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Review

Half a century of scrambling in organic ions: Complete, incomplete, progressive and composite atom interchange

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Abstract

Positional exchange of atoms within the given frameworks of gaseous ions and positional exchange of the framework atoms themselves—generally addressed as atom scrambling—belong to the best-known but, in the same time, most irritating characterics of the reactions of organic ions in the gas phase. Half a century now after the phenomenon of atom scrambling has been uncovered, this article spans arbitrarily a number of examples from the manifold of scrambling reactions in organic mass spectrometry. Starting out from of the best-established systems ($C_7H_8^{\cdot+} \rightarrow C_7H_7^+ + H^{\cdot}$), to illustrate an ubiquitous but very complex case, various organic systems that undergo complete ("statistical") hydrogen scrambling are presented. This includes two chemically very different cases where 21 protons are completely interchanged within the lifetime of the ions. Some tutorial aspects are woven in here on the simple combinatorics which have to be applied for calculating the "statistical pattern" which is to be expected for the relative abundances of the isotopomeric fragment ions (and neutral fragments) formed upon fragmentation of an ion which has undergone complete equilibration of a given set of atoms over a given set of molecular sites. Besides the species undergoing complete scrambling, some incompletely scrambling ones are also discussed, including a case where random distribution is reached separately within two moities of the ions alongside with a slow exchange process between these moieties. Ionic species that undergo incomplete but progressive (i.e. lifetime-dependent) scrambling on way to the full equilibration ("randomization") of the partners are also discussed. Finally, returning to apparently simple even- and odd-electron carbocations, several cases of "fractional" scrambling behavior are demonstrated. Here, two or more fractions of the reacting ions exhibit distinct scrambling behavior, for example, one of them fragmenting specifically, another after slow exchange, and still another after complete hydrogen equilibration, but all of them contributing to the same "composite" pattern of isotopomeric fragment ions in the mass spectrum. Although the selection of examples presented here reflects a part of the author's personal fascination on these systems over the years, it is hoped that studies on the variety, beauty and complexity of scrambling phenomena in gaseous organic ions will remain alive for at least a full century when ions to be studied are getting larger and larger. (Int J Mass Spectrom 213 (2002) 101–144) © 2002 Elsevier Science B.V.

Keywords: Hydrogen scrambling; Carbon scrambling; Hydrogen exchange, intramolecular; Proton exchange, intramolecular; Skeletal rearrangements; Proton transfer; Alkylbenzene ions; Phosphor-organic ions

1. Introduction

Why an article about "scrambling ions"? At a point in time when the trans-disciplinary field of mass spectrometry is more than ever governed by a revolv-

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Dedicated to Seymour Meyerson on the occasion of his 85th birthday.

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ing diversity of instrumental methods, which opens its application to virtually every discipline of the natural sciences, the implications of chemical diversity has to be pointed out all the more [1]. Owing to the development of a whole arsenal of ionization and desorption/ionization techniques, mass spectrometry today serves as the major analytical tool for the identification, and often quantification, of all kinds of materials. This now includes volatile and nonvolatile organic compounds but also inorganic salts, element-organic compounds as well as technical and biopolymers. Although a major trend is now being focused on "mild" ionization techniques, which would allow us to detect molecular or quasimolecular ions, another important trend in mass spectrometry involves very hard ionization enabling the complete decomposition of the samples. Today, the traditional—and still indispensable—electron ionization (EI) and chemical ionization (CI) techniques (as well as various laser ionization techniques), all producing ions containing a wide range of excitation energies, are complemented and in part competed by desolvating and desorptive ionization techniques such as electrospray ionization (ESI) [2] and matrix-assisted laser desorption/ionization (MALDI) [3], which chiefly generate stable quasimolecular ions and adduct ions of low internal energy. However, there are even harder methods at hand, originating from inorganic mass spectrometry. Latest developments on inductively coupled plasma (ICP) ionization [4] may turn this extremely harsh methodology which is known to generate bare metal cations from all kinds of chemical environments, towards milder variants reminiscent of CI and CE (charge exchange) as well as flowing afterglow (FA) techniques.

Thus, in contradiction to a general attitude often manifested by scientific users of mass spectrometry, namely, to pay attention to the molecular mass peaks of their samples and scarcely to anything else, the range of energies transferred during the ionization event in mass spectrometry has become even broader through the advent of novel ionization techniques. Considering, in addition, the diverse options of MS^n methodologies, including metastable ion dissociation and various kinds of postionization excitation of stable ions, such as collision-induced dissociation (CID) and infrared irradiation (IRD), the chemistry occurring in mass spectrometers undoubtedly comprises ions bearing an extremely broad range of internal energies. This renders their chemical reactions more complicated than chemistry in solution, but it opens also insights into unexpected and fascinating chemical behavior under unimolecular reaction conditions and in the absence of counter ions and solvent molecules.

Scrambling of atoms comprises many such aspects of fascination. This article is intended to keep the flavor of atomic scrambling alive in a time when mass spectrometry is more than ever considered an analytical tool rather than a tool to study fundamentals of chemistry. The balance between the characters of these two braches of the same tree has always been fruitful and is expected to survive the upcoming developments in the field. From the early days of organic mass spectrometry to the "new age" of biological mass spectrometry exploring genomics and proteomics, mass spectrometers offer, throughout, the opportunity to reveal the individual steps of bond breaking and bond making, which may lead to exchange of atoms or atomic groups in a giving ionic species. Fascination with these phenomena simply comes from the fact that confidence in the constitution of a molecular species starts getting ambiguous when parts of them start interchanging their positions. Hidden reactivities of a chemical species always enter a realm of mystery, and have often been overlooked. Although their occurrence frequently requires some extra internal energy, as mentioned above, and quite some extra efforts by the experimentalists, we have gained much insight into the diversity of scrambling reactions in gaseous ions over the past five decades. In fact, as recalled in Meyerson's reminiscences on organic mass spectrometry [5–8], intuitions about scrambling ions were articulated in as early as 1950 [9] and persisted about a quarter of a century. Fortunately, our understanding of scrambling processes has been matured since, and mechanistic and structural aspects of gas-phase ion chemistry now dominate apparently complicated chemical behavior. Major parts of this understanding have been based on concepts of formerly unconventional reactive intermediates, such as classical and nonclassical carbocations [10], distonic ions [11–13], and ion/molecule complexes formed during unimolecular fragmentation [14,15], the first idea on the existence of the latter also dating back to the 1950s [16].

This article collects some of the various kinds of scrambling reactions, comprising the meaning of "scrambling" from slow interchange of atoms up to complete equilibration of atoms, or atomic groups. The examples chosen cannot reflect the true broadness of scrambling phenomena and much work, which would have deserved being mentioned has been left out. Instead, the author's preference for "aromatic" ions has governed the selection with specific examples from aliphatic or cycloaliphatic chemistry being spiked in. Beyond this, emphasis has been put on the various cases of scrambling, namely those where scrambling is either (i) complete or (ii) incomplete prior to fragmentation, those where it is progressive with increasing lifetime of the ions, and (iii) those where the same ions are subject of different reactivities, thus giving rise to mixtures of ions yielding the same products but after different extents of scrambling. Also, the simple combinatorial calculations on fast interchanging sets of atoms are detailed beyond the simplest basis [17], because it has been felt over the years that students who come across scrambling phenomena for the first time may appreciate some tutorial introduction to these "puzzling systems".

2. Historical

Starting from the analysis of the constituents of high-boiling petroleum fractions in the 1950's, organic mass spectrometry truly developed from "black magic to chemistry" [5]. Inspired by the apparent analogies between pyrolysis and EI-induced fragmentation of organic compounds, several groups including that of Seymour Meyerson and his associates at Standard Oil Company at Whiting/Indiana, USA, started to study the origins of mass spectrometric fragmentation of alkylbenzenes, in particular [16,18–22]. One of the most striking results of this research led Meyerson to suggest that the loss of a hydrogen atom from toluene radical cations (cf. [5], Scheme 3) takes place "at random", that is, after rendering all of the eight hydrogen atoms equivalent and giving rise to formation of the tropylium, cyclo-$C_7H_7^+$, rather than benzyl cations, $C_6H_5CH_2^+$ [21]. In the following decades, this finding became one of the most intriguing facets of organic mass spectrometry and initiated a deluge of investigations on the chemistry of gaseous $C_7H_8^{\cdot+}$ and $C_7H_7^+$ ions and their derivatives and analogues. In many textbooks on organic mass spectrometry and, even more significantly, on organic chemistry, the degeneration of the constituents of the $C_7H_7^+$ ions has been chosen as a paragon to inform, but also to warn, the reader about the interference of atom scrambling in the energized ions that are produced in a mass spectrometer and which provide, eventually, structural information through the mass spectrum.

Another long-lasting example originating from early "scrambling magics" in organic mass spectrometry concerns the nowadays-accepted formation of ion/molecule complexes as reactive intermediates during the unimolecular fragmentation of organic ions in the gas phase [15]. The very first hypothesis in this regard was forwarded by Rylander and Meyerson in 1956, who supposed the formation of the complex [$C_6H_5^+$ *cyclo*-C_3H_6], a "cationated cyclopropane", during the (secondary) fragmentation of ionized tert-butylbenzene [7,16]. This particular case has initiated a number of studies [23–28], of which the most recent one, a high-level ab initio calculation [28], in fact confirms the formation of ion/molecule complexes (such as $CH_2CHCH_2^+$ C_6H_6) and even leaves some option for the original suggestion for the scrambling mechanism [16].

Since the 1950's, many scrambling phenomena occurring in radical cations and even-electron cations have been reviewed [29–32] and one of their aims has been to demonstrate that, in agreement with the view of Meyerson and other colleagues from the field, atom scrambling is nothing else than often quite complex albeit true chemistry.

3. The “statistical” exchange, or complete equilibration, of atoms

3.1. Scrambling synonyms

There is a certain beauty in the reactions of an ionic species in which a group of atoms or all of them undergo an interchange between their sites at such a high rate that the participating atoms lose their positional identity prior to the indicator reaction—typically unimolecular fragmentation or cleavage of the components of the ion/neutral complex. The beauty lies in the symmetrization of the structure resulting from an apparently infinitely fast distribution of all participants within the given set of positions. This “randomization” allows us to ignore the actual mechanism and the kinetics (including kinetic isotope effects) of the interchange. In the sense of a true chemical equilibrium, we assume “complete equilibration” of the mobile atoms and, in the same sense, simple combinatorial mathematics apply to describe such a system behaving statistically. Therefore, the somewhat diffuse term “statistical exchange” is used frequently, suggesting that the atom exchange is so fast that, at the observation point in time, the probability to locate one or more individual participating atoms at certain parts of the ion corresponds, in its mathematically strict meaning, to the statistical distribution of all participants over all sites available in the ion. The term “atom scrambling” is often used in this latter sense: Atoms have been “scrambled”, or suffered “randomization”, if their distribution has reached the state in which each atom has attained the statistical probability to be sited at one of the positions involved. This is equivalent to “complete equilibration” whereas, in contrast, slow and incomplete interchange of atoms means that (complete) scrambling is not achieved.

3.2. Combinatorics

The ionic species of interest may bear a total of $\mathbf{n}$ sites, each of which bearing one atom or group of atoms of the same element but possibly of isotopically different sorts. After cleavage into fragments (between which the atom exchange may but must not necessarily be intercepted), $\mathbf{n}_F$ sites occupied by one atom each remain on the ionic fragment and $\mathbf{n}_N$ sites remain on the neutral fragment, thus $\mathbf{n} = \mathbf{n}_F + \mathbf{n}_N$. We do not have to consider how the separation of the fragments actually occurs and we can also ignore the mutual bonding of the sites. Also, even more than one neutral fragment may be formed. In fact, it is the number of sites that remain in the ionic fragment, being observable when occupied by atoms bonded to them, which is statistically relevant. Hence we write a chemical reaction of a dissociating ion that bears $\mathbf{n}$ reactive sites and yields a product ion bearing $\mathbf{n}_F$ sites as ion[$\mathbf{n}$] $\rightarrow$ ion[$\mathbf{n}_F$] + neutral(s) [$\mathbf{n}_N$].

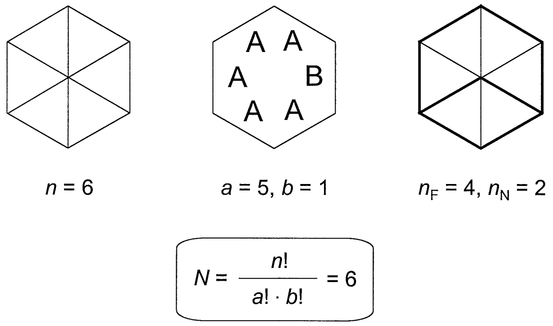


Fig. 1. An ensemble containing six sites, occupied by six (five “A” plus one “B”) completely interchanging partners, falling apart into two fragments containing four and two sites.

The scrambling atoms, or atomic groups, are bonded to the $\mathbf{n}$ sites and may comprise two sets (hardly more) of distinguishable species A and B, such as different kinds of isotopes. With two different isotopes, i.e. $\mathbf{a}$ atoms of A and $\mathbf{b}$ atoms of B, we simply have $\mathbf{a} + \mathbf{b} = \mathbf{n}_F + \mathbf{n}_N = \mathbf{n}$.

Fig. 1 illustrates a six-sited species ($\mathbf{n} = 6$) bearing five atoms A and one atom B ($\mathbf{a} = 5$, $\mathbf{b} = 1$), which separates into two fragments, one of four sites, and another of two sites ($\mathbf{n}_F = 4$, $\mathbf{n}_N = 2$). When A and B are distributed statistically over the six sites, there are $\mathbf{N} = \mathbf{n}!/(\mathbf{a}! \times \mathbf{b}!) = 6!/(5! \times 1!) = 6$ possible situations within the intact species. Its separation into the two fragments makes the six situations distinguishable into two non-equivalent cases (Fig. 2). Case “0” (with zero atoms of type B being sited on the ionic fragment) comprises two situations of identical

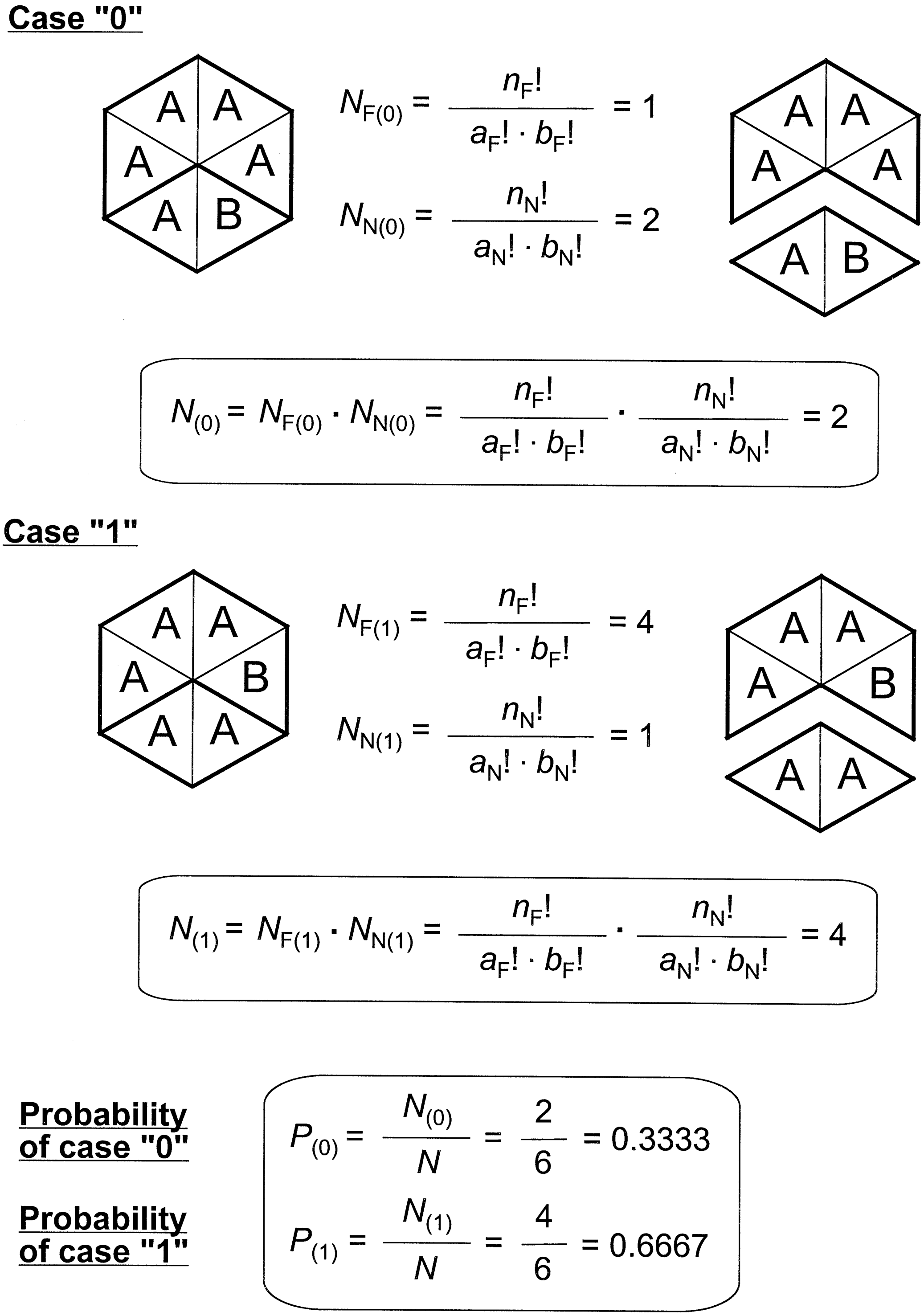


Fig. 2. Absolute numbers and probabilities of cases of the ensemble A_5B to fall apart into two different ways (cases “0” and “1”) after complete scrambling.

