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Nuclear Decay Techniques in Ion Chemistry

FULVIO CACACE

The spontaneous decay of chemically bound radioactive atoms affords a route to ions of well-defined structure and charge location, free of counterions. The nuclear nature of the ionization process makes it insensitive to environmental effects, so that exactly the same charged species can be generated, and its reactivity investigated, in widely varying media, from low-pressure gases to liquids and solids. Techniques based on nuclear decay are used in studies of the production of otherwise inaccessible species, the structural characterization of free ions, and the comparative evaluation of their reactivity in different environments, in particular, gas phase and solution.

IN MOST TRACER APPLICATIONS OF RADIONUCLIDES, THE interest in the fate of a labeled molecule ceases immediately after the decay of the radioactive atom and the emission of a characteristic radiation that allows its detection and localization. In this article, attention is focused instead precisely on what is left of the labeled molecule after the decay of a constituent radioactive atom. In most cases, irrespective of the nature of the precursor and of the specific decay mode, the newly formed species carry an electric charge and hence are commonly referred to as "daughter ions" or simply "decay ions." The interest in these unusual species, which frequently are unstable and extremely reactive, has steadily

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grown far beyond the boundaries of a specialized radiochemical area since an experimental approach based on the decay of selected radioactive precursors has gained wide recognition as a powerful tool for the solution of structural and mechanistic problems in ion chemistry.

The interest in what is currently known as the "decay technique" is justified by those features that set it apart from other approaches to ion chemistry that derive from the nuclear nature of the ionogenic process. In fact, the formation of the decay ion occurs with the same efficiency, and yields the same charged species, irrespective of whether the parent molecule is isolated or is contained in gaseous or condensed media. This feature provides an effective means to bridge the gap between gas-phase and solution-chemistry studies. Furthermore, the ionic species are generated in a free state, their charge being balanced by that of a far-removed particle, for example, an electron, rather than by a closely associated counterion. Finally, even in condensed media, the decay ions are initially unsolvated (more precisely, they are in the same solvation state as their neutral parent molecules) and, in many cases, react before an organized solvation shell has had time to assemble.

Such features allow the decay technique to be used as a tool for connecting our understanding of the structure and the reactivity of ions in the gas phase and in solution, and for linking theoretical and experimental approaches to ion chemistry. In fact, the decay technique shares with mass spectrometry the ability to deal with free, unsolvated ions, as required for a direct comparison with theoretical results, while enjoying the same degree of structural and stereochemical definition typical of solution chemistry.

The decay technique has steadily been improved and adapted to a much broader range of applications than envisioned in the original proposal (*1*), and its experimental design has been correspondingly diversified. The purpose of this article is not to provide an exhaustive coverage of the results [for a review, see (*2–6*)]. Instead, after an outline of the foundations and the salient experimental aspects of the technique, attention will be focused on selected areas of ionic chemistry where the impact of decay studies has proved most significant.

The Ionization Process

The chemical consequences of radioactive decay have been extensively investigated with a variety of theoretical, radiochemical, and mass spectrometric techniques aimed, in particular, at evaluating the charge, the electronic state, and the excess kinetic energy of the daughter species.

In many decay modes, such as emission of β^- and β^+ particles and electron capture, the primary cause of ionization is the change of chemical identity, hence of the nuclear charge, undergone by the radioactive atom. The "transmutation" effect leads to the formation of monovalent cations by β^- decay and of monovalent anions by β^+ decay or by electron-capture processes. The picture is frequently complicated by secondary charging mechanisms; for example, an outgoing β particle or γ photon can eject one or more electrons, especially from the *K* and *L* shells, creating vacancies that are promptly filled by electrons from outer shells. X photons emitted in such transitions are capable in turn of ejecting additional electrons. In this way, the nuclear event can trigger a complex mechanism (Auger cascade) that leads to the formation of a multiply charged, and frequently electronically excited, daughter ion. As an example, the isomeric transition of ^{80m}Br atoms yields multiply charged $^{80}Br^{n+}$ ions, with *n* ranging from 1 to 13 and peaking around 5 (*7*). Although radioactive isotopes of heavy elements find application in decay chemistry, especially in studies aimed at preparing otherwise inaccessible inorganic and organometallic species (see below), the intricacies of their complex ionogenic processes are too complex to present in detail. Instead, a very simple transition is discussed, the β^- decay of tritium, which has been thoroughly investigated by theoretical and mass spectrometric techniques and has been most widely exploited in structural and mechanistic studies.

The half-life of ^3H is 12.26 years, corresponding to a decay rate of ~5.5% per year. The β^- particles, emitted together with antineutrinos, from the transition

$$^3H \rightarrow {}^3He^+ + \beta^- + \bar{\nu} \quad (1)$$

are characterized by a mean energy of 5.6 keV and a maximum energy of 18.6 keV. The increase of the atomic number imparts a positive charge to the daughter species, yielding a $^3He^+$ cation that can be formed in its ground state or in electronically excited states, through the so-called "shaking effect." The latter arises from the fact that the 1*s* orbitals of ^3H and of $^3He^+$ do not overlap exactly; hence, in the sudden transition the electron has a finite probability of finding itself in some orbital other than the ground state of the newly formed $^3H^+$ ion, which leads to electronically excited states. One can evaluate the probability $P_{n,\ell}$ of the transition from the 1*s* ground state of ^3H to a $^3He^+$ orbital characterized by the n,ℓ quantum numbers from the square of the overlap integral

