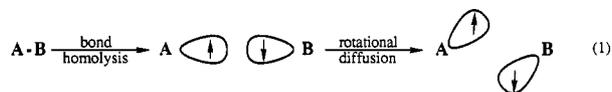# Gas-Phase Analogues of Cage Effects

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When a molecule dissociates, three types of transport phenomena compete with recombination of the fragments. Translational diffusion carries the cleavage products into the bulk medium, diluting them so that reencounters steadily become less probable with time. Heat conduction equilibrates the energies of the products with that of the medium, dissipating any excess energy left over from surmounting an activation barrier. Finally, rotational diffusion washes out the angular correlations dictated by the transition state. At the instant a bond is broken the fragments point toward one another in a way that is most conducive to re-forming the bond. The memory of this nascent relative orientation is soon lost as the fragments start to rotate independently of each other. This is portrayed schematically in eq 1.

$$A \cdot B \xrightarrow{\text{bond}}_{\text{homolysis}} A \bigcirc \quad \bigcirc B \xrightarrow{\text{rotational}}_{\text{diffusion}} A \bigcirc \quad \bigcirc B \quad (1)$$

David McAdoo grew up in western Pennsylvania, received his bachelor's degree from Lafayette College and his Ph.D. from Cornell University (with F. W. McLafferty), and did postdoctoral work at Johns Hopkins University. He has been employed by the USDA, Union Carbide, and Jet Propulsion Laboratory, and he is currently a member of the Marine Biomedical Institute and professor of human biological chemistry and genetics, cellular physiology and membrane biophysics, and neurosciences at the University of Texas Medical Branch at Galveston. Other scientific interests are neurochemistry and neurophysiology. Nonprofessional interests include the exploration of caves.

Tom Morton was born in Los Angeles, where his forebears (both Hellman and Morton) were employed by the motion picture industry. He received his AB from Harvard in 1968 in classics (Greek) and fine arts and his Ph.D. from Caltech under the joint direction of R. G. Bergman and J. L. Beauchamp. Since 1972 he has served on the chemistry faculties of Brown and Brandeis Universities and, from 1981, the University of California, Riverside, where he is professor of chemistry. His research centers around the chemical consequences of internal rotation, including molecular recognition of conformationally mobile molecules by chemosensory systems. He is also affiliated with the Department of Neuroscience.

In condensed phases many intermolecular reactions proceed at rates competitive with translational diffusion. Although heat conduction and rotational diffusion may go to completion, the products of covalent bond fission often sojourn in one another's vicinity long enough to react with each other. Attenuation of translational diffusion relative to chemical reaction is often attributed to a cage effect[1] in which separation of the fragments is inhibited by surrounding solvent molecules. Two caged partners that are born together are sometimes called a geminate pair. One hallmark of cage effects is that rotational diffusion is nearly as fast as (or faster than) the reaction between geminate fragments.[2] Intramolecular rearrangements within the fragments frequently take place as well. Under these circumstances, characteristic products, which could not have been produced by simple unimolecular rearrangements of the intact starting molecules, are formed.

Gas-phase cage effects have been documented, in which photodissociation fragments collide with and ricochet off of nearby inert gas atoms.[3] Collision frequency falls off with the density of bath gas. If there is no bath gas, attraction between a pair of fragments can still produce many of the same features, provided that one of the fragments bears an electric charge. This means that cleavage products from ionized precursors,

in which charge–dipole and charge–induced dipole forces persist long after the fragments have passed out of covalent bonding range, may exhibit behavior at low pressure that parallels cage effects. Such analogues of cage effects might be called "leash" effects (in keeping with the metaphor of restraining an animal). The electrostatic "leash" is elastic and easily broken. Such gas-phase analogues of cage effects operate both in unimolecular and in bimolecular reactions.[4-9] Translational diffusion is not inhibited by solvent molecules. It is constrained, instead, by attraction between the geminate fragments. When intermolecular collisions are infrequent, energy dissipation (as distinguished from internal thermal relaxation) also becomes extremely slow. Nevertheless, processes analogous to rotational diffusion remain rapid, and their operation has been put forth as a defining characteristic of ion–neutral complexes,[8,9] which are gas-phase analogues of caged intermediates at the low-pressure limit.

This Account will focus on positively charged geminate pairs in the gas phase, where ion–neutral complexes behave much like ion pairs in solution. When formed by fission of a single bond, both can be viewed as isomers of the reactants in which ionic bonding remains after covalent bonds have been served. During the past decade, hundreds of articles have appeared describing dissociative reactions that involve ion–neutral complexes. Recent reviews[5,8] list a variety of complex-mediated decompositions. Ion chemists have stressed over the past 30 years that energized, gaseous ions often behave much like their thermalized counterparts in condensed media,[10] and it is the object of this Account to illustrate parallels between gas-phase and solution reactions.