fragment composition, only one of which being shown in Fig. 2. They differ only by the site to which the single isotope B is bonded at the neutral fragment. In detail, the relative probability to encounter this case "0", $\mathbf{N}_{(0)} = 2$, is determined by multiplying the relative probability to occupy the four-sited ionic fragment by four isotopes A, viz. $\mathbf{N}_{F(0)} = \mathbf{n}_F!/(\mathbf{a}_F! \times \mathbf{b}_F!) = 4!/(4! \times 0!) = 1$, with the relative probability to occupy the two-sited neutral fragment by (thus) one isotope A and B each, viz. $\mathbf{N}_{N(0)} = \mathbf{n}_N!/(\mathbf{a}_N! \times \mathbf{b}_N!) = 2!/(1! \times 1!) = 2$. In fact, the product $\mathbf{N}_0 = \mathbf{N}_{F(0)} \times \mathbf{N}_{N(0)} = 2$ reflects two equivalent situations of the total of six, as mentioned above.

Case "1" comprises the four situations which have the isotope B bonded at one of the four sites of the ionic fragment ($\mathbf{b}_F = 1$, $\mathbf{a}_F = 3$), thus producing four times the identical fragment compositions. In this case, $\mathbf{N}_{F(1)} = \mathbf{n}_F!/(\mathbf{a}_F! \times \mathbf{b}_F!) = 4!/(3! \times 1!) = 4$ and $\mathbf{N}_{N(1)} = \mathbf{n}_N!/(\mathbf{a}_N! \times \mathbf{b}_N!) = 2!/(2! \times 0!) = 1$ and thus $\mathbf{N}_{(1)} = \mathbf{N}_{F(1)} \times \mathbf{N}_{N(1)} = 4$. Finally, division of the number of identical compositions by the total number of situations, $\mathbf{N}$, yields the probabilities $\mathbf{P}_{(0)}$ and $\mathbf{P}_{(1)}$ of each of the two cases to occur, with $\mathbf{P}_0 + \mathbf{P}_1 = 1$. The reader has doubtless predicted the result, $\mathbf{P}_0 = 1/3$ and $\mathbf{P}_1 = 2/3$, of this simple example of isotope scrambling by intuition.

The numbering of cases ("0", "1", etc.) in Fig. 2 has arbitrarily been adjusted according to the number of B isotopes present in the ionic fragment bearing $\mathbf{n}_F$ sites. Accordingly, $\mathbf{n}_N$ sites have been assigned to the neutral fragment (or fragments). We use the same order when now turning to more complex examples. One of them, which has in fact been realized with a carbocation bearing ten sites with five protons and five deuterons (see below), is illustrated in Fig. 3, again in an abstract manner. Here, two different fragmentation channels (i.e. ways of separation into different sets of after scrambling) are illustrated which, through different appearance, reflect the same statistical distribution of the two sorts of isotopes over the ten sites prior to fragmentation.

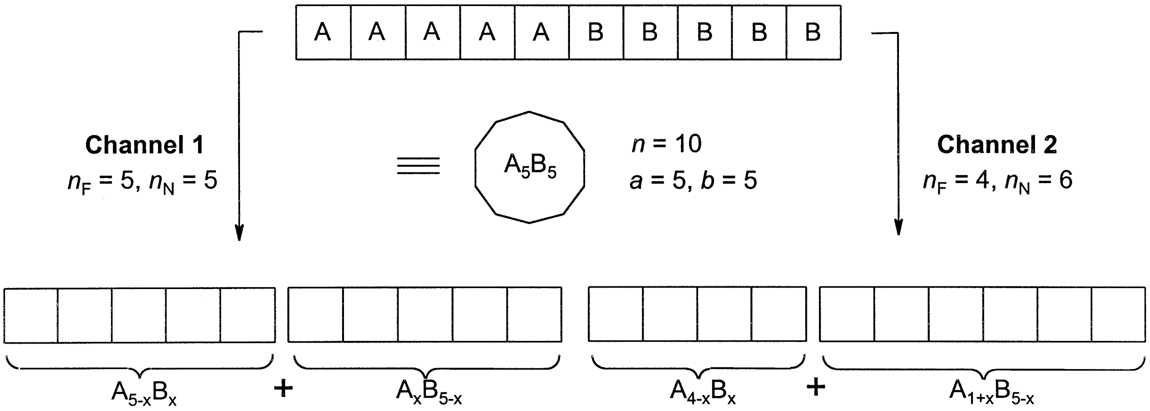
The ten-sited ion of composition "A_5B_5" in two sorts of scrambling atoms ($\mathbf{a} = \mathbf{b} = 5$) may cleave into a five-sited fragment ion ($\mathbf{n}_F = 5$) and a five-sited neutral fragment ($\mathbf{n}_N = 5$). Alternatively, the fragment ion may bear only four sites ($\mathbf{n}_F = 4$) and the neutral fragment six ($\mathbf{n}_N = 6$). When the variable number $\mathbf{x}$ is taken to denominate the number of atoms B in the ionic fragment of a given fragmentation channel (within the limits $0 \leq \mathbf{x} \leq \mathbf{b}$ and $0 \leq \mathbf{x} \leq \mathbf{n}_{F)}$, the probabilities $\mathbf{P}_x$ to generate all possible fragment ions are again expressed by the number of identical compositions (situations) with $\mathbf{x}$ atoms B on the fragment ion times the number of compositions (situations) with ($\mathbf{b} - \mathbf{x}$) atoms B on the neutral fragment, divided by the total number of situations in which $\mathbf{b}$ atoms of B are distributed on the ten-sited reactant ion. Clearly, the range of the variable $\mathbf{x}$ is limited not only by the number $\mathbf{b}$ of B atoms but also by the number of sites on the (either ionic or neutral) fragment that provides the smaller number of sites for scrambling. In the present case, this is reflected by the fact that only five cases result in the second fragmentation channel whereas six cases result in the first one. Fig. 3 illustrates this for both of the fragmentation channels. The symmetrical distributions in $\mathbf{P}_x$ in both cases are the consequence of the same number of the different isotopes, viz. A_5B_5. A concrete example for this branched model system

$$A_{5-x}B_x + A_xB_{5-x}\ (0 \leq x \leq 5) \leftarrow A_5B_5$$
$$\rightarrow A_{4-x}B_x + A_{1+x}B_{5-x}\ (0 \leq x \leq 4) \qquad (1)$$

is protonated 1-phenyl-2-(*p*-tolyl)ethane, which will be presented below.

3.3. Fast H/D equilibrating ions

Protonated aromatic rings very easily undergo rapid isomerization through successive and reversible 1,2-shifts of protons. The height of the energy barrier of this process in the parent benzenium ion (**3**) and related simple arenium ions was studied at length and has converged now to 7.9–8.3 kcal mol^{-1}, not far from the value determined for superacidic solution [33–35]. Prior to unimolecular fragmentation, this leads to complete equilibration of the seven hydrogens in ions **3**. Benzenium ions form the frequent *m/z* 79 peak in the mass spectra of numerous aromatic compounds—not only aromatic hydrocarbons. For



$$P_x = \frac{\dfrac{n_F!}{(n_F - x)! \cdot x!} \cdot \dfrac{n_N!}{[a - (n_F - x)]! \cdot (b - x)!}}{\dfrac{n!}{a! \cdot b!}}$$

Channel 1	**$A_{5-x}B_x$**	**A_xB_{5-x}**	
x	$(n_F - x)! \cdot x!$	$[a - (n_F - x)]! \cdot (b - x)!$	P_x
0	$5! \cdot 0!$	$0! \cdot 5!$	0.00396
1	$4! \cdot 1!$	$1! \cdot 4!$	0.09921
2	$3! \cdot 2!$	$2! \cdot 3!$	0.39683
3	$2! \cdot 3!$	$3! \cdot 2!$	0.39683
4	$1! \cdot 4!$	$4! \cdot 1!$	0.09921
5	$0! \cdot 5!$	$5! \cdot 0!$	0.00396
Channel 2	**$A_{4-x}B_x$**	**$A_{1+x}B_{5-x}$**	
x	$(n_F - x)! \cdot x!$	$[a - (n_F - x)]! \cdot (b - x)!$	P_x
0	$4! \cdot 0!$	$1! \cdot 5!$	0.02381
1	$3! \cdot 1!$	$2! \cdot 4!$	0.23810
2	$2! \cdot 2!$	$3! \cdot 3!$	0.47619
3	$1! \cdot 3!$	$4! \cdot 2!$	0.23810
4	$0! \cdot 4!$	$5! \cdot 1!$	0.02381

Fig. 3. The completely scrambling ensemble A_5B_5 falling apart through two different fragmentation channels. Channel 1 produces two five-sited fragments and channel 2 produces a four and a six-sited fragment).

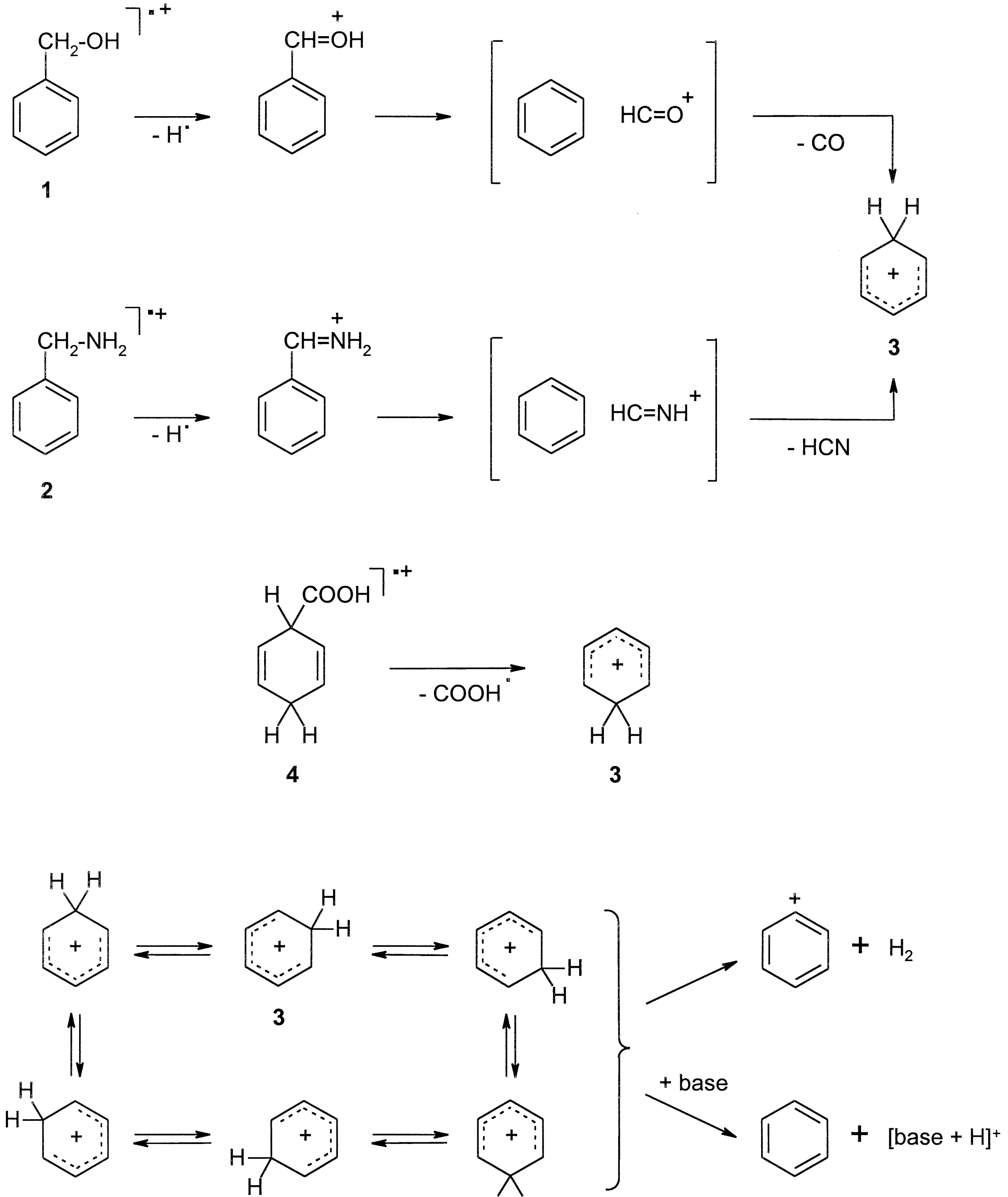
example, benzylic alcohols, e.g. **1**, produce ion **3** or its derivatives by disintegration of the elements of the alcohol functionality [36,37]. The first case of hydrogen scrambling occurring within benzenium ions formed by unimolecular fragmentation was reported by Bruins and Nibbering [38] for the $C_6H_7^+$ ions generated by loss of HCN (or HNC) from the $[M - H]^+$ ions of benzylamine (**2**). A more directed approach was exemplified in our laboratory in the case of the $[M - COOH]^+$ ions of 1,4-dihydrobenzoic acid (**4**) and its derivatives (Scheme 1) [39–41]. Ions **4** are particularly fragile towards loss of the COOH group and hence scrambling prior to this fragmentation is assumed to be neglible.

On energetic grounds and general insights into the chemistry of benzenium ions, it is beyond any doubt that the seven hydrogens in the benzenium ions undergo complete equilibration. However, this behavior is not directly reflected from complementary labeling (Scheme 2), because the loss of dihydrogen is subject to a kinetic isotope effect. Thus, H_2 loss from both $C_6H_5D_2^+$ and $C_6H_2D_5^+$ isotopomers is favored and D_2 loss is disfavored. The so-called “complementary” labeling, i.e. labeling of exactly those positions in one isotopomer which are unlabeled in the other, does not help in such as case. A strict proof would be at hand if two isotopomers with the same isotopic composition but with different positional orientation of the label were compared (e.g. protonated [2,4,6-D_3]- and [1,2,3-D_3]benzene). Actually, this experiment has never been reported with the parent benzenium ions (however, see Sec. 5 for related arenium ions).