$$P_{n,\ell} = |\int \Psi^*_{n,\ell} \Psi_{1s} d\tau|^2 \quad (2)$$

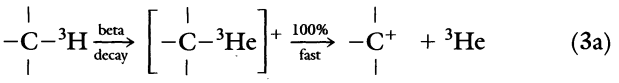
where $d\tau$ is the volume element. Subtracting from unity the sum of the probabilities of all transitions to bound states of the electron, one can compute the probability that the electron is lost to yield $^3He^{2+}$. In the decay of isolated ^3H atoms, ~70% of the transitions lead to ground-state $^3He^+$ ion, 25% to the first excited state, 2.5% to higher excited states, and only 2.5% to doubly charged ions (*3*). Such results can be regarded as reliable because of the simple nature of the species involved and find indirect support in the mass spectrometric studies on chemically bound ^3H atoms. An additional source of excitation is the "recoil" of $^3He^+$ resulting from the momentum transfer from the emission of the β^- particle and of the antineutrino. The recoil mechanism is not particularly significant, because more than 80% of the decay ions are expected to increase their translational energy by less than 0.08 eV.

Molecular Disruption and Excitation

The decay of covalently bound ^3H atoms has been the subject of extensive theoretical and mass spectrometric studies. These studies have been aimed at evaluating the stability and the excess internal energy of polyatomic daughter ions, whose survival depends essentially on the ability of the atom originally bound to ^3H to maintain an attractive interaction with the newly formed He ion.

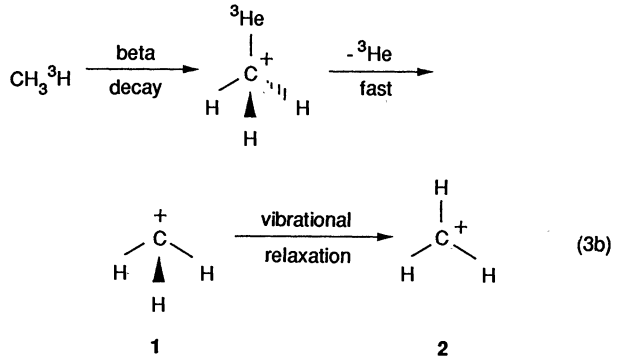
In view of the long-recognized stability of the HeH^+ ion, it is hardly surprising that all computational studies on the decay of isolated ^3H–H molecules concur in the conclusion that the $^3HeH^+$ daughter ions survive dissociation, except when formed in electronically excited states. Calculations performed at different levels of theory show that 70 to 90% of the decay events in ^3H–H molecules yield stable $^3HeH^+$ ions in their electronic ground state. The recoil effect can lead to vibrational excitation; for example, early calculations suggested that ~20% of the $^3He^3H^+$ ions from the decay of $^3H_2$ are formed in the $v = 1$ level, consistent with the infrared emission spectra of $^3H_2$ undergoing decay at 20 K (*8*). Other daughter ions, such as $^3HeLi^+$ and $B_2H_5{}^3He^+$ from the decay of lithium tritide and of tritiated diborane, are predicted to be stable, whereas He-Be, He-C, He-N, He-O, and He-F pairs have purely repulsive interactions, so that the corresponding decay ions are

expected to undergo prompt loss of neutral He (*9*). Thus, decay of tritiated hydrocarbons affords a route to free carbocations



(3a)

An additional source of vibrational excitation, of special interest in structural and kinetic applications, can be traced to the decay ions that are formed in a "wrong" geometry, reminiscent of that of their neutral parent molecules (*10*). Consider, as a typical example, the decay of tritiated methane



(3b)

1 2

The vertical nature of its formation process causes the methyl cations to be born in the pyramidal structure **1**, typical of the CH_3 group of methane, and thus contain excess internal energy ("deformation energy"), whose upper limit corresponds to the stability difference between **1** and the ground state, planar structure **2**. Theoretical calculations show that the deformation energy of the decay ions is not trivial and ranges from 25 to 32 kcal mol^{-1} in the $C_6H_5^+$ ions from tritiated benzene (*11*), to ~30 kcal mol^{-1} in CH_3^+ ions from tritiated methane (*12*), and up to ~50 kcal mol^{-1} in $C_2H_3^+$ ions from tritiated ethylene (*13*).

Vibrational excitation of the decay ions presents at the same time a problem and an opportunity. On the one hand, the excited ions must be quenched (for example, by collision with inert molecules) before being used as a reactant in kinetic studies, where a thermal energy distribution is desired. On the other hand, vibrational excitation can prove an asset in structural studies, allowing intramolecular rearrangements whose direction and rate provide valuable information on the relative stability of isomeric ions and on the barriers to their interconversion.

The fragmentation patterns of tritiated molecules, measured with special mass spectrometers, are consistent with the theoretical results. For example, the high abundance of undissociated $^3HeH^+$ daughter ions confirms the inherent stability of the H–He bond, and the repulsive nature of the C–He bond is reflected by the quantitative loss of ^3He that is promoted by reaction 3 (Table 1).

The mass spectrometric results provide no direct information on the excess internal energy of the daughter ions. However, their survival during the relatively long residence time in the mass spectrometer (10^{-5} s) suggests that, except in those decay events (~20%) leading to electronically excited states of $^3He^+$, the internal energy of the ions does not significantly exceed their deformation energy.

Experimental Approaches

In structural and mechanistic applications, the daughter ions generated from a tritiated precursor in a gaseous or liquid system are allowed to interact with appropriate reactants and give neutral end products whose nature and yields can be determined. If necessary, the end products can be isolated and subjected to spectral analysis or to chemical degradation procedures.