A unifying characteristic of ion–neutral complexes is that at least one partner can rotate relative to the other about an axis perpendicular to the bond that has cleaved. Many weakly bound ions correspond to local potential energy minima that look like hydrogen-bonded or covalently bonded species but behave like "leashed" intermediates in the gas phase. These include $\cdot CH_2CH_2OH_2^+$,[11,12] $H_2O\cdots H_2C=C=O^{\cdot+}$,[11] $CH_2=CHOH^{\cdot+}\cdots OH_2$,[12] and $\cdot CH_2OH\cdots O(CH_3)CH_2^+$[13] (isomers, respectively, of the molecular ions of ethanol, acetic acid, ethylene glycol, and 2-methoxyethanol). The last of these is drawn as a pair of resonance structures

in eq 2. While this intermediate can be pictured as a radical that is hydrogen bonded to a cation, experiment suggests that the fragments must turn so that hydrogen bonding is lost.[14] The major reaction product at low energies is Me_2OH^+. This results from expulsion of a formyl radical subsequent to a double hydrogen transfer, but isotopic labeling demonstrates that the regiochemistry expected for a hydrogen-bonded intermediate is not obeyed. If the radical cation depicted in eq 2 (which preserves the intramolecular hydrogen bond of the neutral precursor) were unable to rotate one part relative to the other in the plane of the paper, then hydrogens would have been expected to transfer from oxygen to oxygen and from carbon to carbon. Instead the hydrogen originally bonded to oxygen (H_a) ends up bound to carbon, and vice versa. There must be in-plane bending motions that disrupt hydrogen bonding.
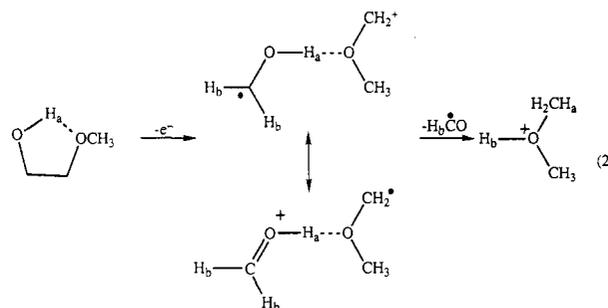
In the large amplitude limit this kind of behavior becomes analogous to rotational diffusion within cages. For geminate pairs in solution, rotational diffusion cannot be detected unless it competes effectively with recombination of the partners. Recombination may be impeded by a potential energy barrier or by a bottleneck that arises when degrees of freedom are constrained (or by both). Similarly, in the gas phase, ion–neutral complexes (which are fluxional) do not instantaneously collapse to the comparatively static structures that can be formed by vertical ionization of neutral precursors. If a potential energy barrier intervenes, the intermediate has been called a type 1 complex; if the barrier is due solely to a bottleneck, it is a type 2 complex.[9] Ion–neutral complexes are usually represented by drawing the partners enclosed by a pair of brackets. Ab initio calculations sometimes reveal potential energy minima corresponding to the bracketed species,[12,15] but the existence (or absence) of such minima may have little relevance to the fluxional nature of the complex or the likelihood of its intermediacy. Within a complex, energy randomization is often assumed to be fast; i.e., rapid exchange is assumed among all the internal degrees of freedom, including energy transfer between partners within the complex.[16,17] However, at energies near threshold, internal vibrational relaxation may become slow.[18]

(1) (a) Franck, J.; Rabinowitch, E. *Trans. Faraday Soc.* **1934**, *30*, 120–131. (b) Rabinowitch, E.; Wood, W. C. *Trans. Faraday Soc.* **1936**, *32*, 1381–1387.

(2) For a recent example, see: Merritt, M. V. et al. *J. Am. Chem. Soc.* **1990**, *112*, 3560–3566.

(3) Murrell, J. N.; Stace, A. J.; Danmell, R. *J. Chem. Soc., Faraday Trans. 2* **1978**, *74*, 1532–1539.

(4) Morton, T. H. *Tetrahedron* **1982**, *38*, 3195–3243.

(5) McAdoo, D. J. *Mass Spectrom. Rev.* **1988**, *7*, 363–393.

(6) Hammerum, S. In *Fundamentals of Gas Phase Ion Chemistry*; K. R. Jennings, Ed.; Kluwer Academic Publishers: Dordrecht, 1990; pp 379–390.

(7) Bowen, R. D. *Acc. Chem. Res.* **1991**, *24*, 364–371.

(8) Longevialle, P. *Mass Spectrom. Rev.* **1992**, *11*, 157–192.

(9) Morton, T. H. *Org. Mass. Spectrom.* **1992**, *27*, 353–368.

(10) (a) McLafferty, F. W. In *Determination of Organic Structures by Physical Methods*; Nachod, B. C., Phillips, W. D., Eds.; Academic Press: New York, 1962; pp 93–95. (b) Wendleboe, J. F.; Bowen, R. D.; Williams, D. H. *J. Am. Chem. Soc.* **1981**, *103*, 2333–2339. (c) McAdoo, D. J.; Hudson, C. E. *Int. J. Mass Spectrom. Ion Processes* **1984**, *62*, 269–276.

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(12) Postma, R.; Ruttink, P. J. A.; van Duijneveldt, F. B.; Terlouw, J. K.; Holmes, J. L. *Can. J. Chem.* **1985**, *64*, 2798–2804.

(13) Biermann, H. W.; Morton, T. H. *J. Am. Chem. Soc.* **1983**, *105*, 5025–5030.

(14) (a) Audier, H. E.; Milliet, A.; Leblanc, D.; Morton, T. H. *J. Am. Chem. Soc.* **1992**, *114*, 2020–2027. (b) Cao, J. R.; George, M.; Holmes, J. L.; Sirois, M.; Terlouw, J. K.; Burgers, P. C. *J. Am. Chem. Soc.* **1992**, *114*, 2017–2020.

(15) Postma, R.; Ruttink, P. J. A.; van Baar, B. L. M.; Terlouw, J. K.; Holmes, J. L.; Burgers, P. *Chem. Phys. Lett.* **1986**, *123*, 409–412.