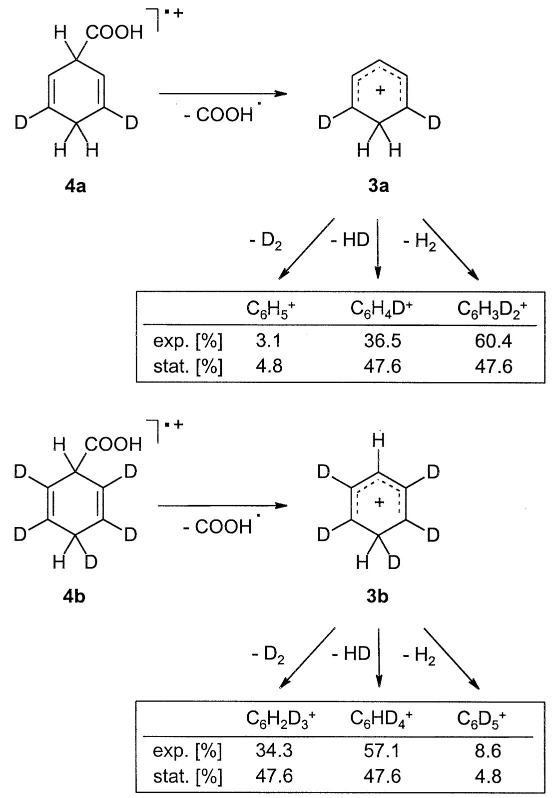
A case where complete scrambling has been proven concerns the $C_7H_8^{\cdot+}$ ions generated from toluene and cycloheptatriene. In a pioneering study, Howe et al. [42] determined the degree of scrambling in the radical cations of toluene and 1,3,5-cycloheptatriene for selected ranges of internal energies (see below). The toluene isotopomers were synthesized such that complementary labeling was in fact achieved with respect to both composition and by site-specificity (Scheme 3). Ions of least internal energy (metastable ions) bearing the same number of deuterium atoms at different positions, viz. $C_6H_5CD_3^{\cdot+}$ (**5a**) and $C_6H_3D_3CH_3^{\cdot+}$ (**5b**), exhibited the same $[M - H]^+/[M - D]^+$ ratios (4.68 and 4.77), indicating complete scrambling prior to fragmentation. For the isotopomer $C_6D_5CH_3^{\cdot+}$ (**5c**) having the complementary composition ($C_7H_3D_5$ in contrast to $C_7H_5D_3$), $[M - H]^+/[M - D]^+$ was found to be 1.68. Normalization of the two values for the different H/D contents (3/5 and 5/3, respectively) led, within experimental error, to the same value, *i*, for all three isotopomers ($i = k_H/k_D = 2.8$), expressing the fact that each single H atom is lost 2.8 times more likely than each single deuterium atom is. A similar treatment for metastable [D_1]- and [D_6]-labeled cycloheptatriene radical cations **6a** and **6b** indicated also (almost) complete H/D scrambling and $i = k_H/k_D = 2.6$. In a later study involving high-resolution mass spectrometry and both deuterium and ^{13}C labeling on high-energy fragmentation channels of **5** and **6** ions, the set of complementarily labeled toluene isotopomers was considerably extended [43].

The rigorous approach of applying complementary labeling allows one to even determine the “degree of scrambling”, α, when scrambling does not occur to completion ($\alpha < 1$). The unimolecular chemistry of ions **5** and **6** has been studied in-depth in this respect [42,43]. When the complementarily labeled $C_7(H,D)_8^{\cdot+}$ ions of increasingly higher internal energies were probed, both the degrees of scrambling and the kinetic isotope effects ($1.22 \leq i \leq 2.33$) associated with hydrogen loss were found to decrease, in accordance with expectation. This result was based on the calculation (Scheme 3) of the contributions of the individual methyl and ring hydrogen isotopes to the fragmentation, including the discrimination of D over H loss. Further discussion on “slow” and “incomplete scrambling”, i.e. limited extent of isotope exchange, will be presented in several sections below.

Complete hydrogen scrambling is not limited to small ions, the fragmentation of which often requires relatively high excitation energies. For example, the losses of H_2 from $C_6H_7^+$ and of $H^{\cdot}$ from $C_7H_8^{\cdot+}$ are endothermic by ~2.7 and 3.0 eV (62 and 69 kcal mol^{-1}), respectively, exceeding by far the energy barriers towards hydrogen shift. Larger ions often have less energy-demanding fragmentation channels owing to the presence of substituted or branched



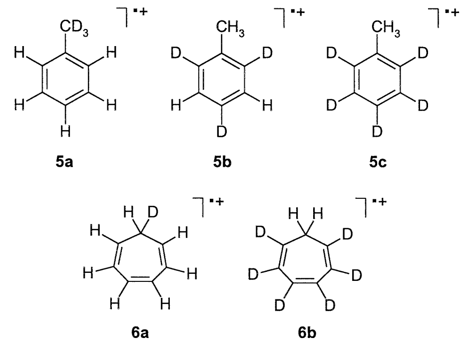
Scheme 1. Formation of benzenium ions from different radical cationic precursors and fast proton ring walk prior to H_2 loss or intermolecular proton transfer.



	$C_6H_5^+$	$C_6H_4D^+$	$C_6H_3D_2^+$
exp. [%]	3.1	36.5	60.4
stat. [%]	4.8	47.6	47.6

	$C_6H_2D_3^+$	$C_6HD_4^+$	$C_6D_5^+$
exp. [%]	34.3	57.1	8.6
stat. [%]	47.6	47.6	4.8

Scheme 2. Loss of dihydrogen isotopomers from long-lived complementarily deuterium labeled benzenium ions.



$\frac{[M - H]^+}{[M - D]^+}$	5a	5b	5c	6a	6b
exp.	4.68	4.77	1.68	17.7	0.89
stat.	1.67	1.67	0.60	7.0	0.33
exp./stat.	2.81	2.86	2.80	2.53	2.67

$$\left[\frac{[M-H]^+}{[M-D]^+}\right]_{5a} = \frac{\alpha \cdot \frac{5i}{5i+3}}{(1-\alpha) + \left(\alpha \cdot \frac{3}{5i+3}\right)}$$

$$\left[\frac{[M-H]^+}{[M-D]^+}\right]_{5b} = \frac{(1-\alpha) + \left(\alpha \cdot \frac{5i}{5i+3}\right)}{\alpha \cdot \frac{3}{5i+3}}$$

$$\left[\frac{[M-H]^+}{[M-D]^+}\right]_{5c} = \frac{(1-\alpha) + \left(\alpha \cdot \frac{3i}{3i+5}\right)}{\alpha \cdot \frac{5}{3i+5}}$$

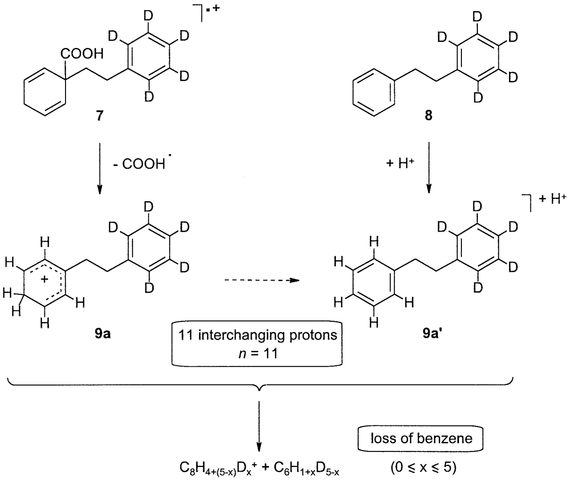
Scheme 3. Loss of hydrogen atoms from long-lived toluene and cycloheptatriene radical cations.

sp^3-hybridized centers and functional groups. For the same reason, however, hydrogen shifts and skeletal rearrangements are often facilitated here. Thus, complete scrambling involving, in particular, all hydrogen atoms of an ion may still be observed. However, larger ions tend to undergo "complete" scrambling regio- and stereoselectively, that is, between sites bearing sufficiently reactive atoms. Of course, such a fast but selective interchange of atoms is mechanistically much more informative than a complete equilibration between all hydrogen or carbon atoms present in a scrambling ion. Alkyl-substituted benzenium ions ($R\text{-}C_6H_6^+$) and certain higher derivatives of toluene radical cations $R\text{-}C_7H_7^{\cdot+}$ (the chemistry of which has been reviewed [31,30]) represent instructive examples for fast regioselective hydrogen exchange. However, these classes of ions also comprise slow exchange processes, i.e. incomplete scrambling, and some examples will be discussed in Sec. 9.

4. Complete hydrogen scrambling between the two or more hydrocarbon groups

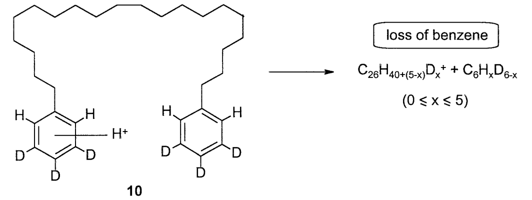
4.1. Protonated α,ω-diphenylalkanes

Complete hydrogen scrambling takes place within larger alkylbenzene cations when two or more aromatic rings are present in the same ion. This was found to be a general phenomenon, which may even be used as a criterion to elucidate isomerization mechanisms (see below). Thus, protonated α,ω-di-



Loss of [%]	C_6HD_5	$C_6H_2D_4$	$C_6H_3D_3$	$C_6H_4D_2$	C_6HD_5	C_6H_6
exp. (**9a'** from **7**)	1.4	17.1	43.8	29.9	7.5	0.3
exp. (**9a'** from **8**)	1.4	16.0	43.0	32.8	6.6	0.2
stat. (H_6D_5)	1.3	16.2	43.3	32.5	6.5	0.2

Loss of [%]	C_6D_6	C_6HD_5	$C_6H_2D_4$	$C_6H_3D_3$	$C_6H_4D_2$	C_6H_5D
exp. (**10**)	1.4	7.4	30.0	39.0	19.0	3.7
stat. (H_5D_6)	0.2	6.5	32.5	43.3	16.2	1.3



Scheme 4. Formation and fragmentation of [ring-D_5]-labeled protonated 1,2-diphenylethane **9a** and frgamentation of [ring,ring-D_6]-labeled protonated 1,20-diphenyleicosane **9a**.

phenylalkanes including ions **9** and **10** undergo a virtually complete interchange of the eleven ring hydrogens within the lifetime of metastable ions in a sector-field mass spectrometer (10–30 μs). This was discovered originally by studying the EI-induced fragmentation of 1,4-dihydrobenzoic acids bearing an ω-phenylalkyl substituent at C-1, e.g. **7** [40], but was found to occur as well with protonated α,ω-diphenylalkanes, e.g. **8**, generated by CI(iC_4H_{10}) (Scheme 4) [44]. All these ions undergo complete scrambling of the eleven ring hydrogens irrespective of the length of the aliphatic chain prior to loss of benzene as the only fragmentation channel. The fact that the presence of up to twenty methylene groups in ions **10** does not slow down the interannular proton exchange has been traced to the attractive interaction between protonated and neutral phenyl rings, in accordance with thermodynamics of protonated benzene dimer and diphenylalkanes [45–47]. The table inserted in Scheme 4 shows that the relative abundances of the benzene isotopomers lost from the "A_6B_5" and "A_5B_6" scrambling systems (**9** and **10**) system are identical, within the limits of experimental error, to the probabilities calculated for complete scrambling [Fig. 4(a), left and right]. Clearly, the mirror-type pattern of the two cases result from the complementary number of H and D atoms at the eleven sites involved into the highly regioselective ring-to-ring ("interannular") scrambling.

A large number of modified and extended protonated α,ω-diphenylalkanes have been studied over the years to gain closer insight into the origins and limitations of this fast interannular proton scrambling. It was found to be as ubiquitous as the "annular" proton ring walk in simple benzenium ions (see above). Substitution of a ring position by a methyl group as in **11** [48] or even by a methoxy group as in **12** [49] or partial restriction of the aliphatic link as in protonated 2-benzylindane (**13**) [50] apparently does not slow down the interannular exchange at all. Likewise, a cyclohexane spacer in protonated *cis*-1,4-dibenzylcyclohexane allows the fast interchange to occur; however, a *trans*-cyclohexanediyl unit hinders this process considerably [51]. Extension of the scrambling system to 15, 16, and even 21 protons in protonated 2,2-dibenzylindane (**14**), tribenzylmethane (**15**), tris(β-phenethyl)methane (**16**) and tetrabenzylmethane (**17**), respectively, does not change the behavior: Long-lived (metastable) ions reflect complete scrambling of all hydrogen at the aromatic rings prior to loss of benzene [50,52]. Interestingly, the oligophenylisoalkane ions, in particular **15** and **17**, dissociate mainly by expulsion of two benzene neutrals instead of only one, and it is obvious that the proton equilibration has to be accomplished before the first molecule of benzene is lost [50,53]. In the case of ions **17**, the lack of competing benzene losses from the corresponding $[M - H]^+$ ions in the normal CI mass spectra (see below) has allowed us to unravel the

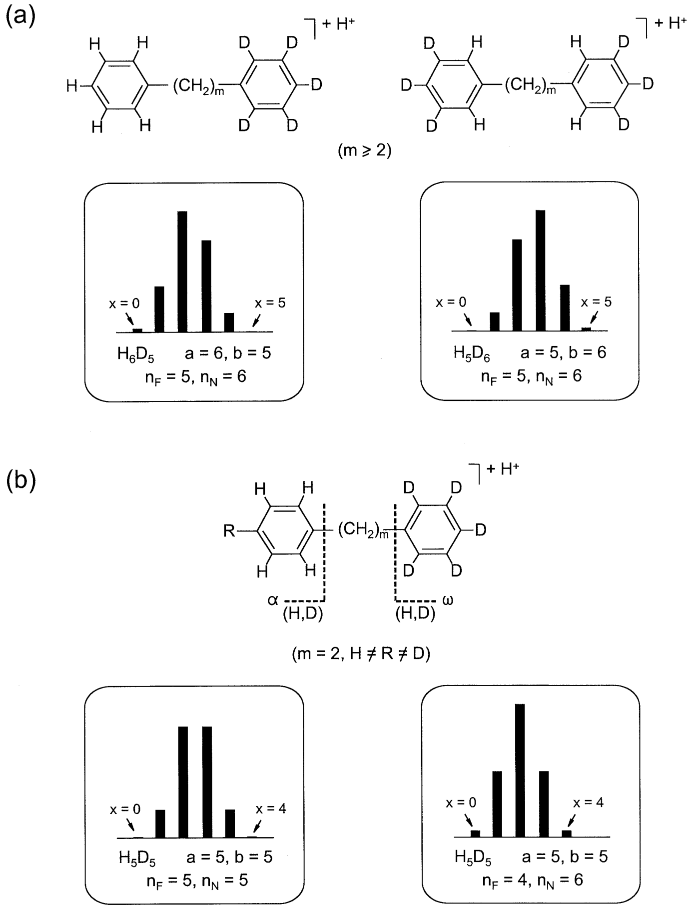


Fig. 4. (a) Relative abundances shown as mirrorlike "statistical pattern" for the loss of deuterated benzenes from [ring-D_5]-labeled and [ring,ring-D_6]-labeled protonated α,ω-diphenylalkanes (cf. Scheme 4). (b) Symmetrical pattern for the loss of benzene isotopomers from [ring-D_5]-labeled protonated *para*-substituted derivatives.

complete interannular proton exchange even in the short-lived $[M + H]^+$ ions fragmentation in the ion source, i.e. within $\sim$1 μs [50]. Fig. 5 illustrates this unusual case for the loss of "$C_{12}(H,D)_{12}$" from metastable ions **17a** dissociating within the first-field-free region of a sector-field mass spectrometer.