The decay experiments lend themselves to the application of many classical techniques, such as the use of radical scavengers and of ionic interceptors, competition kinetics, pressure and temperature dependence studies, and so forth. Of particular interest is the actual isolation of the final products, whose structural and stereochemical features provide valuable information on the structure and the stereochemistry of their ionic precursors. A major experimental problem is the relatively small number of decay ions that can be generated within any reasonable period of time, and especially the swamping of the ions from the decay by those produced by the radiolytic processes promoted by the β^- particles of ^3H, because each decay event produces together with a single daughter ion more than 200 radiolytic ions.

Researchers have neatly circumvented the problem by resorting to precursors containing two (or more) ^3H in the same molecule (*6*). Decay of one of the radioactive nuclei yields a daughter ion whose reactions can be followed, and the final products are identified by the presence of the undecayed ^3H atom or atoms. Such technique allows, in the first place, analysis of the decay products by sensitive radiometric techniques. More important, the decay ions (hence their final reaction products) are labeled, and so they can be distinguished from the unlabeled species formed from the radiolysis of the reaction medium. It is only necessary to guard against the possibility that the β^- particle from the decay of a given parent molecule can affect, directly or otherwise, another tritiated molecule. This is generally achieved by diluting the tritiated precursor with a sufficiently large

Table 1. Charged fragments from the decay of isolated tritiated molecules.

Precursor	Major charged fragments and their percent abundances						
^3HH	$^3HeH^+$: 91	$^3He^+$: 7	H^+ : 2	$^3He^{2+}$: 0.14			
$^3H_2$	$^3He^3H^+$: 94	$^3He^+, ^3H^+$: 5					
$CH_3{}^3H$	CH_3^+ : 82	CH_2^+ : 4.9	CH^+ : 4.0	C^+ : 4.9	H^+ : 2.4		
$C_2H_5{}^3H$	$C_2H_5^+$: 78	$C_2H_3^+$: 6.5	$C_2H_2^+$: 6.9	C_2H^+ : 4.1	C_2^+ : 1.7		
$C_6H_5{}^3H$	$C_6H_5^+$: 72	$C_6H_2^+$: 2.5	C_6H^+ : 1.3	$C_4H_3^+$: 2.3	C_4H^+ : 2.4	$C_2H_4^+$: 2.7	
o-$C_6H_4{}^3H$-CH_3	$C_7H_7^+$: 78	$C_5H_5^+$: 2.1	$C_5H_3^+$: 2.3	$C_5H_2^+$: 1.6	$C_4H_2^+$: 2.0	$C_3H_3^+$: 3.4	
m-$C_6H_4{}^3H$-CH_3	$C_7H_7^+$: 79	$C_5H_5^+$: 1.8	$C_5H_3^+$: 2.2	$C_5H_2^+$: 1.7	$C_4H_2^+$: 2.0	$C_3H_3^+$: 3.7	
p-$C_6H_4{}^3H$-CH_3	$C_7H_7^+$: 76	$C_5H_5^+$: 2.1	$C_5H_3^+$: 2.2	$C_5H_2^+$: 1.4	$C_4H_2^+$: 2.6	$C_3H_3^+$: 3.6	
C_6H_5-$CH_2{}^3H$	$C_7H_7^+$: 79	$C_5H_5^+$: 2.3	$C_5H_3^+$: 2.3	$C_5H_2^+$: 1.8	$C_4H_2^+$: 1.7	$C_3H_3^+$: 2.8	
$CH_3CH_2CH_2{}^3H$	$C_3H_7^+$: 41	$C_3H_5^+$: 29	$C_3H_3^+$: 4.0	$C_3H_2^+$: 3.7	$C_2H_5^+$: 3.5	$C_2H_3^+$: 6.0	
$CH_3CH^3HCH_3$	$C_3H_7^+$: 56	$C_3H_5^+$: 7	$C_3H_3^+$: 5.3	C_3H^+ : 3.8	$C_2H_3^+$: 4.3	$C_2H_2^+$: 3.6	
c-$C_4H_7{}^3H$	$C_4H_7^+$: 80						
c-$C_5H_9{}^3H$	$C_5H_9^+$: 75						
$CH_2{}^3HI$	CH_2I : 56						

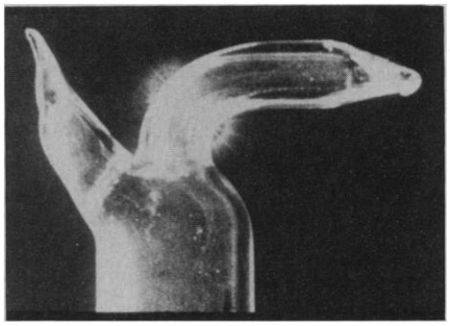


Fig. 1. The halo radiating from the elbow of the side tube is produced by the ultraviolet fluorescence of glass, excited by the radiation from ~50 Ci of condensed C^3H_4.

excess of the inactive species that is working at sufficiently low levels of specific activity. In any case, one can easily detect any interference from radiolytic processes by carrying out blank experiments in which the multitritiated precursor is replaced by the corresponding monotritiated species. Finally, when the position of the ^3H atoms in the parent molecule is known, one can obtain valuable structural and mechanistic insight by measuring the intramolecular tritium distribution in the products.

In summary, the study of a given ion (such as $C_6H_5^+$) requires the following steps: (i) preparation of its monotritiated precursor (such as $C_6H_5{}^3H$) and mass spectrometric study of its decay-induced fragmentation pattern; (ii) synthesis of the multitritiated precursor (such as $C_6H_4{}^3H_2$), and its introduction into gaseous or liquid systems; (iii) analysis of the tritiated decay products; and (iv) "blank" runs involving the monotritiated precursor to exclude radiolytic artifacts.