(16) Chronister, E. L.; Morton, T. H. *J. Am. Chem. Soc.* **1990**, *112*, 133–139.

(17) Morton, T. H. *Org. Mass Spectrom.* **1991**, *26*, 18–23.

(18) McAdoo, D. J.; Traeger, J. C.; Hudson, C. E.; Griffin, L. L. *J. Phys. Chem.* **1988**, *92*, 1524–1530.

The forces that hold the partners together in ion–neutral complexes are generally described using the electrostatic multipole approximation. Classical theory suggests that ion–dipole forces dominate (so long as the distance r that separates the partners is large compared to the dimensions of the fragments). Two terms express the potential energy, an ion–permanent dipole potential (which falls off as $1/r^2$ for a fixed orientation of the dipole toward the charge) and an ion–induced dipole attraction (which falls off as $1/r^4$ and is roughly proportional to the molecular volume of the neutral).[6] The effect of r on stability in the absence of a permanent dipole has been used to explain why the fragmentation in eq 3 favors simple cleavage (pathway i) over formation of an ion–neutral complex (pathway ii), while the competition in eq 4 favors pathway ii (which leads to ethane loss).[19] Both reactions initially produce secondary nonyl cations. In eq 3 the bond fission forms a 2-nonyl cation, which sweeps out a large radius around its center of charge as it rotates about its own center of mass. In eq 4 the center of mass and center of charge of the 5-nonyl cation are much closer to one another, and the steric radius of the alkyl cation (relative to its center of charge) is smaller as it rotates about its own center of mass. This leads to a stronger attraction and more frequent access to a geometry suitable for hydrogen atom abstraction in eq 4.
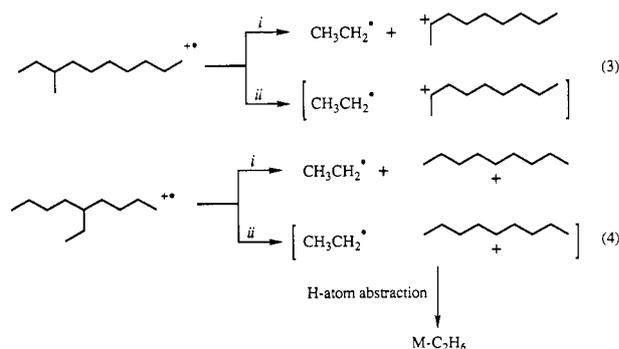

Heterolysis versus Homolysis

Because complex-mediated reactions usually have electrically charged reactants and products, they are widely (although not exclusively) studied by mass spectrometry. In the mass spectrometer, as in solution, it is useful to distinguish between two classes of bond cleavage, homolyses and heterolyses. These categories are unambiguous when a precursor has an even number of electrons and is electrically neutral: homolysis produces radical pairs, while heterolysis usually yields ion pairs. But when the precursor is an ion (especially if it is a radical ion), the distinction becomes less obvious. It the electrical charge can be viewed as localized in some portion of an ion, the following convention can be applied (provided that that portion of the precursor goes wholly into one of the fragments). If the charge remains localized in the fragment that originally contained it, then the cleavage is a homolysis. If the charge is found in the other fragment, the cleavage is a heterolysis. Equation 5 depicts this convention schematically.

(19) McAdoo, D. J.; Hudson, C. E. *Rapid Commun. Mass Spectrom.* **1991**, *5*, 357–358.
(20) Nguyen, V.; Morton, T. H. Unpublished results.

$$RY^+ \rightarrow R^\cdot \ {}^\cdot Y^+ \qquad \text{homolysis}$$

$$RY^+ \rightarrow R^+ \ :Y \qquad \text{heterolysis} \qquad (5)$$
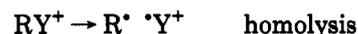
Homolyses and heterolyses often compete. For instance, the radical cation of p-methoxy-β-fluorophenetole, drawn in eq 6, may be portrayed as having its charge localized in the oxygenated aromatic portion of the molecule. In its mass spectrum, simple homolytic cleavage preponderates over simple heterolysis. While the choice between homolysis and heterolysis may be influenced by orbital symmetry,[21] the relative proportions in eq 6 are nevertheless in agreement with what would be expected from thermochemical considerations: the fragment with the higher ionization energy (IE) is the one that is preferentially produced as a neutral radical, while the one with the lower IE prefers to be ionized.[22] Ion–neutral complexes occur when, unlike the case of eq 6, the cleavage fragments do not rapidly escape, but remain in the vicinity of one another long enough to undergo ion–molecule reactions.
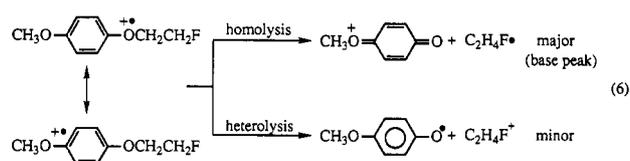
As in eq 3 and 4 above, we picture the fission of a covalent bond as partitioning between two cognate pathways, (i) simple cleavage and (ii) formation of an ion–neutral complex. Many complex-mediated mechanisms can be designated as gas-phase analogues of homolytic or heterolytic cage reactions, depending on the allocation of charge in the cognate simple cleavage. The transient intermediates themselves, however, must be viewed as resonance hybrids (like the radical cation in eq 2). While this tends to blur the distinction between a homolytic cage and a heterolytic cage, the following notion regarding substituent effects nevertheless emerges: as a bond fission acquires more heterolytic character (e.g., by replacing the methoxy in eq 6 with a hydrogen), complex formation becomes more favorable relative to simple cleavage. This will be discussed more fully below.