4.2. (ω-Phosphorylidenealkyl)phosphonium ions

The fast and virtually complete exchange between 21 protons in protonated tetrabenzylmethane **19** represents a record in the world of hydrogen scrambling in organic ions. Kinetic simulations on this kind of isomerization have led to an estimation for the rate of the individual proton transfer steps in this sort of ions (see Sec. 8). Recently, Runge and Veith [54] observed a virtually complete multiproton exchange occurring in a series of singly charged (ω-phosphorylidenealkyl)-phosphonium ions, e.g. **19**, generated via the "monosalt" cations such as **18** obtained from the corresponding α,ω-alkane-bis(trimethylphosphonium) diiodides under ESI conditions (Scheme 6). Amusingly, and in quite striking coincidence with protonated tetrabenzylmethane, 21 protons are again involved in the fast and regioselective proton scrambling within ions **19** prior to loss of trimethylphosphine. Scrambling in the precursor ions of **19** can be strictly excluded [54]. Ions **19** and their higher homologues may all be

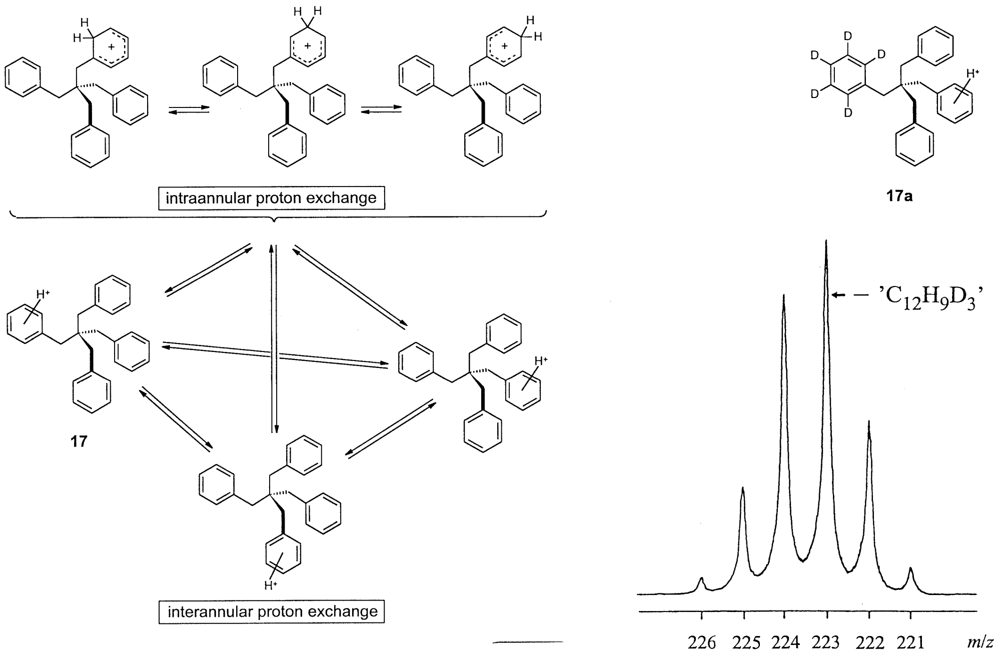


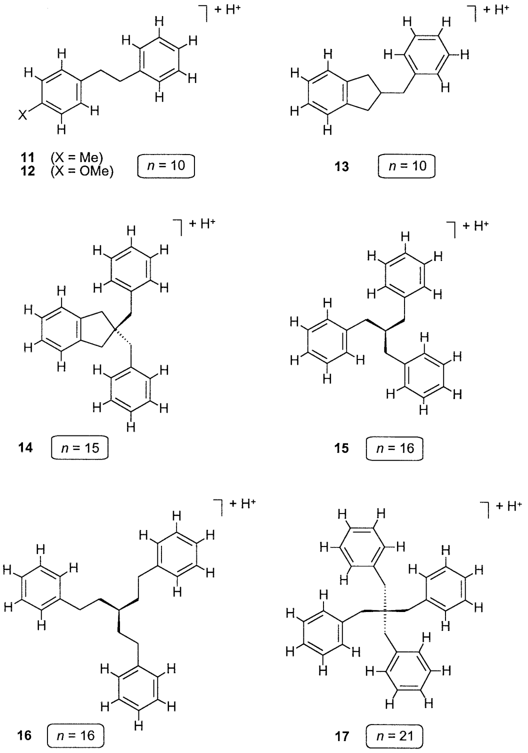
Fig. 5. 21-Proton-exchange processes in protonated tetrabenzylmethane **17** and experimentally observed pattern for the loss of two benzene isotopomers from its [ring-D_5]-labeled analogue **17a**.

regarded as protonated bis-ylides (cf. **19′**) in analogy to the protonated α,ω-diphenylalkanes.

In the case of the [D_{18}]-labeled precursor **18a**, five isotopomers of the phosphonium ion **20** are formed. This observation indicates that the iodide anion abstracts both H^+ and D^+ in **18a**, thus enabling fast unimolecular H^+/D^+ equilibration to occur in both the [D_{18}]- and [D_{17}]-isotopomers **19b** and **19a**, respectively (cf. Scheme 6). Combinatorial calculations show that these intermediates are generated in similar amounts. In further parallel with the protonated α,ω-diphenylalkanes, long-chain homologues of **19**, such as the tetradecamethylene congener, behave in the same way. Sterically hindered analogues show no long-range proton exchange, corresponding to the largely suppressed interannular proton exchange in protonated trans-1,4-dibenzylcyclohexane [51]. It is quite interesting to speculate about the fine details of the proton transfer in these two chemically much different species. Whereas the intraannular proton exchange in ions **17** may even accelerate the overall scrambling by interannular proton transfer (cf. Fig. 5) [50], scrambling between the methylene and methyl groups at the same phosphorus centre appears to be difficult and probably requires intervention of the remote phosphonium group. It appears tempting to increase the number of sites and interchanging hydrogen atoms far beyond $n = 21$ in both systems. Finally, it is noted that the intramolecular proton exchange in ions **19** occurs independently from an intermolecular proton exchange process with the residual water present in the ion trap mass spectrometer [54]. Thus, starting from unlabeled **19** and flushing the trap with D_2O, up to 21 deuterons can be incorporated, an observation also pointing to the crucial role of the phosphorylidene functionality in these species.

4.3. Substituted protonated α,ω-diphenylalkanes

The interannular proton exchange in protonated α,ω-diphenylalkanes such as **11** and related benzocycloalkanes such as **13** deserves further comment. First, it provides illustrative examples for the obser-



Scheme 5. Various protonated α,ω-diphenylalknes and their branched congeners undergoing interannular proton equilibration prior to fragmentation.

vation of two different but symmetrical distribution pattern indicative of complete scrambling of the ten “aromatic” protons [cf. Fig. 3 and 4(b)]. Second, this kind of proton exchange has gained importance for the fragmentation of cations, which, at first glance, should not undergo this isomerization process (see below).

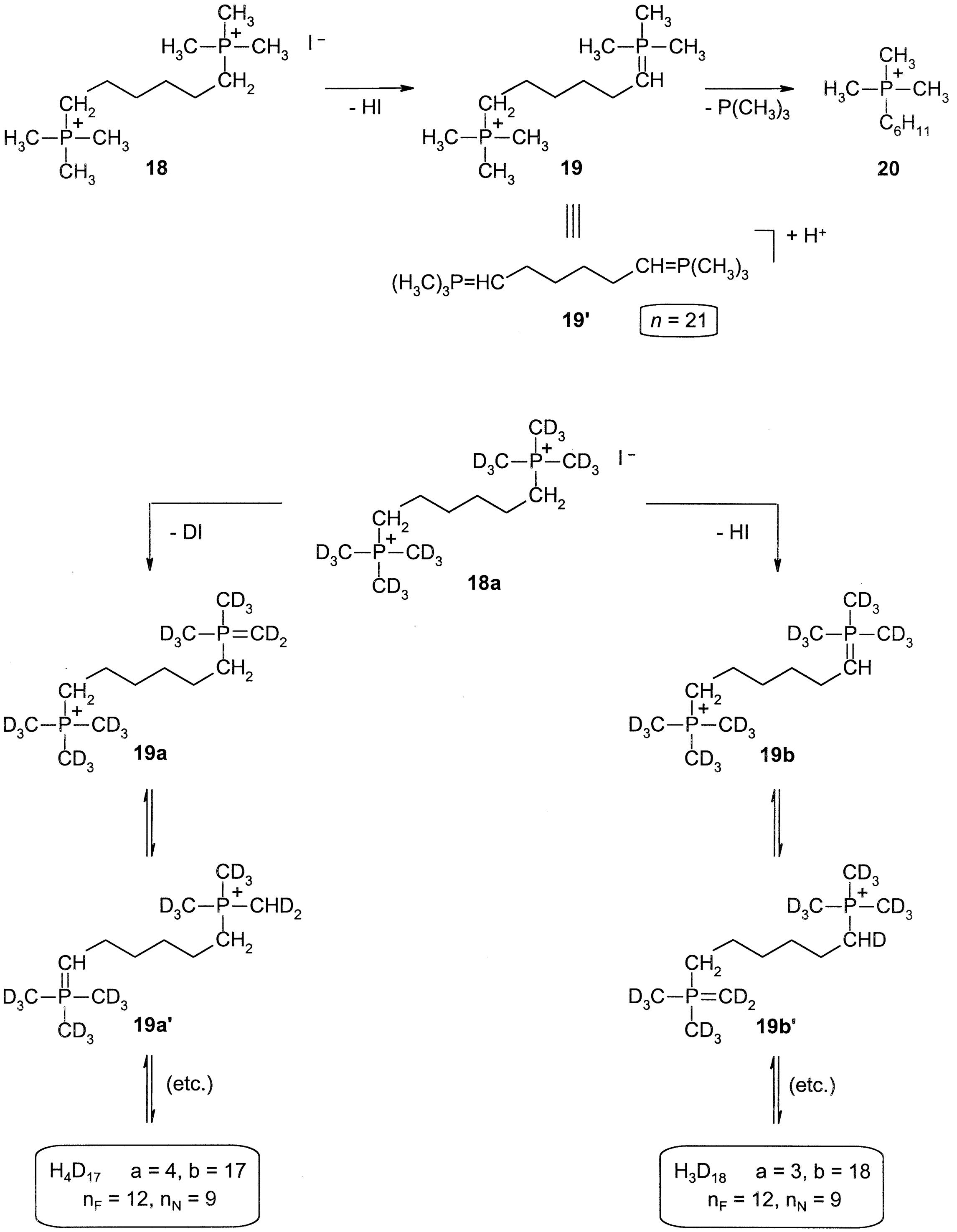
Metastable ions **11a** undergo competing loss of toluene and benzene, and both fragmentation channels exhibit complete equilibration of the ten hydrogens at the aromatic rings (Scheme 7). The actual mass-analyzed ion kinetic energy (MIKE) spectrum is reproduced in Fig. 6 [48]. The observed distributions of six toluene and five benzene isotopomers agree almost perfectly with those calculated for an A_5B_5 scrambling system which falls apart either into two five-sited fragments ($\mathbf{n}_F = \mathbf{n}_N = 5$) or into a four- and a six-sited fragment ($\mathbf{n}_F = 4$, $\mathbf{n}_N = 6$) [Fig. 4(b)]. In the latter case, the number of possible isotopomers (i.e. the number of compositions, $x + 1$, cf. Fig. 3) is diminished to $x + 1 = 5$ since one of the fragments contains only four sites ($\mathbf{n}_F = 4$). The same limitation holds for protonated 2-benzylindane **13a**, where one of the five H and also one of the five D atoms has to remain on the neutral (benzene) fragment.

There are many other examples of complete but regiochemically restricted scrambling of protons and hydrogen atoms. In this respect, the contrasting behavior between protonated aromatic molecules and the corresponding radical cationic species is particularly interesting. In fact, several examples concern the radical cations of the alkylbenzenes, the protonated forms of which have been discussed above. Also, suitably functionalized arene radical cations fall into this category.

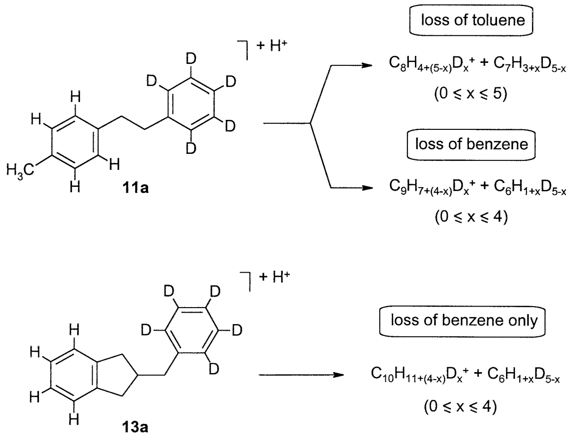
4.4. Complete hydrogen scrambling involving only the ortho positions of aromatic rings

As discussed above, intra- and interannular hydrogen exchange are, in general, fast and ubiquitous processes in protonated arenes [31]. In the radical cations of aromatic compounds, however, the facile proton ring-walk was found to be largely suppressed, although certain ring hydrogen atoms may participate in the scrambling processes [30]. Thus, hydrogen atoms sited at ortho positions with respect to suitable functional groups undergo an interchange which may reach “statistical” completeness without involving the other ring hydrogen meta and/or para to that functional group. There are only few well-studied cases but they are quite telling in terms of (distinct) reaction mechanisms.

The classical case here concerns the radical cations of benzoic acid. The long-lived ions **23** were found to exchange the three hydrogen atoms at the carboxyl and the ortho positions prior to loss of $OH^{\cdot}$ [55,56] (Scheme 8). Achieving the fully statistical distribution ($n = 3$) in the metastable ions strongly depends on the excitation energy and ion lifetime [57] and, in fact, ions **23** were used as a prototype system to investigate the effect of lifetime on the extent of scrambling using various techniques [55–61] (cf. Sec. 8). It appears



Scheme 6. (a) Primary and secondary fragmentation of the "salt ions" **18** via the phosphorylidenephosphonium ions **19** and (b) 21-proton-exchange in the corresponding $[D_{17}]$- and $[D_{18}]$-isotopomers generated by HD and HI loss from the analogue **18a**.



Loss of [%]	$C_7H_3D_5$	$C_7H_4D_4$	$C_7H_5D_3$	$C_7H_6D_2$	C_7H_7D	C_7H_8
exp. (**11a**)	0.8	10.2	38.9	39.2	10.3	0.6
stat. (H_5D_5)	0.4	9.9	39.7	39.7	9.9	0.4
Loss of [%]	C_6HD_5	$C_6H_2D_4$	$C_6H_3D_3$	$C_6H_4D_2$	C_6H_5D	
exp. (**11a**)	2.4	23.9	47.1	24.4	2.2	
exp. (**13a**)	2.6	21.9	46.7	24.6	3.8	
stat. (H_5D_5)	2.4	23.8	47.6	23.8	2.4	

Scheme 7. Two cations undergoing complete H_5D_5 scrambling prior to competing losses of benzene and toluene (**11a**) and of benzene isotopomers (**12a**).

