroscopic methods available at present, efforts to verify their existence must be inferential in nature. Three principal approaches are possible.

1. Analysis of Isomerizations Associated with INCs. If rearrangements that would otherwise be inexplicable can be interpreted in terms of INCs, this is evidence in favor of the intermediacy of INCs, especially if the behavior of uninvestigated ions can be correctly predicted. The rearrangements may be reversible (e.g., the RHTs discussed in section B2b[2b]) or irreversible (e.g., the behavior of immonium ions depicted in Scheme VI[18]). The predictive capacity is illustrated in the latter system by the hypothesis that

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$CH_3CD_2CH_2{}^+N(CH_3)=CH_2$ should isomerize to $[CH_3CD^+CH_2D\ CH_3N=CH_2]$ and so expel C_3H_5D and $C_3H_4D_2$ in the ratio of 1:5 (β-D and β-H transfer, respectively). This expectation was subsequently verified by experiment (actual ratio 1:4.3); in contrast, a 1,2-elimination, without isomerization of the propyl cation, predicts exclusive C_3H_5D loss.

2. Demonstration of Reversible Hydrogen Exchange between the Components of an INC. This method is exemplified by the fragmentation of ionized ethers (section B2a); in this case, the abnormally low KE releases that accompany dissociation provide additional evidence supporting the involvement of INCs.[23]

3. Verification That the Longevialle Criterion Is Satisfied. This technique is probably the most powerful. It is illustrated by the long-range hydrogen transfers that are observed between substituents on steroid structures.[4,28,29] Such processes cannot be understood without supposing that detachment of one substituent occurs, followed by mutual rotation of the ionic and neutral components, thus facilitating hydrogen transfer between groups which were originally locked apart.

Future research will probably be directed toward refining existing methods and developing new criteria for demonstrating the intermediacy of INCs. It is especially desirable to devise means whereby the circumstances in which INCs are encountered can be predicted.

D. Conclusion and Prognosis

The advent of INCs has initiated a debate that has led to a thorough revision of many aspects of mass spectrometry. Moreover, it is clear that the chemistry displayed by INCs is inherently of wide interest in other fields, notably physical organic chemistry and theoretical chemistry. There is good reason to believe that INCs will provide a valuable unifying concept for interpreting the diverse reactions of ions which are encountered in many scientific disciplines.

Sponge Sterols: Origin and Biosynthesis[†]

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The pioneering work of Bergman, begun in the late 1940s, pointed toward the existence of a variety of sterols in marine sponges.[1] Not until the 1970s, however, was the potential hinted at by his work realized. The characterization of a bewildering variety of novel sterols[2] was made possible by the development of sophisticated analytical techniques necessary for the separation and structure elucidation of these sterols. These techniques, notably gas chromatography alone or coupled with mass spectrometry, high-field NMR, and HPLC, heralded the renaissance of the sterol field that continues today. This renaissance has branched in three distinct directions.

The initial discovery of sterols with structures having few or no terrestrial counterpart prompted a continuing search for novel sterols.[2] As very recent examples, we cite the novel cyclopropane-containing sterols šormosterol (1b)[3] and 29-norhebesterol (2b);[4] a multiply alkylated sterol, sutinasterol (3f);[5] and the cyclopropene-containing sterol (23S)-23H-isocalysterol (4b)[6] (Charts I and II).

The discovery of such novel sterols—by now well in excess of 100—prompted the obvious question of their biosynthesis. The answer to this question was delayed until satisfactory protocols were established for feeding the sterol precursors to the sponges and keeping them alive for the period of incorporation.[7] There are many

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