The second step is undoubtedly the most demanding. In fact, although the activity of the precursor required for the decay experiment is low, generally <1 mCi, introduction of two or more ^3H atoms into the same molecule dictates that isotopically pure tritiated reactants be used. Given the specific activity of $^3H_2$, 58,200 Ci mol^{-1}, even preparative procedures scaled down to the limit of experimental feasibility require large activities, especially in the initial steps of the synthetic sequence (Fig. 1). An additional constraint is posed by the random nature of the radioactive decay, which requires introducing the ^3H atoms in equivalent positions of the parent molecule to obtain daughter ions of a single structure and charge location. Finally, the fast self-radiolytic decomposition of pure tritiated compounds calls for rapid purification, followed by dilution with excess inactive material.

The starting reagent is generally $^3H_2$, which is available in a state of high isotopic purity and is unaffected by self-radiolysis. All other intermediates undergo rapid decomposition and must be prepared immediately before use. $^3H_2$ is used directly (for instance, in catalytic reduction of unsaturated compounds) or is converted to ^3H_2O, which is used in a variety of synthetic approaches, such as reactions with metallic carbides, Grignard reagents, isotope exchange, and so forth. The crude products are generally purified by chromatographic techniques, whose resolving power allows, in favorable cases, preparative separation of isotopomers containing a different number of ^3H atoms (Fig. 2). Characterization of the multitritiated products, and determination of their intramolecular ^3H distribution, is currently achieved by ^3H nuclear magnetic resonance (NMR) spectroscopy or by chemical degradation (*14*).

Application of the above techniques has allowed the preparation of many multitritiated molecules, including ^3H_2O, N^3H_3, alkanes, cycloalkanes, arenes, alcohols, alkyl halides, heterocyclic compounds, and so forth. Worthy of note are the syntheses of $C_6{}^3H_6$, whose specific activity exceeds 170,000 Ci mol^{-1}, of $C_2H_2{}^3H_2$ and $C_2{}^3H_2$ in spite of their fast radiation-induced polymerization, and of selectively labeled molecules, such as benzene-1,4-$^3H_2$ and toluene-α,α-$^3H_2$ (*6*).

Structural Applications

Among the numerous studies aimed at the structural characterization of free ions, a typical example concerns cyclohexylium ion **3**

3 **4**

long recognized as a solvated species in solution. Attempts at detecting free **3** in the gas phase by structurally diagnostic mass spectrometric techniques or in superacid solutions by NMR spectroscopy invariably met with failure, the only observable species being the more stable 1-methyl-1-cyclopentyl isomer, **4**. These results led to the general consensus that cyclohexylium ion does not exist in the free state but rearranges to **4** without activation.

Application of the decay technique has shown that free cyclohexylium ion **3** does exist and has provided reliable estimates of its lifetime and of the barrier to its rearrangement into **4**.

Doubly tritiated cyclohexane, c-$C_6H_{10}{}^3H_2$, obtained from the reaction of $^3H_2$ with cyclohexene and purified by preparative gas chromatography (GC), was allowed to decay at 25°C for periods of 9 to 12 months in liquid and gaseous systems containing a suitable nucleophile such as MeOH (Me, methyl), $SiMe_4$, or 1,4-$C_4H_8Br_2$ (*15*). Derivatives of unrearranged cyclohexylium ion are the only products seen by radioactive detection from liquid systems [for example, only tritiated cyclohexyl methyl ether (49%) and cyclohexene (51%) are formed in liquid MeOH].

The product pattern from gaseous systems is dominated instead by derivatives of the rearranged ion **4** and shows a characteristic dependence on the pressure, but not on the nature, of both the bulk gas and the trapping nucleophile. For example, the fraction of the products retaining the cyclohexyl structure formed in CMe_4 in the presence of MeOH decreases from 38% at 720 torr to 10% at 200 torr, becoming nearly undetectable below 50 torr.

The daughter ions, formed in a distorted structure and therefore

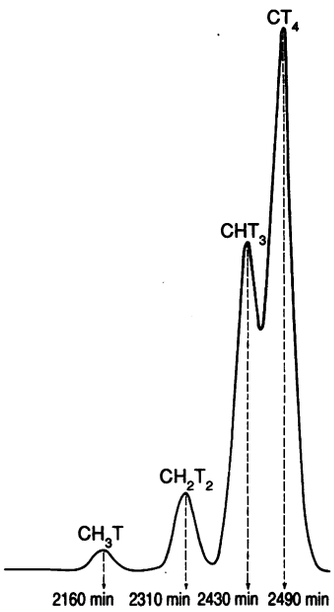


Fig. 2. Separation of tritiated methanes by gas-solid chromatography, with a 64-m-long soft-glass capillary column, internally etched with NaOH, operated at 77 K.

containing excess internal energy, can either be collisionally stabilized or rearranged into **4**

$$c\text{-}C_6H_{10}{}^3H_2 \xrightarrow[-{}^3He]{\text{beta decay}} (c\text{-}C_6H_{10}{}^3H^+)_{exc}$$

$$\xrightarrow[\text{Deactivation}]{+M,-M^*} \text{cyclohexyl derivatives} \quad (4a)$$

$$\xrightarrow{\text{Isomerization}} \mathbf{4} \rightarrow \text{1-methyl-1-cyclopentyl derivatives} \quad (4b)$$