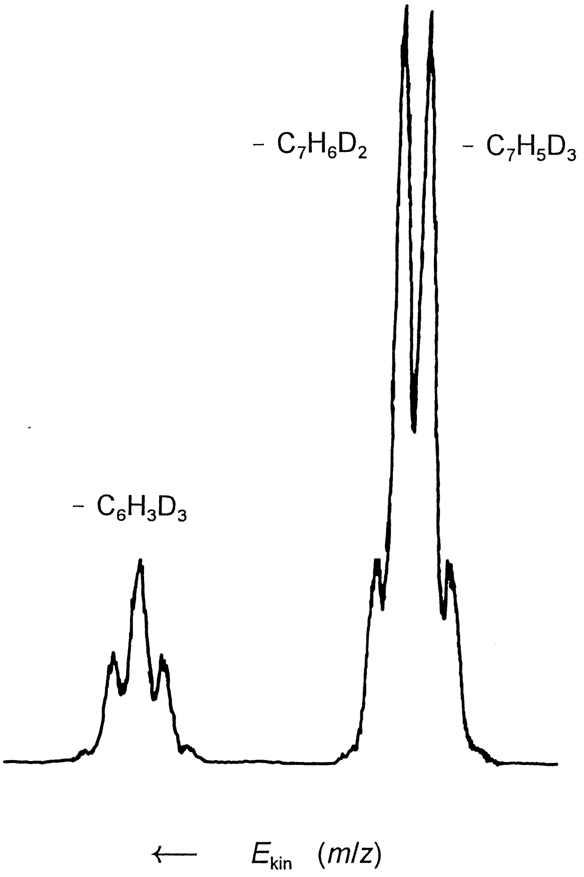
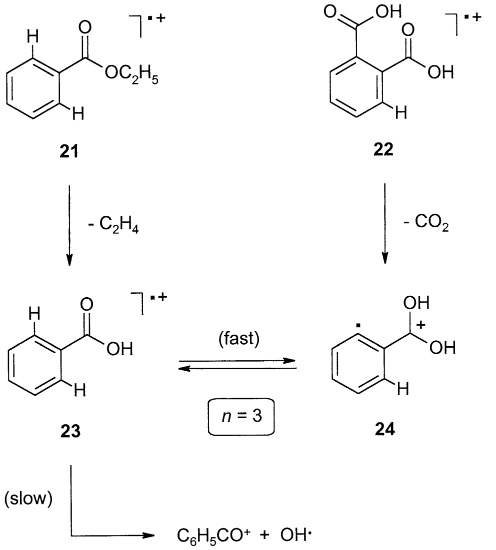


Fig. 6. MIKE spectrum of ions **11a** (cf. Fig. 4 and Scheme 7).

obvious that ions **24** are formed as intermediates during the exchange process, as suggested from the finding that ionized phthalic acid (**22**) undergoes the same scrambling prior to secondary fragmentation (i.e. loss of OH$^\bullet$) [55,58]. However, complications arise from competing fragmentation channels [58]. Detailed studies on the corresponding fragmentation path of ionized ethyl benzoates (e.g. **21**) [59,60] using combined ^{18}O and deuterium labeling also allowed one distinguish between the equilibration of the three hydrogen atoms and the progressive chemical equivalence of the two oxygen atoms [58,61]. In fact, the mixed isotope labeling even revealed the fact that the oxygen atoms are lost with the same probability but that they remain nonequivalent in their bonding relation to the initial carboxyl and ortho hydrogen atoms. It is worth noting that the early interpretation that the hydrogen scrambling in ions **21** involves exclusively the hydrogen at the ortho but not at the meta and para positions was intuitive in that it was based essentially on the [*O*-D_1]-isotopomer only. However, the remarkable ortho-regioselectivity was confirmed later by complementary labeling [56,61b,62].

It may amuse the reader to learn that the ortho-selective hydrogen scrambling in ionized benzoic acid has been used even as analytical tool. Thus, the regiospecificity and the deuterium content of [2,6-D_2]-labeled 1,3-diphenylpropanes were determined after classical permanganate oxidation of the hydrocarbon to give the corresponding [2,6-D_2]-benzoic acid [63,64].

A phenomenologically similar but mechanistically quite different case of ortho-regioselective hydrogen scrambling was observed very recently [65]. The long-lived radical cations of dimethylphenylphospane (**25**) undergo a complete exchange between the two ortho- and the six-methyl hydrogen atoms prior to loss



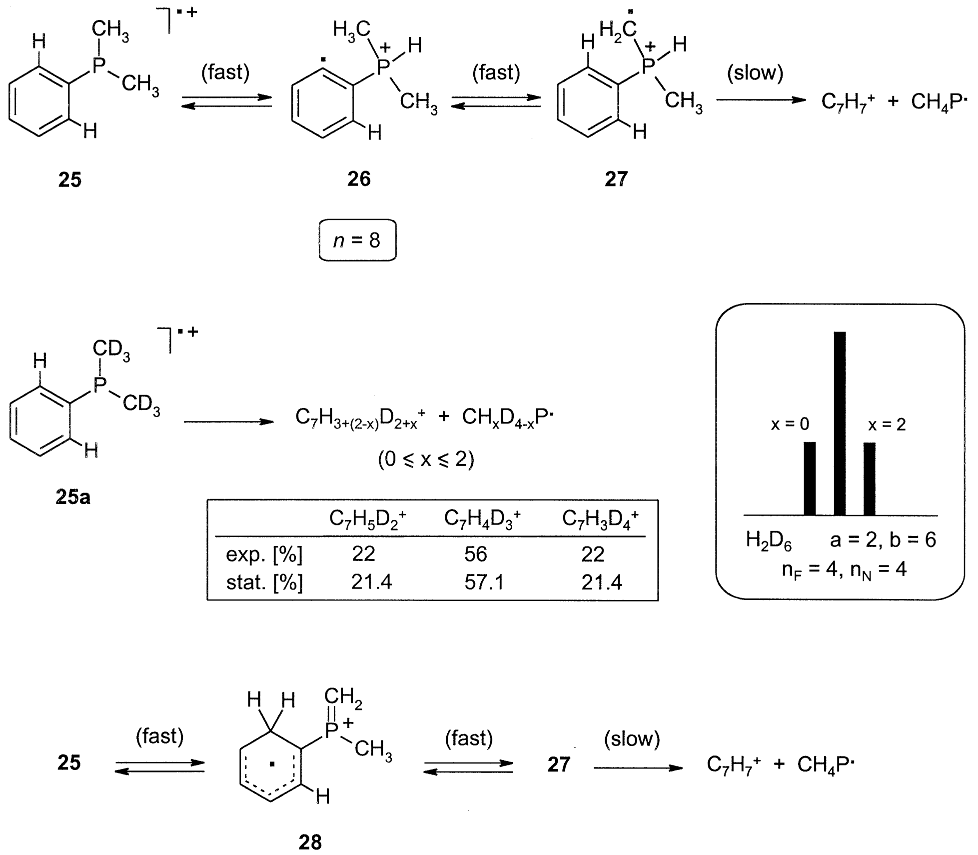
Scheme 8. Regioselective hydrogen exchange in the radical cations of benzoic acid (**23**) involving its distonic isomer **24**.

of the methylphosphanyl radical. This becomes evident from the symmetrical peak pattern of the $C_7(H,D)_7^+$ ions formed from the isotopomer **25a** (Scheme 9). Clearly, symmetry is achieved here when the hydrogen isotopes are distributed statistically over the equal number of sites, viz. $\mathbf{n}_F = 4$ in the ionic and $\mathbf{n}_N = 4$ in the neutral fragment. Two distonic ions, **26** and **27**, were suggested to mediate this eight-hydrogen scrambling. The former of these ions corresponds to the phenyl radical ion **24**, whereas the latter represents an α-ylide ion which has to rearrange further to lose $CH_4P^{\cdot}$ [65]. An alternative scrambling mechanism would involve the σ-complex-type species **28** instead of ion **26**.

The regioselective participation of the ortho-hydrogen atoms in scrambling processes with hydrogen atoms of a ring substituent is also known to occur in the radical cations of alkylbenzenes, e.g. **29** (Scheme 10). It is closely related to the first mechanistic step of the McLafferty reaction of these species yielding, in the case of unsubstituted alkylbenzenes, mainly the $C_7H_8^{\cdot+}$ fragment ions and a neutral alkene. This hydrogen scrambling is particularly noteworthy since it should involve distonic ions of type **30** containing a protonated arene unit, which should undergo the fast annular proton exchange known for even-electron cations of this type (cf. Scheme 1). However, the intermediate formation of meta- and para-tautomers such as **31** and **32** has been largely excluded by site-specific deuterium labeling [66].

Importantly, simple alkylbenzene ions such as **29** do not undergo complete scrambling, even on the timescale of metastable ion decompositions. When the hydrogen-atom donor sites, viz. the γ-CH_2 group of the aliphatic chain, is activated by suitable substitution, the rate of hydrogen scrambling is increased and H/D exchange may achieve completeness in the labeled long-lived ions. Localized bond activation [67] is effected best by attaching aromatic rings to the γ-position, thus rendering the γ-C–H bonds benzylic. In fact, the metastable radical cations of 2-benzylindane (**33**) were found to undergo a virtually complete scrambling between the two hydrogen atoms at the ortho-positions of the pendant benzyl group and the two hydrogen atoms oriented cis to it at the five-membered ring [68] (Scheme 11). The strict regio- and stereoselectivity was revealed by extensive site-specific deuterium labeling experiments at both the benzylic positions and at the five-membered ring. Substituents at the meta and para positions of the benzyl group were found to strongly affect the scrambling (cf. Sec. 8) [68,69].

In contrast to ions **23** and (probably) ions **25**, hydrogen scrambling cannot take place via abstraction of $H^{\cdot}$ from the ortho positions; rather, it occurs by transfer of $H^{\cdot}$ or H^+ to one of those. By analogy to the mechanism for simple alkylbenzene ions (cf. Scheme 10), the distonic ions **34** may be formed which contain a radical site at one of the benzylic positions of the indane unit and a remote benzenium ion moiety, as displayed in Scheme 11a. Here again, it appears intriguing that there is no intraannular ring proton walk in such a species, which would involve ions such as **35**. In the case of 2-benzylindane ions, we may assume alternatively the formation of an electromeric distonic ion **36**, in which the charge resides at the indanyl moiety and the σ-complex represents a cyclohexadienyl radical (Scheme 11b). Ions **36** should be more stable than ions **34** and 1,2-$H^{\cdot}$ shifts in cyclohexadienyl radicals (and radicals in general) require



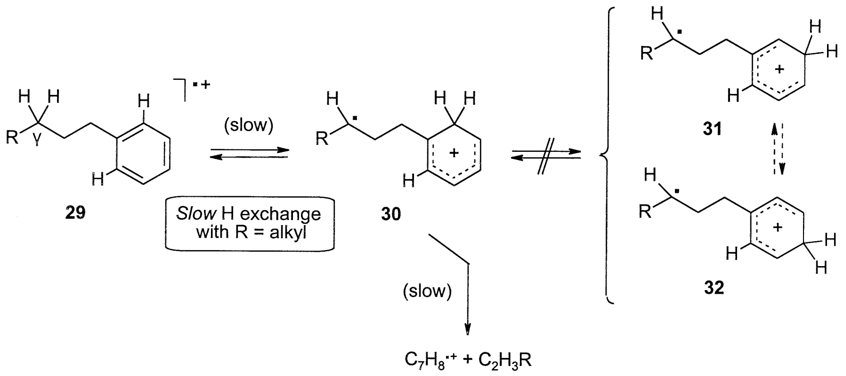
	$C_7H_5D_2^+$	$C_7H_4D_3^+$	$C_7H_3D_4^+$
exp. [%]	22	56	22
stat. [%]	21.4	57.1	21.4

Scheme 9. Regioselective hydrogen exchange in the radical cations of dimethylphenylphospane (**25**) and complete H/D equilibration in its [methyl,methyl-D_6] isotopomer **25a**. Distonic ions **26** and/or **28** may be involved here.

more energy than 1,2-H^+ shifts [70]. Thus, formation of neutral σ-complexes would preclude the formation of isomers such as **37** and offers an explanation for the observed, and still intriguing, lack of proton ring walk.

Although 2-benzylindane ions **33** may appear somewhat special, they behave in fact much more straightforwardly than simple ionized alkylbenzenes. A related case, studied earlier than ions **33**, concerns the radical cations of 1,3-diphenylpropane (**38**) (Scheme 12). Although the ortho regioselectivity of the hydrogen scrambling pertains also to **38**, these ions actually turned out to exhibit more complicated behavior than ions **33** due to the structural symmetry of the system [71,72].

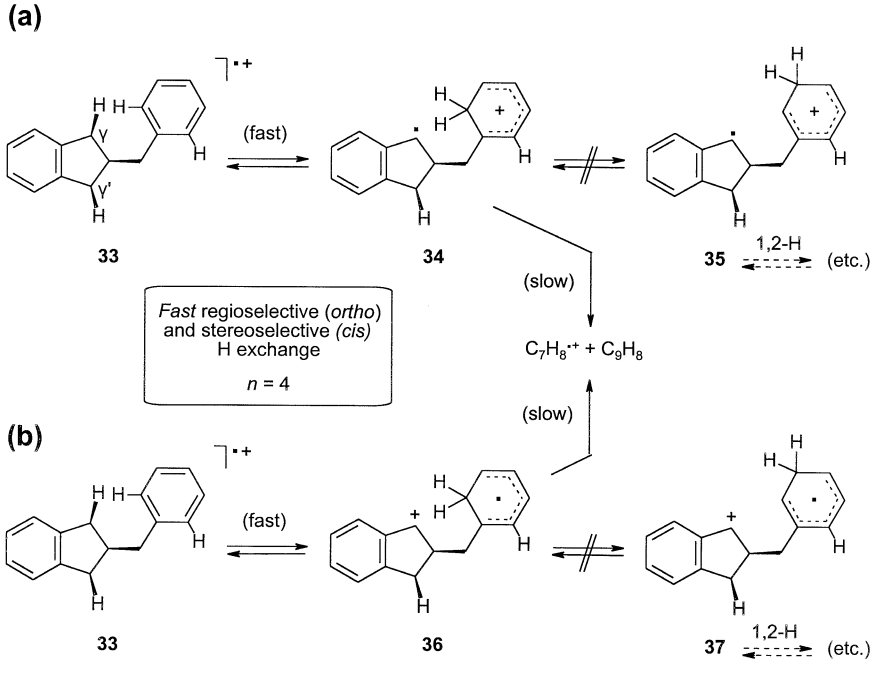
Ions **38** contain two sets of four interchanging hydrogen atoms. The loss of styrene giving, again, $C_7H_8^{\cdot+}$ as the ionic fragments is the by far major fragmentation channel of the long-lived ions and was again used as the probe reaction. One complication arises from the fact that two hydrogens of each set reside at the same moiety of the molecular ion. Moreover, a hydrogen transfer channel was unraveled connecting the two $n = 4$ sets to result in an eight-hydrogen scrambling system. It may be assumed that, in analogy to the metastable ions **33**, the scrambling within each set of ortho- and γ-sited hydrogen atoms in metastable ions **38** occurs to completion but extensive model calculations revealed that the equilibration between the eight hydrogen atoms is not achieved completely. As shown in Scheme 12, the distonic ions **39** formed by the first hydrogen transfer ions may regenerate either ions **38** or, by



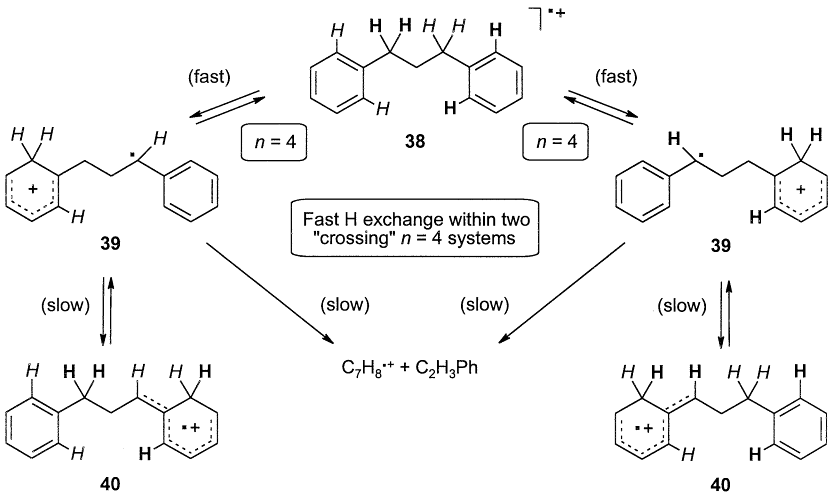
Scheme 10. Slow hydrogen echange in ionized higher *n*-alkylbenzenes.

interannular ortho-to-ortho hydrogen transfer, give rise to another isomer, tautomer **40**. It is assumed that this "long-distance" interaction is relatively slow as compared to regeneration of the intact molecular ions **38**.

Again, the ortho-regioselectivity of the hydrogen scrambling in ionized 1,3-diphenylpropane **38** is in contrast to the fast and complete equilibration of all of the ring hydrogens in protonated alkylbenzenes and α,ω-diphenylalkanes. Therefore, alternative (formal) distribution of the charge and radical density may contribute to the lack of 1,2-H shifts along the "protonated" ring in the distonic ions **39**. Thermochemical estimations suggest that the stability differ-



Scheme 11. Fast hydrogen exchange in ionized 2-benzylindane **33** via two electromeric distonic ions (**34** and **36**).