Homolytic Cage Reactions

We wish to draw a parallel between geminate radical pairs in solution and ion–neutral complexes formed by homolytic bond fission. The cage reaction is usually disproportionation via hydrogen atom transfer, and the competing processes are recombination and cage escape. Site-specific, reversible hydrogen exchanges—for example, at the middle carbon of propane prior to its elimination from 3-methyl-2-butanol[23] (summarized in eq 7) and 2-methyl-3-pentanone[24] ions—provide evidence for this kind of competition. The scrambling that results from the reversible interconversion iii

(21) Osterheld, T. H.; Baer, T.; Brauman, J. I. *J. Am. Chem. Soc.*, in press.
(22) Stevenson, D. P. *Discuss. Faraday Soc.* **1951**, *10*, 35.
(23) (a) Hammerum, S.; Audier, H. E. *J. Chem. Soc., Chem. Commun.* **1988**, 860–862. (b) George, M.; Holmes, J. L. *Org. Mass Spectrom.* **1990**, *25*, 605–608.
(24) Traeger, J. C.; Hudson, C. E.; McAdoo, D. J. *Int. J. Mass Spectrom. Ion Processes* **1988**, *82*, 101–109.

demonstrates that the alkane elimination is complex-mediated. Observation of the same exchange in the bimolecular, ion–molecule reactions of propane with vinyl alcohol ions lends further support for this interpretation.[25]

$$(7)$$
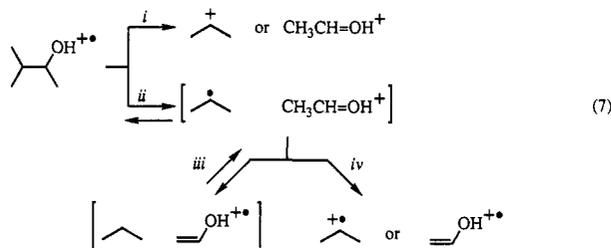
In the gas phase, variations in the energy dependence with the properties of the partners probe the competition between simple cleavages (i) and the formation of the cognate ion–neutral complexes (ii). When neutral precursors are ionized by absorption of a single photon, the yield of a given fragment ion (as a function of internal energy in the parent ion) is proportional to the slope of its photoionization efficiency curve (the plot of the number of ions formed versus photon energy). If the photon energy minus the IE of the neutral precursor is above the energy range in which the ion is formed, its photoionization efficiency curve becomes horizontal.[26] The shapes of the photoionization efficiency curves for alkane losses demonstrate that those reactions typically become minor pathways above the onset for the corresponding simple cleavage.[18,27]

One well-investigated gas-phase example is the expulsion of methane from the molecular ion of acetone.[28] For the case R = methyl, eq 8 depicts the branching between the simple homolysis that expels a methyl radical, i, and the fission to form a complex, ii, which in turn leads to disproportionation to expel methane. The thermodynamic threshold for ii is lower than that for i, and photoionization experiments reveal that the branching ratio i/ii goes from 0 to ≥100 as internal energy is increased above the threshold for i.

$$(8)$$
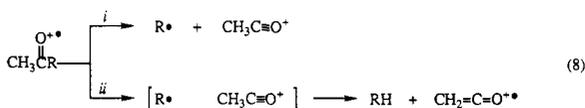
Alkane loss often represents the sole decomposition pathway at energies below those where simple homolytic cleavage is feasible. Since concerted 1,2-eliminations tend to be high-energy processes,[29] alkane expulsions must take place via ion–neutral complexes. Homolytic complexes usually predominate over a narrow energy range (observable by photoionization or by metastable ion mass spectrometry), but they can persist up to higher energies. A quantitative model has been presented[16] and applied to predict (using ab initio calculations) the

ratio of methyl loss to methane expulsion in the mass spectrum of acetamide.[17]

As the size of R in eq 8 increases, it becomes more polarizable, and, all else being equal, the corresponding neutral fragment should be more strongly attracted to the ion. As the radical within the complex gets larger in homolyses of ionized ketones[27] (and ethers[30]), alkane eliminations become more favorable relative to the cognate simple cleavages. Conversely, as the ionic partner within a complex gets larger, alkane elimination becomes less favored, a consequence attributable to an effective increase in the average distance of the neutral from the center of charge. By manipulating sizes of the partners, alkane eliminations can be made to appear and disappear, demonstrating the sensitivity of such processes to the magnitude of the attractive forces between the fragments.[30] Photoionization appearance energies have established thresholds for alkane eliminations that are from 0 to 8 kcal mol^{-1} below the thresholds for the associated alkyl losses. There are typically very small differences between observed onsets for losses of methyl versus methane, larger differences for losses of ethyl versus ethane, and sometimes still larger differences for losses of propyl versus propane.[18,27,30] Since the differences in appearance energies are generally not identical to the thermochemical differences between the net products of pathways i and ii, they can be ascribed to the increasing attraction between the ions and their radical partners with increasing size and polarizability of the latter.