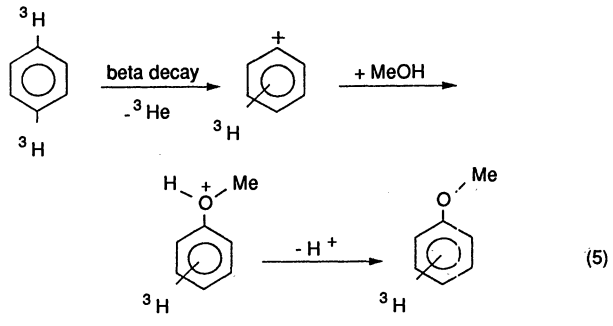
In the liquid phase, isomerization is prevented by fast collisional deactivation and by the short lifetime of free **3** before trapping. In the gas phase, the competition between deactivation and isomerization is controlled by the pressure of the bulk gas and by the concentration of the nucleophile, which affects the lifetime of the free ion. The results of pressure-dependence studies lead to a lifetime of free **3** in excess of 10^{-8} to 10^{-7} s. Furthermore, a Rice-Ramsperger-Kassel-Marcus theory treatment, based on the assumption that the deformation energy of the cyclohexylium ion from the decay is ~30 kcal mol^{-1}, leads to a calculated energy barrier for the **3** → **4** rearrangement of 5 to 9 kcal mol^{-1}, depending on the number of effective oscillators chosen (*15*). Such estimates have later been verified by a temperature-dependence study carried out in dense gases with a different technique, in which an activation energy of 7.4 ± 1 kcal mol^{-1} (*16*) has been measured.

The relatively low barrier to the isomerization process explains the failure to detect gaseous **3** with structurally diagnostic mass spectrometric techniques, because complete rearrangement to **4** can be expected to occur well before structural assay under typical mass spectrometric conditions. From the example illustrated, the very short sampling time emerges as a most valuable feature of the decay technique, which, in fact, has allowed structural characterization of many short-lived free ions, such as protonated cyclopropanes, cyclobutyl and cyclopropylcarbinyl ions, and other species.

Automerization and Isomerization of Free Ions

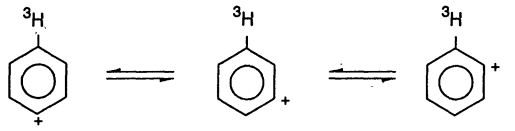
A typical example concerns the problem of phenylium ion, whose intrinsic interest is enhanced by the lively interplay between theoretical and experimental approaches stimulated by the decay work. The occurrence of phenylium ion as a charged intermediate from the decomposition of benzenediazonium salts in condensed media, its electronic configuration, and its reactivity have been the focus of active interest during the past 50 years.

The decay study has been based on *p*-$C_6H_4{}^3H_2$, which is prepared from hydrolysis of *p*-$C_6H_4(MgBr)_2$ in ^3H_2O, purified by preparative GC, and characterized by ^3H NMR. The precursor was allowed to decay at 25°C in liquid and gaseous systems, for example, in neat liquid MeOH and in MeOH vapor at pressures from 5 to 65 torr (*17*). Ring-tritiated anisole from the reaction sequence



(5)

is formed in gaseous and liquid systems in yields ranging from 82 to 96%. The daughter phenylium ion, which is formed from the decay in a distorted geometrical structure, and hence with excess internal energy, reacts nevertheless in its singlet state. Even more interesting is the intramolecular ^3H distribution, as measured by chemical degradation of anisole. Although the product from liquid systems retains 100% of the label in the original position, the ^3H distribution in the product from gaseous systems depends on the MeOH pressure, that is, on the lifetime of the free phenylium ion. For example, tritiated anisole formed in MeOH at a pressure of 5 torr, corresponding to a lifetime of ~2×10^{-9} s, has the following ^3H distribution: 75% para, 17% meta, and 8% ortho, which indicates significant ^3H scrambling. The label migration and its pressure dependence point to the degenerate rearrangement of free phenylium ion via 1,2 hydride shifts



(6)

The process is slow in comparison with the collision frequency in the liquid phase, as shown by its suppression in neat liquid MeOH, and analysis of the gas-phase results leads to a rate constant for H shifts from 10^{-8} to 10^{-7} s^{-1}.

Automerization of free phenylium ion suggested by decay experiments has stirred a lively debate. In fact, the results of early theoretical studies led to high values, from 44 to 77 kcal mol^{-1}, of the activation barrier $E^‡$ to 1,2 H shifts within $C_6H_5{}^+$. Even taking into account the excess internal energy E^* associated with the "wrong" geometry of the decay ions, the theoretically calculated energy difference $\Delta E = E^‡ - E^*$ was sufficiently large (21 to 52 kcal mol^{-1}) to call into question the automerization process. Hence it was suggested that ^3H scrambling might be a secondary process, involving charged species other than free phenylium ion (*18*).

Much experimental and theoretical work has since been devoted to the question. Further decay experiments conclusively show that ^3H migration does occur within free phenylium ion, before its trapping by the nucleophilic reagent (*19*). Refinement of the computational techniques, in particular use of extended-basis ab initio methods, has actually succeeded in reconciling theory with the experiment. Gradually, the theoretically calculated ΔE gap has narrowed down to the present value of ~8 kcal mol^{-1}, deduced from the latest estimate of $E^‡$, 40 kcal mol^{-1}, and an E^* value of 32 kcal mol^{-1}, computed at the MP2/6 31G* level of theory (*11*). In conclusion, the debate raised by the automerization of phenylium ion represents an excellent example of the impact of the decay technique on theoretical ionic chemistry and of the incentive it has provided to its refinement.