Scheme 12. Fast hydrogen exchange in ionized 1,3-diphenylpropane.

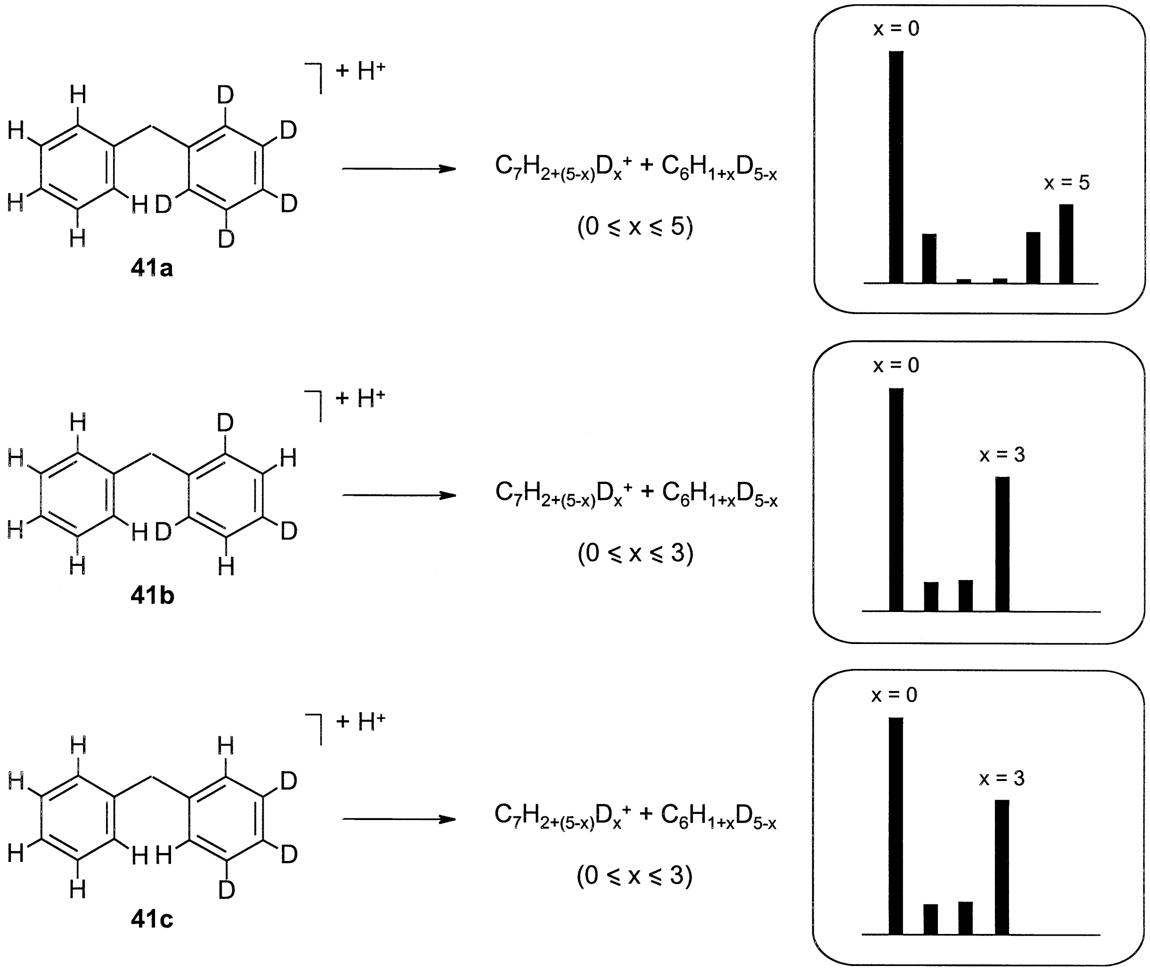
ence between **39** and its electromer is certainly less than for the pair of electromers **34** and **36** [69].

5. Slow hydrogen exchange in protonated diphenylalkanes: Diphenylmethane

Not all of the protonated diphenylalkanes undergo complete interannular proton exchange prior to fragmentation. Protonated diphenylmethane **41** represents the prototypical case for slow proton exchange between the rings with concomitant fast intraannular proton exchange within the (temporarily) protonated ring [52,73]. As will be shown below, this behavior is typical for protonated diphenylalkane-type ions in which presence of a single methylene (or substituted methylene) group between the rings causes steric restriction and thus hinders the free ring-to-ring proton transfer. As another important factor, less excited ions are sampled when benzene is lost from the ipso-protonated tautomers of **41** and related protonated “benzylbenzenes”, as compared to the corresponding benzene loss from the higher homologues.

The low extent of interannular hydrogen scrambling in ions **41** is evident from the concave abundance pattern of $C_6(H,D)_6$ losses from the [*ring*-D_5]-labeled metastable isotopomers **41a** (Scheme 13). This is in sharp contrast to the pattern observed with the corresponding higher homologues such as ions **9a** [Fig. 4(a), Scheme 4), which shows the strongly convex distribution characteristic for fast interannular exchange. Also, loss of benzene from ions **41a** reflects a kinetic isotope effect giving rise to the favored elimination of the heavier benzene isotopomers, again in contrast to the fragmentation of the higher homologues, which does not reflect any isotope effect on the preceding interannular proton exchange. Obviously, the critical energies for the interannular H^+ and D^+ transfer in ions **41** are close to the critical energy for fragmentation. In the higher homologues, such as ions **9a**, kinetic discrimination of D^+ against H^+ transfer is hidden because of the much higher energy requirements for fragmentation as compared to isomerization [73].

The fact that the intraannular hydrogen scrambling remains a fast process and occurs to completion in those ions which undergo a slow interannular proton transfer is reflected from the two spectra measured for the isotopomers **41b** and **41c** (Scheme 13). These ions contain the same number of protons and deuterons within the same ring. The two spectra are identical within experimental error, both showing the same concave pattern and hence the same isotope effect.

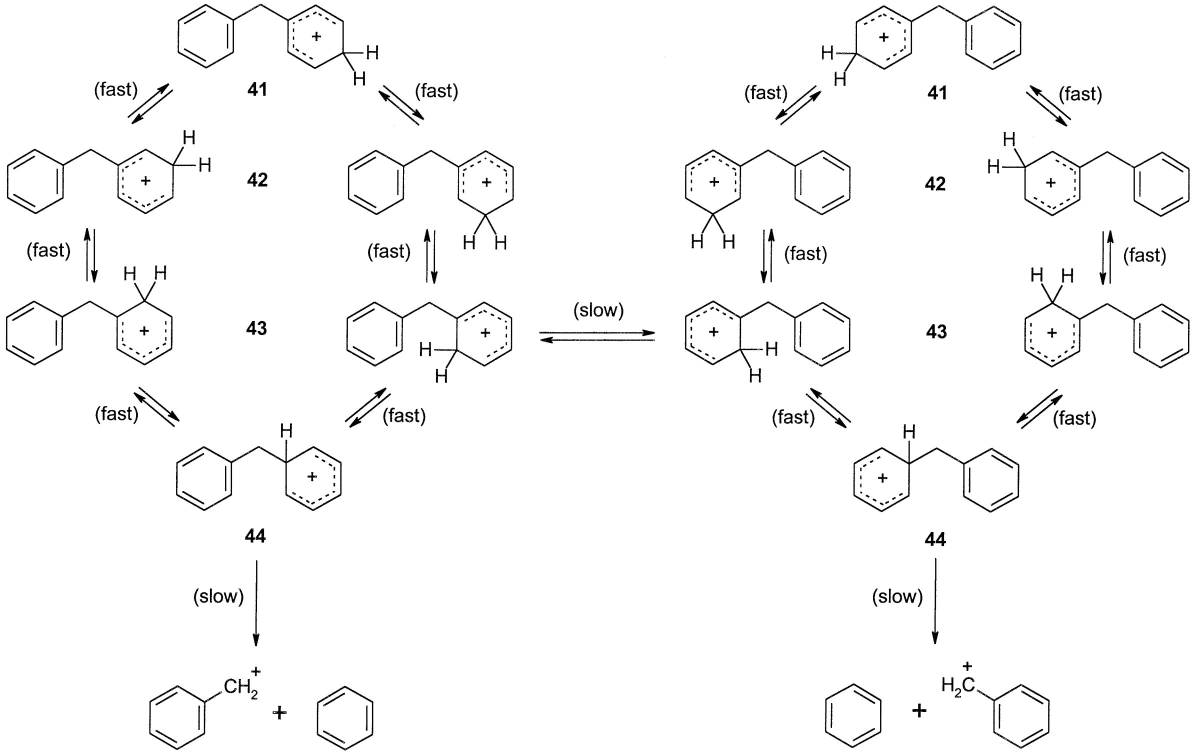


Scheme 13. Observed relative abundances ("concave patterns") for the loss of benzene isotopomers from [*ring*-D]-labeled protonated diphenylmethanes.

The same mutual identity was encountered for the [D_3]-labeled radical cations **5a** and **5b** bearing the label at different sites (Scheme 3). The case of ions **41** represents a rare situation where not only two different scrambling processes could be identified as competing isomerization channels but where, in addition, their relative rates could be estimated (cf. Sec. 8). Owing to its prototypical character, the complete scrambling system of protonated diphenylmethane **41** comprising two fast-exchanging domains within a larger, slow exchanging one is exemplified in Scheme 14.

6. Slow versus fast interannular proton transfer as a probe for ion structure elucidation

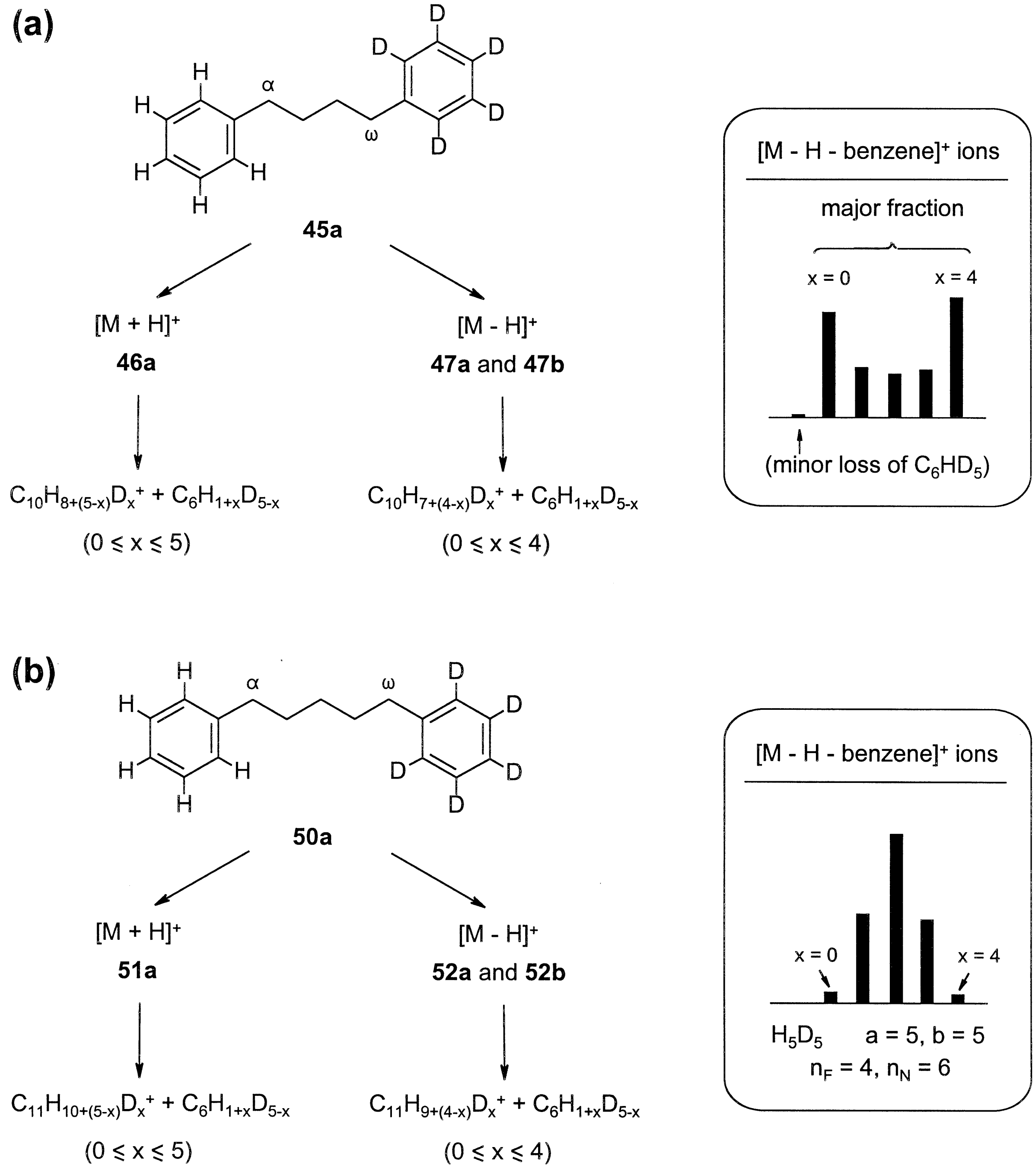
With the focused insight into this kind of multiproton exchange processes, more subtle mechanistic details may be revealed through the scrambling features. This is illustrated for the case of the carbocations generated by intermolecular hydride abstraction from α,ω-diphenylalkanes in the plasma of a CI(CH_4) or CI(i-C_4H_{10}) source [74–76]. In fact, these $[M - H]^+$ ions are formed to a much greater extent than the corresponding $[M + H]^+$ ions. Scheme 15 shows the



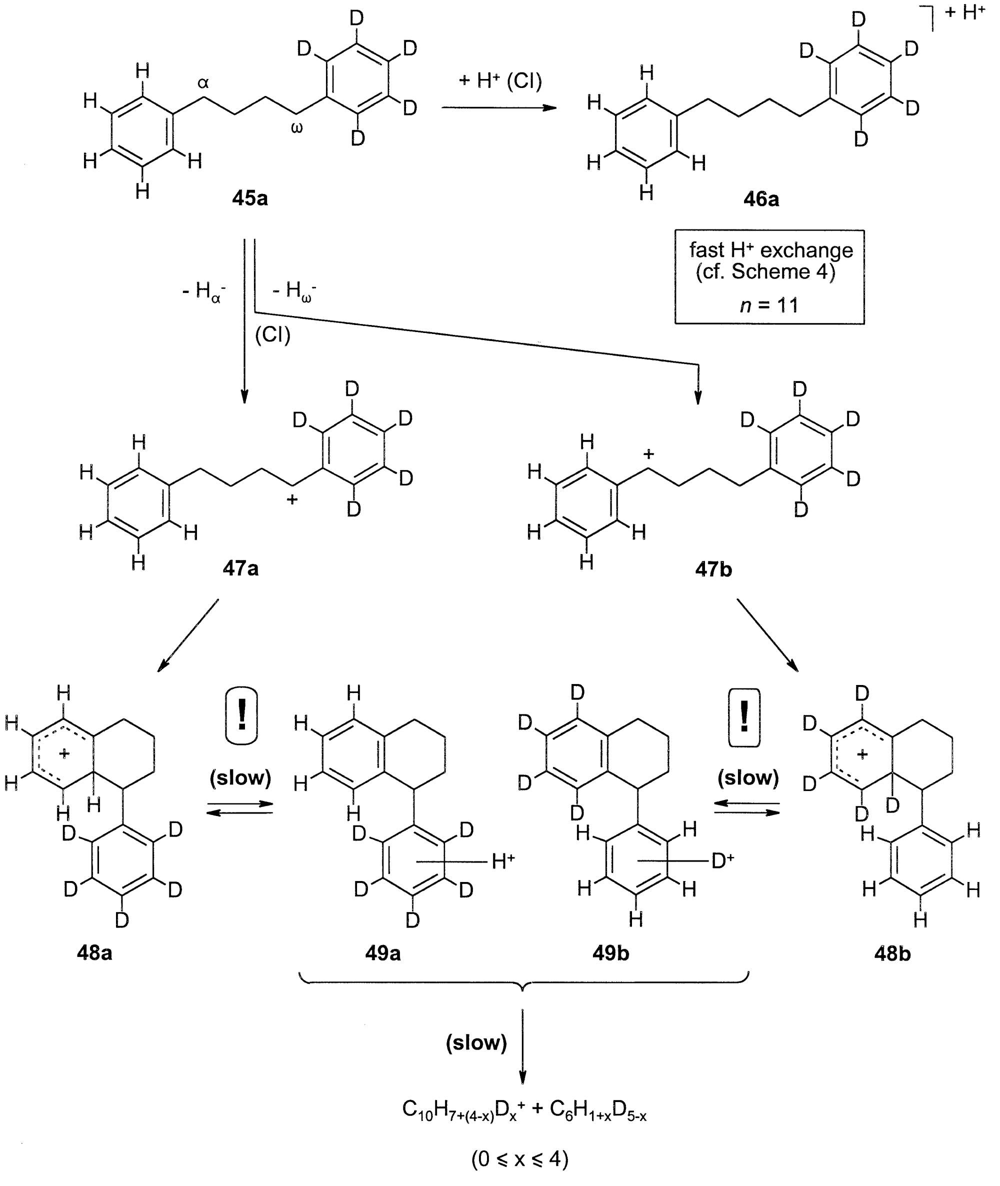
Scheme 14. Explicite view of the combined fast intraannular and slow interannular proton scrambling in protonated diphenylmethane.