Vibrationally excited ions can be formed by isomerization. In metastable ion mass spectra, a parent ion produced by isomerization sometimes has a higher energy content than one formed by direct ionization of a neutral. Comparison of two routes to the same precursor structure demonstrates the narrowness of the energy range in which alkane eliminations are important.[31] Losses of alkyl radicals in the metastable ion decompositions of the ionized secondary ethers are close to negligible. For example, ionized *sec*-butyl ethyl ether (eq 9) loses ethane 20 times more often than it loses ethyl. However, ionized *n*-butyl ethyl ether loses ethyl about 100 times more often than it loses ethane, even though it isomerizes entirely to the *sec*-butyl structure prior to its metastable decomposition.[32] This dramatic switch accompanies an increase of only about 4 kcal mol^{-1} in the energy content of the system.[31]

$$(9)$$

One of the best known decompositions of gaseous cations is the McLafferty rearrangement. It can be viewed as analogous to the photochemical Norrish type

(25) Mourgues, P.; Audier, H. E.; Hammerum, S. *Org. Mass Spectrom.* **1991**, *26*, 339–341.

(26) Traeger, J. C.; McLoughlin, R. G. *Int. J. Mass Spectrom. Ion Phys.* **1978**, *27*, 319–333.

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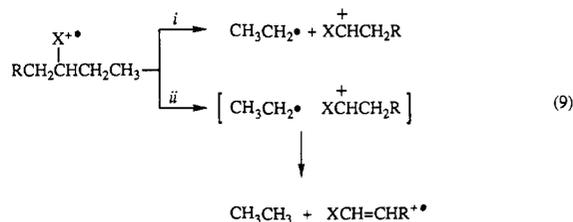
(28) (a) Hudson, C. E.; McAdoo, D. J. *Int. J. Mass Spectrom. Ion Processes* **1984**, *59*, 325–332. (b) Heinrich, N.; Louage, F.; Lifshitz, C.; Schwarz, H. *J. Am. Chem. Soc.* **1988**, *110*, 8183–8192. (c) Osterheld, T.; Brauman, J. I. *J. Am. Chem. Soc.* **1992**, *114*, 7158–7164.

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(30) (a) Traeger, J. C.; Hudson, C. E.; McAdoo, D. J. *J. Am. Soc. Mass Spectrom.* **1992**, *3*, 183–187. (b) McAdoo, D. J.; Hudson, C. E.; Traeger, J. C.; Grose, A.; Griffin, L. L. *J. Am. Soc. Mass Spectrom.* **1991**, *2*, 261–269.

(31) Traeger, J. C.; Hudson, C. E.; McAdoo, D. J. *J. Phys. Chem.* **1990**, *94*, 5714–5717.

(32) Hudson, C. E.; McAdoo, D. J. *Org. Mass Spectrom.* **1979**, *14*, 109–113.

Gas-Phase Analogues of Cage Effects

Acc. Chem. Res., Vol. 26, No. 6, 1993 **299**

II cleavage of neutral carbonyl compounds and is believed to take place in two steps: a γ-hydrogen shift (the first step of eq 10) and then a simple homolytic cleavage (pathway i of eq 10) to yield an enol ion.[33] In recent years a unified mechanism for a number of reactions has been proposed, whereby ion–neutral complexes are formed by a McLafferty rearrangement, and the partners then react with each other in a variety of ways.[34-36] Elimination, isomerization, and addition reactions can all be rationalized by invoking a single intermediate, as formed by pathway ii in eq 10. The

(10)
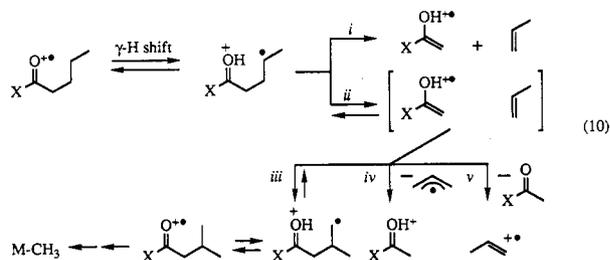
most prominent product of the complex from ionized pentanoic acid (X = OH) is an even-electron "McLafferty + 1" ion formed by hydrogen abstraction (pathway iv).[34] A related process is the "McLafferty rearrangement with charge reversal", in which hydrogen transfers back and forth between the partners to produce a charged olefin and a neutral carbonyl compound (e.g., pathway ν for X = OH, which expels acetic acid, a reaction that also occurs in hexanoic acid[35]). Recombination of the fragments (pathway iii) leads to isomerized molecular ions that can lose a methyl radical. Pathways ii and iii are reversible and interconvert linear and branched ions through common intermediates. A photoionization study[36] of the loss of methyl via pathways ii and iii from ionized 2-hexanone (X = CH₃) demonstrates that M – CH₃ is confined to a narrow energy range near threshold. This again reveals the sensitivity to internal energy characteristic of many complex-mediated reactions in which the neutral has a small dipole moment.

Heterolytic Cage Reactions

Ion–neutral complexes formed by bond heterolyses play the same role in the gas phase as ion–pair or ion–dipole intermediates do in solution. Since the electric charge shifts locale in the course of a heterolysis, an atom that has an ionized lone pair in the parent ion becomes an uncharged, electronegative atom in the complex, often conferring a large permanent dipole moment upon the neutral partner. A permanent dipole in the neutral should increase the attractive force between it and the ion, especially at distances where ion–induced dipole attraction falls off. Thus a large dipole moment can increase the importance of an ion–

neutral complex relative to simple dissociation. This has been observed in the formation of $CH_3OH_2^+$ from ionized isobutanol (eq 11, R = H)[37] and in the decompositions of neopentyl alcohol (eq 11, R = CH₃).[38] Reaction occurs by consecutive hydrogen-transfer steps starting with pathway ii.
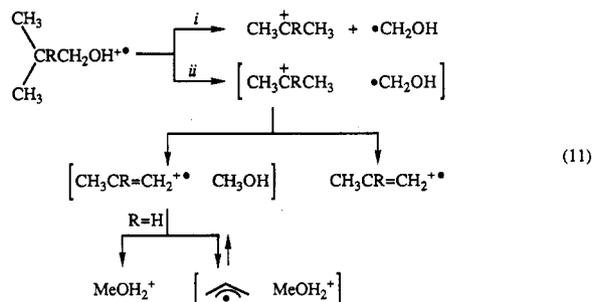