Automerization is just a particular kind of isomerization, a class of reactions extensively investigated by the decay technique. Representative examples include interconversion of the various butyl cations from the decay of selectively multitritiated butanes (*20*); skeletal rearrangements of cycloalkylium ions, such as the classical cyclobutylium to cyclopropylcarbinyl ring contraction (*21*); and the intraannular H migration in free arylium ions (*17*).

Comparative Studies in Different Media

Because of the nuclear nature of the ionogenic process, the decay technique has found useful application in comparative kinetic and mechanistic studies. The reactivity of the same charged species can be evaluated in different media, especially in cases where conventional approaches are deeply affected by changes in the reaction

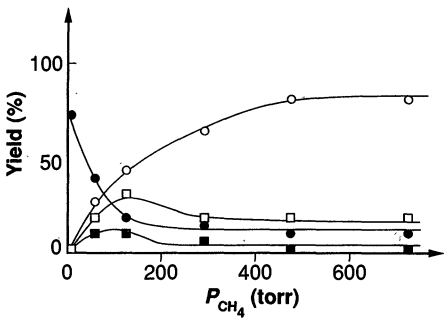


Fig. 3. Yields of the products from vinyl ions in CH_4: isopropyl (○), *n*-propyl (□), allyl (■), and vinyl (●) derivatives at different CH_4 pressures.

environment that modify the very nature of the ionic species, and therefore its reactivity.

An example concerns Friedel-Crafts alkylation, a class of ionic reactions well known for their sensitivity to the influence of the medium, the counterion, the catalyst, and so forth. In recent years, several such reactions, in particular benzylation, have been the subject of detailed kinetic analysis, aimed at rationalizing their peculiar selectivity in the framework of general models of aromatic reactivity. Aromatic benzylation does not follow the Brown relationship between reactivity and orientation, in that its low substrate discrimination, reflected by a low ratio of the rate constant for toluene to the rate constant for benzene, contrasts with its high positional selectivity. To explain this and other results, Olah has suggested a variable transition-state model, in which the high reactivity of strong electrophiles, such as the benzyl ion, is determined by an early transition state leading to an oriented π complex, which subsequently evolves into isomeric σ complexes (*22*). Other workers, noting that formation of the benzylating species by Friedel-Crafts catalysts is frequently rate-determining, suggested that alkylation occurs at, or near to, the diffusion limit, which provides an alternative explanation for the low substrate selectivity that does not conflict with the observed positional discrimination (*23*).

The problem is particularly amenable to the decay technique, because in liquid-phase decay experiments one does not have to worry, as in conventional studies, that the selectivity changes observed in different media are affected by simultaneous modifications of the electrophile, from a solvated ion to a tight ion pair to a polarized complex, and so on. Instead, the influence of the medium can be traced essentially to its specific interaction with the benzyl cation, initially free and lacking a counterion.

Application of the decay technique has involved dissolution of toluene-α,α-$^3H_2$ into different solvents, such as neat aromatics, *n*-hexane, carbon tetrachloride, and nitromethane, all containing benzene, toluene, methanol, and their mixtures (*24*). The labeled products from the decay are diphenylmethane, isomeric benzyltoluenes, and benzyl methyl ether, whose yields, measured in competition experiments, allow evaluation of the relative reactivity of the nucleophiles toward free benzyl ions and whose isomeric composition allows determination of the positional selectivity.

The first clear-cut answer provided by the decay experiments is that reaction of bona fide benzyl ions with benzene and toluene is not diffusion-controlled (for instance, benzylation of C_6H_6 occurs at a specific rate of $\sim 5 \times 10^7$ mol^{-1} liter s^{-1}, well below the limiting value, 2×10^{10} mol^{-1} liter s^{-1}, calculated for diffusion-controlled processes in the system of interest).

The kinetic and mechanistic features emerging from the decay experiments, in particular, the substrate and positional selectivity of the benzyl cation in different solvents and their dependence on the experimental conditions, outline a general reactivity pattern based on the sequence

$$\text{Ph-CH}_2^+ + \text{solvent} \leftrightharpoons [\text{Ph-CH}_2^+ \ldots \text{solvent}] \xrightarrow[-\text{ solvent}]{+\text{ PhR}}$$
$$[\text{Ph-CH}_2^+ \ldots \text{PhR}] \rightarrow \sigma \text{ complexes} \quad (7)$$

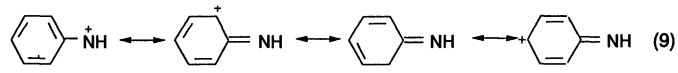
(Ph, phenyl) where the formation of an arene-electrophile adduct, probably the π complex envisaged by Olah, is the rate-limiting step, while the orientation is controlled at a later stage, involving formation of isomeric σ complexes.