loss of essentially five benzene isotopomers from the $[M - H]^+$ ions of [*ring*-D_5]-labeled 1,4-diphenylbutane **45a** and from those of [ring-D_5]-labeled 1,5-diphenylpentane **50a**. Whereas the corresponding protonated molecules **46a** and **51a** undergo complete interannular scrambling prior to benzene loss as do their lower and higher homologues discussed above, the two (formally benzylic) $[M - H]^+$ ions formed from 1,4-diphenylbutane **45a**, i.e. **47a** and **47b**, exhibit a slow exchange involving ten protons. This is clearly reflected by a concave pattern for the distribution of benzene isotopomers lost (Scheme 15a). The scrambling in the $[M - H]^+$ ions is the result of the cyclization of ions **47a** and **47b** to ions **48a** and **48b**, respectively, thus generating protonated (and deuteronated) aromatic intermediates (Scheme 16). Benzene loss from the $[M + H]^+$ and $[M + D]^+$ ions of the underlying 1-phenyletralins is preceded by slow interannular H/D exchange, since these ions represent derivatives of protonated diphenylmethane **41**. In the present case, loss of benzene from the ipso-protonated forms **49a** and **49b** should even more facile than in the case of ions **41**, thus further attenuating the extent of interannular H/D exchange. A similar behavior was found for the $[M - H]^+$ ions of 1,3-diphenylpropane [74].

As evident from Scheme 15b, the next higher homologue, 1,5-diphenylpentane **50a**, exhibits a distinct behavior. In this case, the $[M - H]^+$ ions **52a** and **52b** undergo a fast and complete interannular exchange involving five protons and five deuterons, as do the corresponding $[M + H]^+$ ions **51a**. This finding points to the formation of protonated diphenylalkane-type ions in which the interannular hydrogen scrambling is facile and can easily compete with the loss of benzene. Obviously, the initially formed $[M - H]^+$ ions do not simply cyclize to protonated 1-phenylbenzocycloheptane

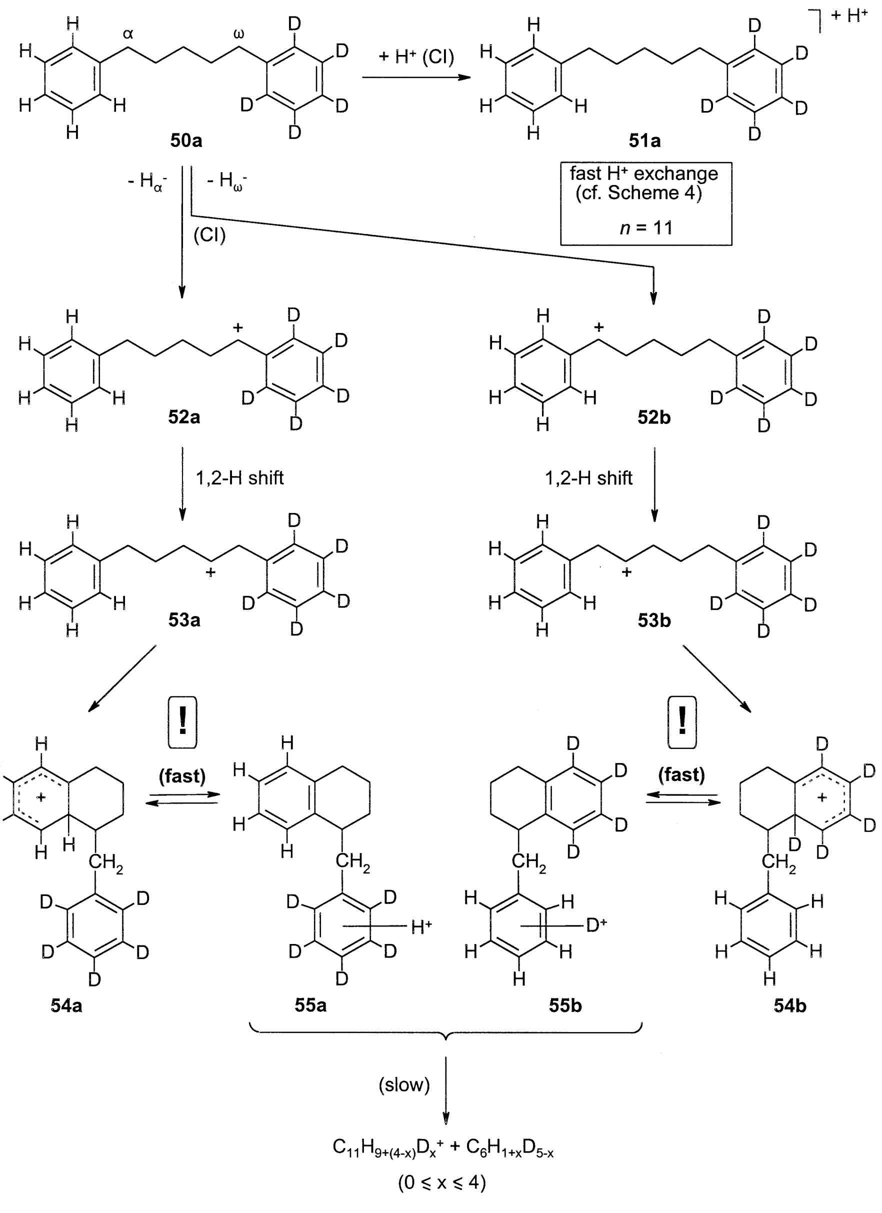


Scheme 15. Fragmentation of $[M + H]^+$ and $[M - H]^+$ ions of protonated [*ring*-D_5]-labeled 1,4-diphenylbutane **45a** and 1,5-diphenylpentane **50a**. (a) Concave vs. (b) convex patterns observed for the losses of benzene isotopomers from the $[M - H]^+$ ions.



Scheme 16. Loss of benzene isotopomers from the [M − H]$^+$ ions **47a** and **47b** by cyclization and *slow* interannular proton transfer.

(in analogy to **47** → **48**). Rather, protonated (and deuteronated) 1-benzyletralins **54a** and **54b** are formed. The cyclization paths should be opened by 1,2-hydride shifts involving ions **53a** and **53b** during the electrophilic attack. In fact, the [M + H]$^+$ and [M + D]$^+$ ions **54**, representing higher homologues of ions **48**, fulfill the requirements for fast and complete interannular H/D scrambling mentioned above, and independent CID experiments confirmed the mechanistic interpretation based on the distinct scrambling behaviour of the [M − H]$^+$ ions **46** and **50**. Moreover, H/D scrambling in the next-higher homologue, i.e. the [M − H]$^+$ ions of 1,7-diphenylheptane, was also found to be fast.

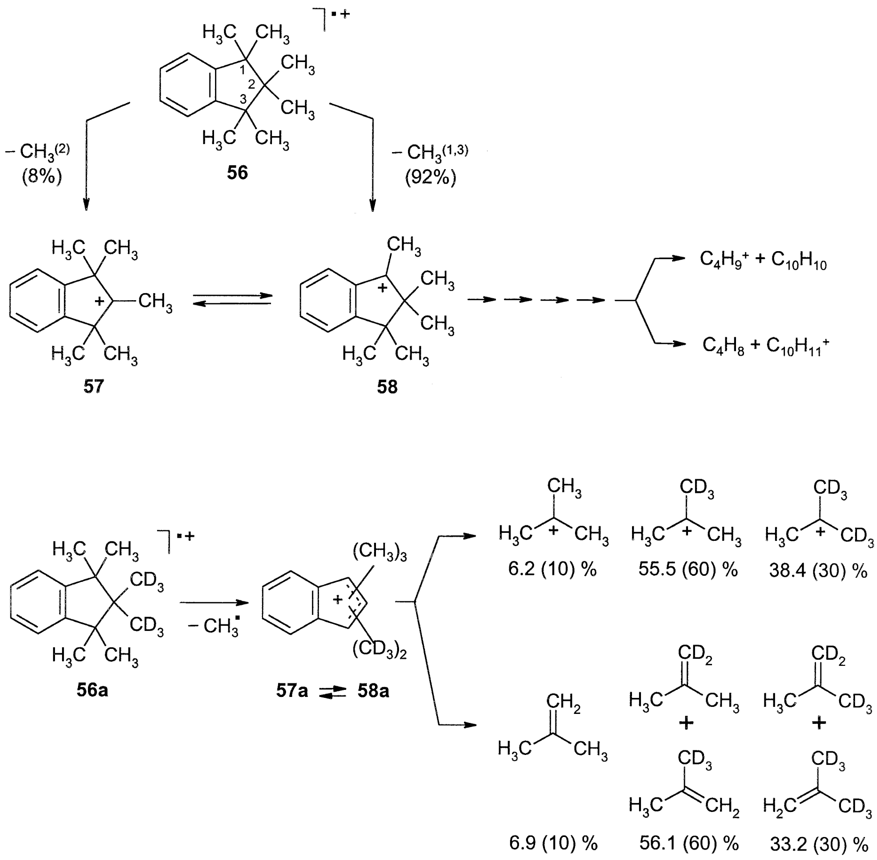


Scheme 17. Loss of benzene isotopomers from the $[M - H]^+$ ions **52a** and **52b** by cyclization, 1,2-hydride shift and fast interannular proton transfer.

7. Scrambling of methyl groups

Scrambling of protons, or hydrogen scrambling in general, is certainly that prominent because of the low activation barriers of 1,2-H shifts and the ubiquity of hydrogens in organic ions. Among the other monovalent atoms or groups, scrambling of halogen atoms has only been studied only very rarely. However, there are a few cases where alkyl groups undergo extended scrambling. Complete equilibration of five methyl groups in analogy to formal proton scrambling was encountered in a single case [77].

Methyl groups have been shown to undergo ring walk in toluenium ion derivatives, leading to skeletal



Scheme 18. Major fragmentation routes of ionized 1,1,2,2,3,3-hexamethylindane **56** and of its [*methyl,methyl*-D_6]-labeled analogue **56a**.

isomerization [78–81]. Thus, *para*-xylene is converted to *meta*-xylene via the protonated forms of which the *para*-protonated *meta*-xylene is the thermodynamically most stable isomer [31,34c,46,82,83]. However, it is not known whether the methyl groups in di- and oligomethylated benzenium ions interchange as fast and efficiently as protons do. It would be interesting to study methyl group scrambling in heptamethylbenzenium ions by intermolecular methyl group transfer.

It appears that gem-dimethyl-substituted cycloalkyl cations and related species exhibit fast methyl group scrambling. Notably low activation barriers have been found for the degenerate methyl group scrambling in nonamethylcyclopentyl cations in solution [84]. In the gas phase, pentamethylindanyl ions **57** and **58**, both being formed by methyl loss from ionized 1,1,2,2,3,3-hexamethylindane **56**, undergo complete scrambling of the five methyl groups prior to secondary fragmentation [77]. Among the three fragmentation channels of the [M - CH_3]$^+$ ions, the release of *tert*-$C_4H_9^+$ ions and the "conjugate" elimination of isobutene is most informative (Scheme 18). A multistep isomerization mechanism has been suggested to precede these fragmentation reactions.

The complete equilibration of intact methyl groups is evident from the fragmentation of deuterium labeled hexamethylindane ions such as **56a**. For example, the [M − CH_3]$^+$ ions release the three isotopomers $C_4H_9^+$, $C_4H_6D_3^+$, and $C_4H_3D_6^+$ in the ratios 6.2 : 55.5 : 38.4, which are close to those calculated for randomization of three CH_3 and two CD_3 groups (10.0 : 60.0 : 30.0). The losses of C_4H_8 (6.9%), $C_4H_6D_2$ and $C_4H_5D_3$ (Σ 56.1%), and $C_4H_3D_5$ and

$C_4H_2D_6$ (Σ 33.2%) also reflect the scrambling of intact methyl groups. The slight deviations have been traced to kinetic isotope effects operating during isomerization.

8. Kinetic simulations of progressive hydrogen scrambling

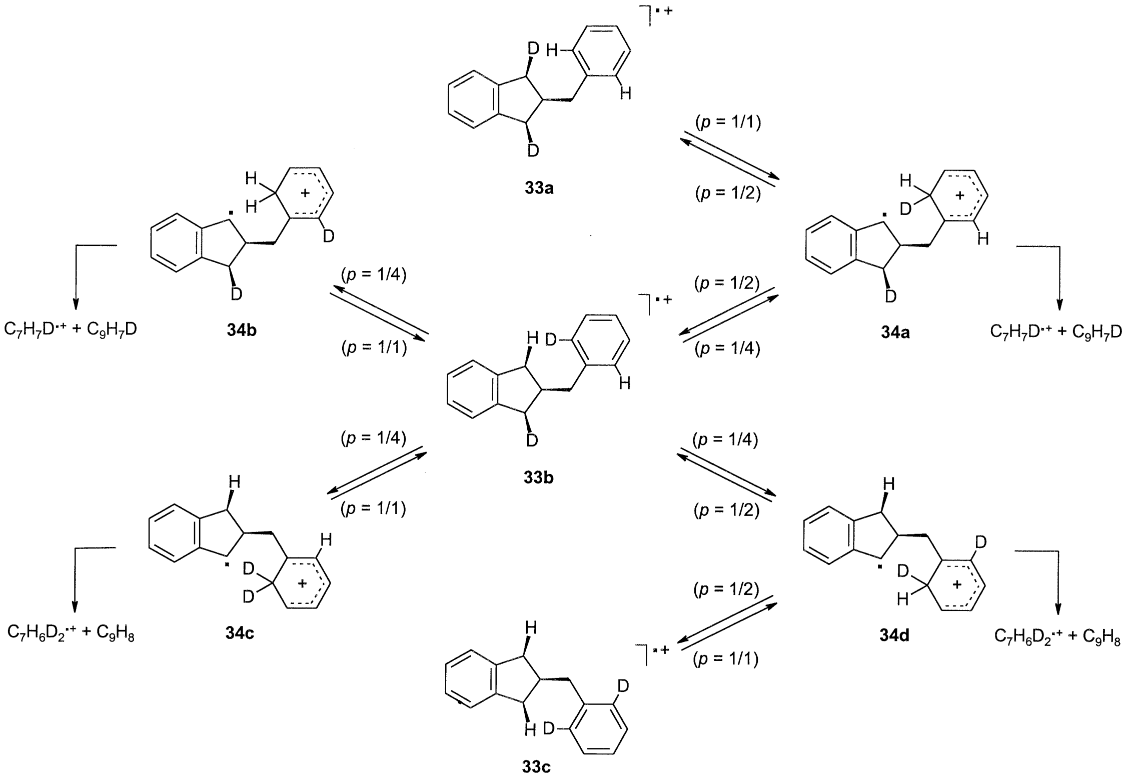
8.1. General remarks

The study of the progression of hydrogen exchange with the ions' lifetime represents another facet of scrambling processes in gaseous organic ions. Time dependence of scrambling processes may provide more mechanistic insight than the mere statistical exchange since it reveals how fast this final status is reached eventually. A number of efforts have been published to determine the kinetics of hydrogen scrambling. In several cases, the extent of H/D exchange within ions of different ion lifetimes (τ) has been evaluated. This includes the method of field ionization kinetics (FIK) comprising a continuous range of relatively short lifetimes ($10^{-11} \leq \tau \leq 10^{-9}$ s), fragmentation within the EI or CI ion sources ($\tau \leq 10^{-6}$ s after 70 eV ionization or $\tau \approx 10^{-6}$ s after low electron-energy ionization, e.g. 12 eV), and metastable ion fragmentation in various field-free regions ($10^{-5} \leq \tau \leq 10^{-4}$ s) [85]. In general, the extent of scrambling is found to increase markedly with increasing ion lifetime. The studies on H/D scrambling in deuterium labeled $C_7H_8^{\cdot+}$ ions mentioned in Sec. 3.3. (Scheme 3) represent lucid examples as they demonstrate the time-dependence of both the scrambling extent and the kinetic isotope effect associated with isomerization and fragmentation. Examples for FIK studies on time-dependent H/D scrambling concern the loss of ethylene from ionized cyclohexene [86] in a formal retro-Diels-Alder type reaction and the hydrogen exchange between the γ-CH_2 group and the ortho positions of ionized alkylarenes [87,88] and related species, e.g. ionized 3-phenyl-1-propanol [89].