(11)

In contrast to the low abundance of many alkane eliminations in the ion source, $CH_3OH_2^+$ is a very abundant species in the mass spectrum of isobutanol. The measured threshold for its formation is 13 kcal mol⁻¹ below the thermodynamic threshold for producing isopropyl cation (i). Furthermore, photoionization efficiency curves show that $CH_3OH_2^+$ formation competes effectively with $C_3H_7^+$ formation well above the onset for formation of the latter, illustrating the effect of stronger attractive forces. Kinetic studies of deuterated precursors on the subnanosecond time scale reveal the sequence of steps.[39] The first hydrogen transfer is fast and essentially irreversible. The second hydrogen transfer, however, is both slower and reversible. It exchanges the proton on oxygen with those originally on methyl. Scrambling in the $MeOH_2^+$ and in the propene·⁺ fragments follows nearly the same time course. This result is hard to explain unless [propene·⁺ MeOH] and [allyl radical $MeOH_2^+$] complexes interconvert.

Let us briefly turn our attention to analytical mass spectrometry, a realm of ion chemistry that is familiar to most chemists. We enunciate the following principle regarding fragmentation patterns: heterolyses are more likely to produce complexes than are closely related homolyses. Compare the abundances of the homolysis-derived, complex-mediated products from step iv of eq 7 (propane or vinyl alcohol, both of which have masses of 44 Da) with those for a lower homologue (R = H) or an isomeric starting material (R = CH₃) that heterolyzes as in eq 11. The i/ii branching ratio in the published 70-eV mass spectrum for eq 7 can be estimated as the relative peak intensities m/z 45:m/z 44 = 9. In eq 11, by contrast, an upper bound for the branching ratio of isobutanol can be assigned as (m/z 43 + m/z 31):m/z 33 = 2.5, while that for neopentanol (where the complex just expels MeOH) is (m/z 57 + m/z 31):m/z 56 = 3.[40]

Often the formation of an ion–neutral complex takes place with concomitant cyclization of the cation. This

(33) (a) Smith, J. S.; McLafferty, F. W. *Org. Mass Spectrom.* 1971, *5*, 483–485. (b) Hudson, C. E.; Griffin, L. L.; McAdoo, D. J. *Org. Mass Spectrom.* 1989, *24*, 866–870.

(34) (a) McAdoo, D. J.; Hudson, C. E.; Skyiepal, M.; Broido, E.; Griffin, L. *J. Am. Chem. Soc.* 1987, *109*, 7648–7653. (b) Masur, M.; Sprafke, A.; Grutzmacher, H.-F. *Org. Mass Spectrom.* 1987, *22*, 307–310. (c) Bouchoux, G.; Tortajada, J.; Dagaut, J.; Fillaux, J. *Org. Mass Spectrom.* 1987, *22*, 451–457.

(35) van Baar, B. L. M.; Terlouw, J. K.; Akkok, S.; Zummack, W.; Schwarz, H. *Int. J. Mass Spectrom. Ion Processes* 1987, *81*, 217–225.

(36) McAdoo, D. J.; Traeger, J. C.; Hudson, C. E. *Rapid Commun. Mass Spectrom.* 1988, *4*, 163–169.

(37) (a) Bowen, R. D.; Williams, D. H. *J. Chem. Soc., Chem. Commun.* 1981, 836–838. (b) Traeger, J. C.; Hudson, C. E.; McAdoo, D. J. *J. Am. Soc. Mass Spectrom.* 1992, *3*, 409–416.

(38) (a) Hammerum, S.; Audier, H. E. *J. Chem. Soc., Chem. Commun.* 1988, 860–861. (b) Bissonnette, M. C.; George, M.; Holmes, J. L. *Org. Mass Spectrom.* 1990, *25*, 689–693.

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has been demonstrated in the gas phase for ions derived from ω-alkenyl ethers,[41] propanol,[42] propyl ethers,[43] and for the distonic ions derived from 1-alkoxyhexanes, depicted in eq 12.[44] Isotopic labeling shows that many of the final product ions, ROH_2^+, have acquired two hydrogens from position 5 of the n-hexyl chain.[45] This is what would be expected if pathway ii in eq 12 ultimately leads to the most stable neutral fragment, the tertiary 1-methylcyclopentyl radical. Evidence for ii is that the distribution of isotopically labeled fragment ions from decomposition of $EtO(CH_2)_4CD_2CH_3^{\bullet+}$ is reproduced by the ion–molecule reaction of *1-d*-methylcyclopentane$^{\bullet+}$ with EtOD.[44] Therefore the same complex (with the same isotopic transpositions) intervenes in the unimolecular reaction and its bimolecular analogue.