Reactivity of Uncommon Charged Species

Free ionic species, which are almost inaccessible by conventional approaches, have successfully been prepared and their reactivity has been investigated by specifically designed decay experiments. A recent example concerns aromatic substitution by free phenylnitrenium ions from aniline-α-α-$^3H_2$

$$\text{Ph-N}^3\text{H}_2 \xrightarrow[-^3\text{He}]{\text{beta decay}} \text{Ph-N}^3\text{H}^+ \quad (8)$$

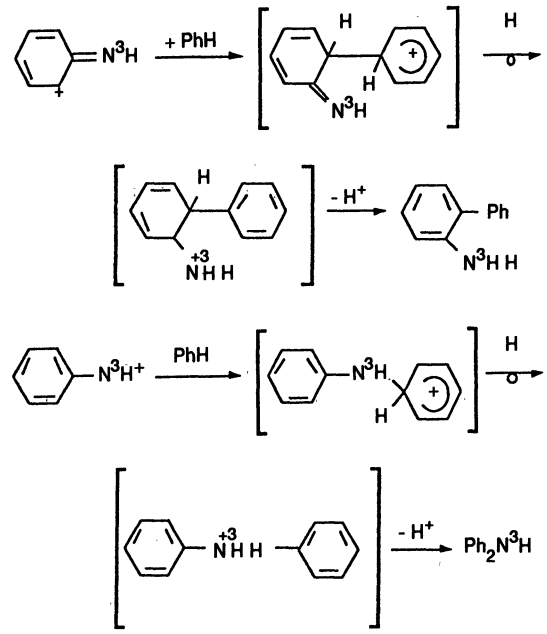
prepared directly in benzene solution by a technique that guarantees the presence of ^3H exclusively in the amino group (*25*). Substantial charge delocalization can be expected in the free phenylnitrenium ions from the decay, consistent with the resonance structures



(9)

and with the results of ab initio calculations.

Indeed, the results of the decay experiments in liquid benzene show that phenylnitrenium ion reacts both as a carbenium ion and as a nitrenium ion, with a slight preference (55:45) for the cationic center at the N atom, yielding respectively isomeric aminobiphenyls and diphenylamine, as in the following example:



(10)

(11)

Thus, decay experiments unambiguously demonstrate the two types of reactivity of free $PhNH^+$, a much needed clarification of the variegated picture provided by conventional studies that are deeply complicated by the presence of the solvent and of the counterion and other effects. For example, the electrophiles obtained upon addition of Lewis acids, or of CF_3COOH and CF_3SO_3H, to PhN_3,

behave as N-electrophiles, whereas those formed upon addition of HCl or H_2SO_4 to PhN_3 behave as C-electrophiles.

Another illustrative example is provided by the preparation of free vinyl ion and the study of its reactivity in gaseous and liquid media. Substituted vinyl cations have long been recognized in solution, but the parent $C_2H_3^+$ ion has been extremely elusive, with only transient derivatives, such as vinyl fluorosulfate, having been characterized at low temperature by NMR spectroscopy. Gaseous $C_2H_3^+$ ions can easily be obtained by mass spectrometry, but the study of their ion-molecule reactions is seriously hampered by extensive decomposition of the products at the low pressures typical of mass spectrometric approaches.

The decay technique has allowed the above limitations to be overcome. In a typical experiment, gaseous $C_2H_2{}^3H^+$ ions from the decay of 1,2-$C_2H_2{}^3H_2$ have been allowed to react with methane (60 to 720 torr) containing a gaseous nucleophile (*26*). Under such conditions, the highly exothermic addition

$$C_2H_2{}^3H^+ + CH_4 \rightarrow [C_3H_6{}^3H^+]_{exc} \quad (12)$$

which is undetectable by mass spectrometry because of the complete fragmentation of the excited adduct, becomes not only detectable but largely predominant (Fig. 3). In fact, as the CH_4 pressure is raised, an increasing fraction of the excited adducts is collisionally stabilized and survives until trapped by the nucleophile, for example,

$$[C_3H_6{}^3H^+]_{exc} \xrightarrow[-M^*]{+M} C_3H_6{}^3H^+ \xrightarrow[-C_4H_8Br^+]{+1,4\text{-}C_4H_8Br_2} C_3H_6{}^3HBr \quad (13)$$

Thus the decay experiments have allowed the first direct observation of the insertion of free vinyl ion into the H–CH_3 bond and positive characterization of the reaction product, whose structure could only be speculated upon on the basis of indirect mass spectrometric evidence.

More recently, the reactivity of free vinyl ion toward aromatic substrates, including benzene, toluene, chlorobenzene, bromobenzene, and anisole, has been investigated in the gas phase and in the liquid phase (*27*). The results obtained in neat liquid aromatics characterize vinyl cation as a typical, if unselective, electrophile, whereas the gas-phase data point to extensive fragmentation and isomerization of the arenium ions formed in the kinetically controlled step of the substitution, justified by its exceedingly high exothermicity, 73 kcal mol^{-1} in the case of benzene (Table 2). The decay experiments have provided the only information so far available on the reactivity and the orientation of the elusive vinyl cation.

Table 2. Selectivity and orientation of the aromatic substitution by free vinyl ions in the liquid phase and in the gas phase. Data in parentheses refer to gas-phase reactions in excess Ar (720 torr).

	Me	Cl	Br	o Me
	44 (17) 30 (69)	48 (20) 26 (75)	44 32	40 (12) 30 (60)
	26 (14)	26 (5)	22	30 (28)
$\frac{k_S}{k_{PhH}}$	1.1 (1.4)	0.8 (1.8)	0.7	2.5 (9.6)

Decay Synthesis

So far, attention has been focused on structural and mechanistic studies based on precursors containing covalently bound ^3H atoms. The decay of other radioactive nuclei has found useful application in the preparation of species inaccessible by conventional chemical methods.

A classical example concerns the perbromate anion, BrO_4^-, that has long defied preparation, to the point that many studies have been published justifying its nonexistence on theoretical grounds (*28*). The breakthrough was accomplished by an approach exploiting the decay of radioactive ^{83}Se

$$^{83}SeO_4{}^{2-} \xrightarrow[decay]{beta} \beta^- + {}^{83}BrO_4^- \quad (14)$$

The perbromate ions labeled with ^{83}Br, a β^- emitter with a half-life of 2.4 hours, were thoroughly characterized by radiochemical techniques, such as coprecipitation with $RbClO_4$, extraction with CCl_4, and reduction with I^- in HCl (*29*).