$$(12)$$

Carbocations typically react with other molecules by donating a proton (E1 elimination) or by undergoing nucleophilic attack. Nucleophilic substitution within gas-phase complexes occurs in phenyl alkyl carbonate molecular ions. While CO_2 expulsion from ionized carbonate esters has been well-known for a long time,[46] stereochemical experiments showing that it proceeds as drawn in eq 13 are relatively recent. Because the phenoxy radical is resonance-stabilized, heterolysis to produce the complex drawn in eq 13 is the dominant reaction pathway. The charged partner is an alkoxyacylium ion, a type of cation that, in solution, readily expels CO_2 via an S_N1 process.[47] But in the gas phase (in the absence of solvent) the loss of CO_2 occurs principally via a backside displacement, as portrayed by eq 13, which gives rise to inversion of configuration.[48] This stereochemistry is opposite to the retention of configuration observed in thermal, gas-phase elimination of CO_2 from neutral chloroformates,[49] but it does mirror the shift from retention to inversion of stereochemistry observed in solution-phase elimination of SO_2 from neutral alkyl chlorosulfites when one goes from polar to nonpolar solvents.[50] If we are to search for analogies between molecular ion decompositions

and extrusions from neutral molecules, the stereochemical evidence suggests that a comparison with reactions of the latter in nonpolar solvents (where cage effects operate) is more apt than with gas-phase thermal rearrangements, where cage effects are improbable.

$$(13)$$

A recent study of reversible Friedel–Crafts acylations exemplifies the importance of the size of the neutral fragment in formation of an ion–neutral complex: the interaction between para substituents goes up as the number of intervening benzene rings is increased.[51] The tautomeric protonated acetophenones drawn in eq 14 can be generated either by methyl loss from a tertiary alcohol, as depicted, or by protonation of the corresponding neutral acetophenone. The prominent loss of methyl acetate has been carefully examined for $0 \leq n \leq 2$. While a sequence of σ-complexes might readily be envisaged, an ion–neutral complex seems more likely in view of the competition between the cognate pathways i and ii. The i/ii branching ratio decreases with n, from 0.2 for $n = 0$ to 0.03 for $n = 1$ and 0.01 for $n = 2$. A mechanism involving only σ-complexes would have predicted the opposite trend: as the number of discrete steps needed to walk the electrophilic acylium ion over to the nucleophilic methoxy oxygen goes up, the probability of that pathway ought to have decreased. Electrostatically the likelihood of a complex should increase with the size of the neutral, as observed.

$$(14)$$

Solvolyses without Solvent

The heterolytic reactions that have received the closest scrutiny are gas-phase analogues of solvolysis. This category embraces decompositions of both odd- and even-electron ions where the bond that cleaves corresponds to a single bond between an sp^3-carbon and a heteroatom in the parent neutral. Consider the decomposition in eq 6. Ionization energies for the 2-fluoroethyl and p-methoxyphenoxy radicals can be estimated to be in the range 8–8.5 eV for the former

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(51) (a) Grützmacher, H.-F. *Int. J. Mass Spectrom. Ion Processes* **1992**, *118/119* 825–855. (b) Thielking, G.; Filges, U.; Grützmacher, H.-F. *J. Am. Soc. Mass Spectrom.* **1992**, *3*, 417–426.

and <8 eV for the latter.[52] Now suppose the IE of the aromatic fragment is raised by removing the p-methoxy substituent. The IE of phenoxy is >8.5 eV,[53] so thermochemistry now predicts that heterolysis should prevail over homolysis. This does occur, but (probably because the neutral phenoxy radical has a large dipole moment) the heterolysis yields a complex >20 times more often than free fragments. The observed products are fluoroethylene and ionized phenol, as eq 15 portrays.

$$PhOCH_2CH_2F \xrightarrow{-e^-} [PhO^\bullet \quad C_2H_4F^+] \rightarrow$$
β-fluorophenetole

$$PhOH^{\bullet+} + CH_2{=}CHF \quad (15)$$
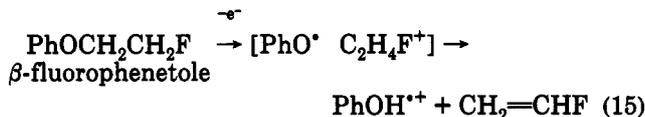
While one might plausibly suggest that this involves a hydrogen transfer via a cyclic transition state (similar to the McLafferty rearrangement), isotopic labeling studies show that net transfer of hydrogen from carbon to oxygen is accompanied by other transpositions.[54]

When primary alkyl phenyl ethers are ionized, their mass spectrometric decompositions show that the alkyl groups often rearrange. For instance, the ratio of the phenol ions from deuterated isobutyl phenyl ether, represented in eq 16, rules out a McLafferty-type rearrangement, which would have produced PhOD[•+] exclusively. Instead the one deuterium scrambles with the eight alkyl hydrogens, as would be expected for an isobutyl → *tert*-butyl cation isomerization in the course of heterolysis to form a complex.[55] Detailed analyses of isotopic scrambling in other alkyl phenyl ether ions show that it results from the intermediacy of ion–neutral complexes.[4] At present, the extent to which rearranged alkyl cations recombine with phenoxy radicals is not known. On the one hand, there appear to be potential energy barriers for proton transfer to and from phenoxy radicals.[56] On the other hand, there may also be potential energy barriers to recombination of the ion and neutral (analogous to the barrier that has lately been reported for recombination of neutral methyl and phenoxy radicals in the gas phase[57]).