The successful decay experiment has stimulated attempts to obtain perbromates by chemical methods, which eventually led to a convenient preparative route, based on the oxidation of bromates in alkaline solutions with F_2. A number of other decay syntheses have been reported, including those of phenylxenonium salts from the decay of ^{133}I and those of many organometallic derivatives of Po from the decay of ^{210}Bi (*30*).

Conclusions

The results illustrated in this article represent only a small fraction of what chemical investigations based on radioactive decay have been able to tell us about the existence, the structure, and the reactivity of free ions. Undoubtedly, stimulated by vigorous interest in ionic chemistry, experimental ingenuity will further increase the scope and the sophistication of the decay technique. Yet its unusually demanding experimental requirements will continue to discourage indiscriminate application to unexceptional problems of ion chemistry. Instead, the decay technique will maintain its role as a powerful tool, capable of providing conclusive answers to structural and mechanistic problems whose crucial importance justifies recourse to a sophisticated and yet laborious approach.

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Transport and Storage of Vitamin A

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The requirement of vitamin A (retinoids) for vision has been recognized for decades. In addition, vitamin A is involved in fetal development and in the regulation of proliferation and differentiation of cells throughout life. This fat-soluble organic compound cannot be synthesized endogenously by humans and thus is an essential nutrient; a well-regulated transport and storage system provides tissues with the correct amounts of retinoids in spite of normal fluctuations in daily vitamin A intake. An overview is presented here of current knowledge and hypotheses about the absorption, transport, storage, and metabolism of vitamin A. Some information is also presented about a group of ligand-dependent transcription factors, the retinoic acid receptors, that apparently mediate many of the extravisual effects of retinoids.

THE TERM "VITAMIN A" IS USED FOR RETINOIDS THAT exhibit the biological activity of retinol (Fig. 1). Humans require only minute amounts of vitamin A in their diets (400 to 1300 μg of retinol equivalents per day, depending on age and sex). This amount can easily be obtained in most countries, but an inadequate intake of vitamin A—especially by children—is a common health problem in some areas of the world. Vitamin A deficiency can result in blindness and is associated with increased risk of severe infection and death (*1*).

Intestinal Absorption of Retinol

The main sources of vitamin A in the diet are provitamin A carotenoids from vegetables and retinyl esters from animal tissues (*2*). Essentially all of the retinyl esters are enzymatically converted to retinol in the intestinal lumen before absorption by intestinal cells (enterocytes); carotenoids are partially converted to retinol in the enterocytes (*2*) (Fig. 2).

In the enterocytes, retinol reacts with long chain fatty acids to form retinyl esters before these esters are incorporated into the chylomicrons, the main intestinal lipoproteins. The two enzymes that seem to be involved in the intestinal esterification of retinol are an acyl coenzyme A:retinol acyltransferase (ARAT) (*3*) and a lecithin:retinol acyltransferase (LRAT) (*4*). Under optimal in vitro conditions, ARAT is far more active than LRAT and is induced by large oral doses of retinol (*3*).

Retinol complexed to an intracellular, retinol-binding protein found in the intestine [CRBP(II)] is the preferred substrate for LRAT (*5*). In contrast, uncomplexed retinol in membranes may be esterified by ARAT (*6*). Thus, it is possible that LRAT esterifies retinol during absorption of a "normal" load of retinol, and ARAT esterifies excess retinol (perhaps for temporary storage) when large doses are absorbed and CRBP(II) becomes saturated.

Tissue Uptake of Chylomicron Remnants

Chylomicrons are exocytosed into the intestinal lymph and then move into the general circulation where several processes, such as triacylglycerol hydrolysis and apolipoprotein exchange, result in the formation of chylomicron remnants (*7*). Chylomicron remnants, which contain almost all of the absorbed retinol in the form of retinyl esters, are primarily cleared by the liver (*8, 9*) (Fig. 2; see below).

Extrahepatic uptake of chylomicron remnants occurs mostly in the bone marrow and the spleen and to a lesser extent in the adipose tissue, skeletal muscle, testes, lungs, and kidneys (*8–10*). Thus, chylomicron remnants may be important in the delivery of retinyl esters to tissues such as the bone marrow and the spleen that may experience periods of intensive cell proliferation and differentiation. It was recently demonstrated that chylomicron remnants effectively deliver retinyl esters to myeloid leukemic cells and thereby inhibit proliferation and induce differentiation of such cells (*11*).

The mechanism for cellular uptake of chylomicron remnants is not fully understood. Both the low-density lipoprotein (LDL) receptor and a recently characterized protein that has strong homology with the LDL receptor (LDL receptor–related protein or LRP) can bind apolipoprotein E on chylomicron remnants and may be involved in uptake (*12*). The quantitative role of these two receptors is unknown and may vary in different cells.

Hepatic uptake of chylomicron remnants. In the liver, parenchymal cells (hepatocytes) are responsible for uptake of chylomicron remnant retinyl esters (*9*). The retinyl esters are probably hydrolyzed at the plasma membrane or in early endosomes by a retinyl ester hydrolase (*13*). Retinol is subsequently found in endosomes with other ligands that are taken up by receptor-mediated endocytosis. In contrast to many other ligands that are transferred to lysosomes after processing in endosomes, retinol is transferred to the endoplasmic

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