(16)   PhOH[•+] 90%   PhOD[•+] 10%
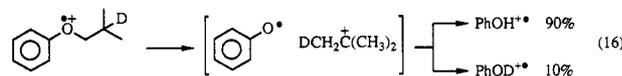
Characterization of the rearrangements of alkyl cations in the course of unimolecular eliminations has played a major role in demonstrating that primary alkyl phenyl ether ions heterolyze to form ion–neutral complexes. However, mass spectrometry by itself cannot reveal what is taking place in these ions, except in terms of distributions of translational kinetic energy release or isotopic label in the fragments. The bulk of the mechanistic information is frequently contained within the neutral products (whose regio- or stereochemistry cannot be detected by mass spectrometry).

Therefore many of the investigations of this class of reaction have been performed in a specially designed electron bombardment flow (EBFlow) reactor. The EBFlow reproduces conditions in a mass spectrometer ion source but permits collection of the neutral fragments for subsequent analysis by GC–MS or NMR spectroscopy.[54,58–61]

EBFlow studies have recently provided information about monofluorinated carbocations, for which there are many ab initio computations but few experimental data. Complex-mediated decompositions such as those in eq 15 can be exploited in order to study cations that have not been accessible in solution. For instance, the Wagner–Meerwein rearrangement that produces the intermediate complexes in eq 17 raises the question as to what happens when substituent R is changed from a methyl group (as in solvolysis of neopentyl derivatives) to a fluorine (a β-fluoroisobutyl derivative). How do
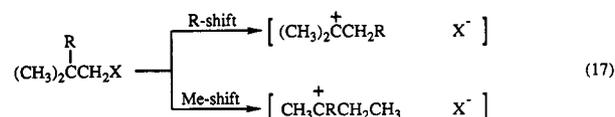
the migratory aptitudes of fluorine and methyl compare? Solvolysis of the β-fluoroisobutyl triflate (R = F, X = OTf) does not provide an answer, for in solution the tertiary C–F bond heterolyzes in preference to the primary C–O bond.[62] On the other hand, the gas-phase analogue of solvolysis (eq 18) displays the competing Wagner–Meerwein shifts and shows that the migratory aptitude of a methyl is only about twice as great as that of fluorine.[58]
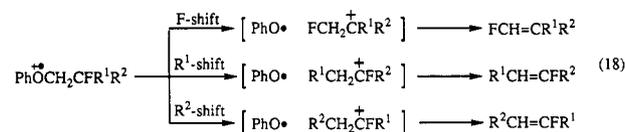
Gas-phase analogues of cage effects are not confined to radical cations. Conjugate acids (protonated parent ions) also expel alkenes via ion–neutral complexes. In eq 17, the gaseous conjugate acid (X = DOPh[+]) of β-fluoroisobutyl phenyl ether (R = F) yields approximately the same ratio of rearranged alkenes as does the corresponding radical ion (X = OPh[•+]).[63] Likewise the mass spectrometric decompositions of conjugate acid ions of isotopically labeled β-fluorophenetole afford the same proportions of D-transfer and H-transfer as do the isotopically labeled analogues of the radical cation decomposition summarized in eq 15. This parallelism between unimolecular eliminations from

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Table I. Migratory Aptitudes (Relative to Fluorine Shift) of β-Substituents in β-Fluoroalkyl Phenyl Ether Radical Cations (Normalized per R Group) in Eq 18

molecular ion	deuterium	methyl	ref
$R^1 = R^2 = CH_3$		2.2	58
$R^1 = D, R^2 = CH_3$	4	2.1	59
$R^1 = R^2 = D$	0.6		54

even- and odd-electron cations is a characteristic feature of many gas-phase analogues of solvolysis.[64]

fluoriranium   methylfluoriranium

Gas-phase analogues of solvolysis give an affirmative answer to the longstanding question as to whether fluorine is capable of bridging. For deuterated β-fluorophenetoles, the distribution of label in the neutral fluoroethylenes requires that a bridged intermediate (fluoriranium) possess a nonzero lifetime.[54] Table I summarizes relative migratory aptitudes measured from the neutral fluoroalkene yields of eq 18. The effects of varying R^1 and R^2 provide additional experimental evidence that the fluoriranium ion is stable (as predicted by theory[65]), even though its substituted homologues are not. When $R^1 \neq R^2$ (e.g., one group is hydrogen and the other methyl), ab initio calculations indicate that the methylfluoriranium is a transition state, not a stable intermediate.[60] Experimentally, deuterium shift competes more effectively with fluoride shift here than in the case of β-fluorophenetole (where unsubstituted fluoriranium is an intermediate).

Concluding Remarks

Gas-phase analogues of cage reactions offer a glimpse of organic chemistry on the subnanosecond time scale. We have treated unimolecular decompositions of positive ions that pass through dissociative intermediates, which behave like ion pairs or radical cages, and we have emphasized two cognate, competing reactions: (i) simple cleavage and (ii) formation of an ion–neutral complex. The i/ii branching ratios in the gas phase can, in many cases, be explained in terms of simple physical models. In particular, heterolyses tend to yield higher proportions of complexes (i.e., a smaller i/ii branching ratio) than do closely related homolyses.

As understanding of mechanistic analogies between solution and the gas phase increases, so does the ability to examine ion–neutral complexes. Supersonically cooled jets can now give access to neutral precursors having vibrational temperatures on the order of 10 K. When thermal effects are thus reduced, single conformational isomers can be selectively ionized in the gas phase using resonance-enhanced multiphoton laser ionization (REMPI).[66] This technique can be extended to find out whether different conformers give different branching ratios in their REMPI mass spectra.[67] With additional refinements, new experimental probes for gas-phase analogues of cage effects will improve our knowledge of how chemical bonds break.

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