In cases where the mechanism of H/D exchange is well defined, the progression of this process can be simulated in various ways. In a simple approach, the step-by-step evolution of the scrambling may be simulated by assuming equal rates for the forward and the backward reaction. This very simple kind of "kinetic model" has been used to elucidate details on the hydrogen exchange in ionized benzoic acid **23** discussed above (Scheme 8) [61]. Similarly, the progression of the hydrogen exchange between the γ-CH_2 group and the ortho positions of ionized 1,3-diphenylpropane **38** (Scheme 12) and 2-benzylindane **33** (Scheme 11) has been calculated and compared with the extent of the H/D exchange determined experimentally [68,69,71]. The case of the 2-benzylindane radical cations will be used to illustrate this in some detail, including the influence of various substituents on the rate of hydrogen exchange [69].

8.2. Time dependent scrambling in radical cations: 2-Benzylindanes

According to the simple scheme mentioned above, stepwise progression of the hydrogen exchange in ions **33** requires only some seven "exchange cycles" (i.e. the sequence **33** → **34** → **33**, cf. Scheme 11) to reach the statistical distribution. Starting from [D_2]-isotopomers **33a** or **33c** (Scheme 19) which are chosen here as hypothetical examples (cf. Scheme 20, however), the two deuterium atoms at either the cis (!) positions of the five-membered ring of **33a** or at the ortho positions of the benzyl group of **33c** were assumed to scramble "stepwise" between the four sites [90]. Fragmentation by McLafferty reaction is used to monitor the progression of the H/D exchange and reflects the statistical distribution when equal abundances of ions $C_7H_7D^{\cdot+}$ and $C_7H_6D_2^{\cdot+}$ are observed. Fig. 7 illustrates this for the case of pentadeuterated ions **33d** which were studied experimentally among other isotopomers. Whereas simple (unidirectional) H transfer generates exclusively ions $C_7H_3D_5^{\cdot+}$ (*m/z* 97), progressive exchange between the two cis-oriented γ-H atoms and the two ortho-D atoms gives rise to increasing contributions of ions $C_7H_4D_4^{\cdot+}$ (*m/z* 96) and eventually results in the 1 : 1 abundance ratio of ions $C_7H_3D_5^{\cdot+}$ and $C_7H_4D_4^{\cdot+}$. Experimentally, ions fragmenting within three different ranges of (mean) lifetimes reflect the predicted progression,



Scheme 19. Stepwise progression of the H/D exchange in ionized 2-benzylindanes **33a** and **33c** and fragmentation. The values *p* denote the probabilities for H and D transfer. Ions **33a** and **33b** are shown as [D_2] isotopomers and, for the sake of clarity, the presence of additional D atoms in positions that are not involved into the H/D exchange are not shown.

allowing us to estimate the degree of progression by the mean numbers of exchange cycles occurring in these ions. Thus, ~50% of ions **33** undergo one cycle within the ion source at ionization energies of 70 eV. Using 12 eV ionization (hence decreasing the ions' mean internal energy and increasing the mean lifetime) increases the number of exchange cycles by a factor of two, and metastable ions fragmenting in the second field-free region have apparently reached the complete interchange of the four hydrogen atoms prior to fragmentation.

Interestingly, the presence of electron-releasing substituents markedly affects the progression of hydrogen scrambling in this kind of radical cation [68,69]. For example, a para-methoxy group largely suppresses the exchange such that metastable ions, e.g. **59a**, exhibit one single exchange cycle only [Fig. 7(b)]. In contrast, a meta-methoxy substituent in ions **61a** gives rise to acceleration of the scrambling, as reflected by the increased number of exchange cycles for ions fragmenting in the ion source after 70 eV and 12 eV ionization [Fig. 7(c)]. The origin of this marked effect has been traced to the relative thermochemical stability of the intermediate distonic ions **34a**-**34d**, as compared to the conventional molecular radical cations **33**. In fact, the σ-complex moiety within the meta-substituted distonic ion **62a** renders the γ-H transfer **61a** → **62a** exoergic whereas the σ-complex moiety in the para-substituted distonic ion **60a** makes the corresponding isomerization **59a** → **60a** endoergic. As a result, the kinetic control of the ions' fragmentation reflects a part of the thermodynamic situation: The four-hydrogen scrambling in the ions bearing an electron-releasing meta substituent is faster and also proceeds faster with increasing lifetime than it does in the corresponding para-substituted isomers.

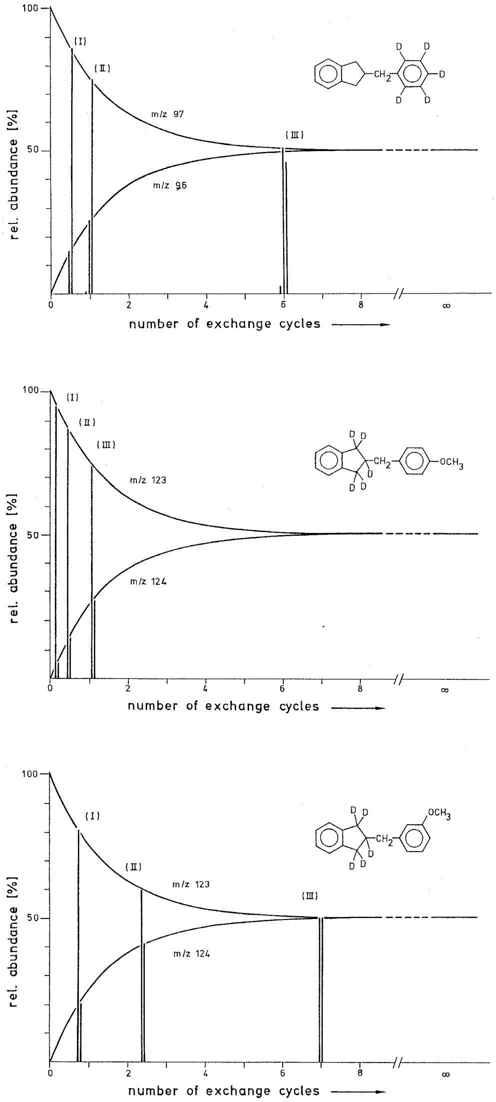
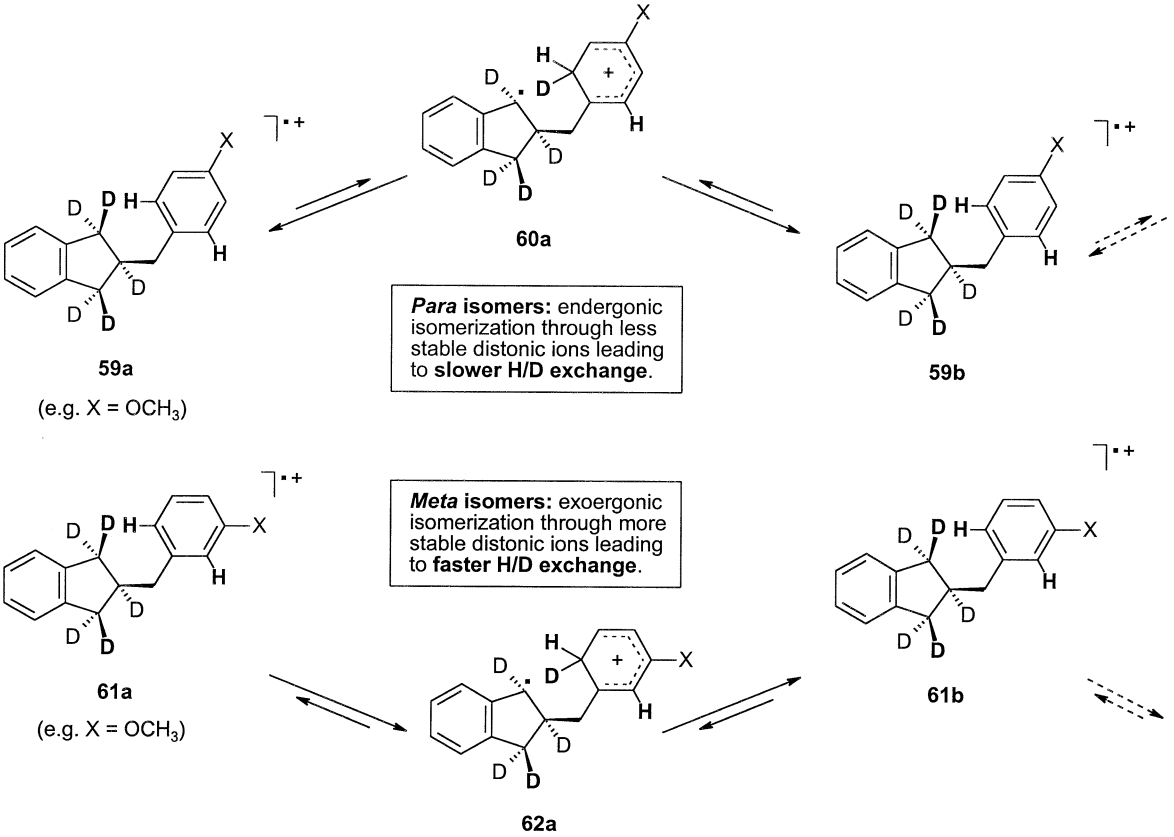


Fig. 7. (a) Extent of H/D exchange in ionized 2-benzylindane **33d** as number of exchange cycles, as determined from the fit of the experimentally obtained abundance ratios [*m/z* 97]/[*m/z* 96] with the calculated dependence of the ratio $[C_7H_6D_2^{\cdot+}]/[C_7H_7D^{\cdot+}]$ (cf. Scheme 19). The experimental ion abundance ratios were obtained for (I) short-lived ions undergoing in-source fragmentation after 70 eV ionization, (II) for less short-lived ions undergoing in-source fragmentation after 12 eV ionization, and (III) for long-lived, metastable ions dissociating in the second field-free region of a sector-field instrument). (b) Decelerated H/D exchange in ions **59a** effected by an electron-releasing substituent ($X = OCH_3$, cf. Scheme 20) in the para position, and (c) accelerated H/D exchange of ions **61a** effected by an electron-releasing substituent ($X = OCH_3$, cf. Scheme 20) in the meta position, as determined from the fits of abundance ratios of ions $[C_8H_9DO^{\cdot+}]/[C_8H_8D_2O^{\cdot+}]$ ([*m/z* 123]/[*m/z* 124]). [Taken from 68].

An extended set of other electron-releasing meta- and para-substituted deuterium labeled 2-benzylindanes have been studied comprising, besides the methoxy derivatives, the CH_3, F, OH, and $N(CH_3)_2$ substituents [69]. As expected from the "local proton affinities" [31,34c,82,83] of the ortho positions at the benzyl groups in **33** and its derivatives, methyl and fluorine substitution affects the hydrogen scrambling in the benzylindane ions only moderately whereas hydroxy substitution does most (even more than methoxy groups). Strikingly, when the most electron-releasing dimethylamino group is introduced in the meta position (i.e. **59a**, $X = NMe_2$), the back transfer of a hydrogen atom in the intermediate distonic ion and hence the whole scrambling process are completely suppressed. In turn, the presence of a para-dimethylamino group in **61a** ($X = NMe_2$) intercepts the forward $H^{\cdot}$ transfer step, thus totally suppressing the McLafferty reaction [69].

8.3 Time-dependent scrambling in even-electron ions: Protonated α,ω-diphenylalkanes

Returning to the closed-shell species, protonated α,ω-diphenylalkanes such as **9a** and **41a** have also been studied with respect to the progression of proton exchange with the ions' lifetime. A simple step-by-step calculation of the proton scrambling, similar to the scheme applied to the ionized 2-benzylindanes **33a**, **59a** and **61a**, revealed for these H_6D_5 scrambling systems that some 14 ring-to-ring proton transfer steps are necessary to reach a degree of isotope scrambling which would be indistinguishable, within the limits of experimental error, from the statistical distribution [40]. It is important to note that fast intraannular scrambling of the six protons within the temporarily protonated ring has been assumed in this case; without the interplay of this "extra-fast" process, the number of interannular proton transfer steps would have to be much higher. Since, by experiment, the relative abundances of $C_6(H,D)_6$ isotopomers lost from metastable protonated 1,2-diphenylethane **9a** and its higher homologues were found to be "statistical", at least 14 exchange cycles take place prior to fragmentation.



***Para* isomers:** endergonic isomerization through less stable distonic ions leading to **slower H/D exchange**.

***Meta* isomers:** exoergonic isomerization through more stable distonic ions leading to **faster H/D exchange**.

Scheme 20. H/D exchange in para- and meta-substituted [D$_5$-labeled] 2-benzylindane radical cations **59a** and **61a** (e.g. X = OCH$_3$) via the energetically unfavorable distonic ion **60a** and the energetically favorable distonic ion **62a**. The four H and D atoms participating in the exchange are indicated by boldface letters.

Interestingly, a more realistic kinetic simulation model has corroborated this result and also allowed us to extend the insight into the slowly exchanging systems such as protonated diphenylmethane **41** [52,73]. In this model, the development of the relative abundances of the interconverting isotopomers and of the fragment ions, $[M + H - C_6(H, D)_6]^+$, during the ions' lifetime is expressed by a system of interdependent differential equations, including the isotope contents of the individual benzenium rings as well as the rate constants for H^+ and D^+ transfer and for fragmentation (k_H, k_D and k_f, respectively). For example, with a given mean lifetime of 20 μs for the metastable ions **9a** dissociating within the second field-free region of a sector-field mass spectrometer, the average value for the fragmentation rate constant is set at $k_f = 5 \times 10^4$ s^{-1}, the rate constants for the interannular proton and deuteron transfer have to be $k_H \approx k_D \geq 1 \times 10^6$ s^{-1} to achieve complete equilibration of the eleven protons and deuterons. Thus, ignoring a kinetic isotope effect on the transfer steps, the ratios $k_H/k_f \approx k_D/k_f \geq 20$ hold for protonated higher α,ω-diphenylalkanes [44] (Fig. 8). This is surpringly close agreement with the previously obtained estimate of at least 14 proton transfer steps occurring within the ions' lifetime [40].

In the case of protonated diphenylmethane **41a**, however, both the proton and the deuteron transfer steps are considerable slower (cf. Sec. 5) for ions of about the same lifetime (20 μs) [73]. In fact, the kinetic model calculations provide a good agreement between the simulation and the experimentally observed abundance pattern when the rate constants for

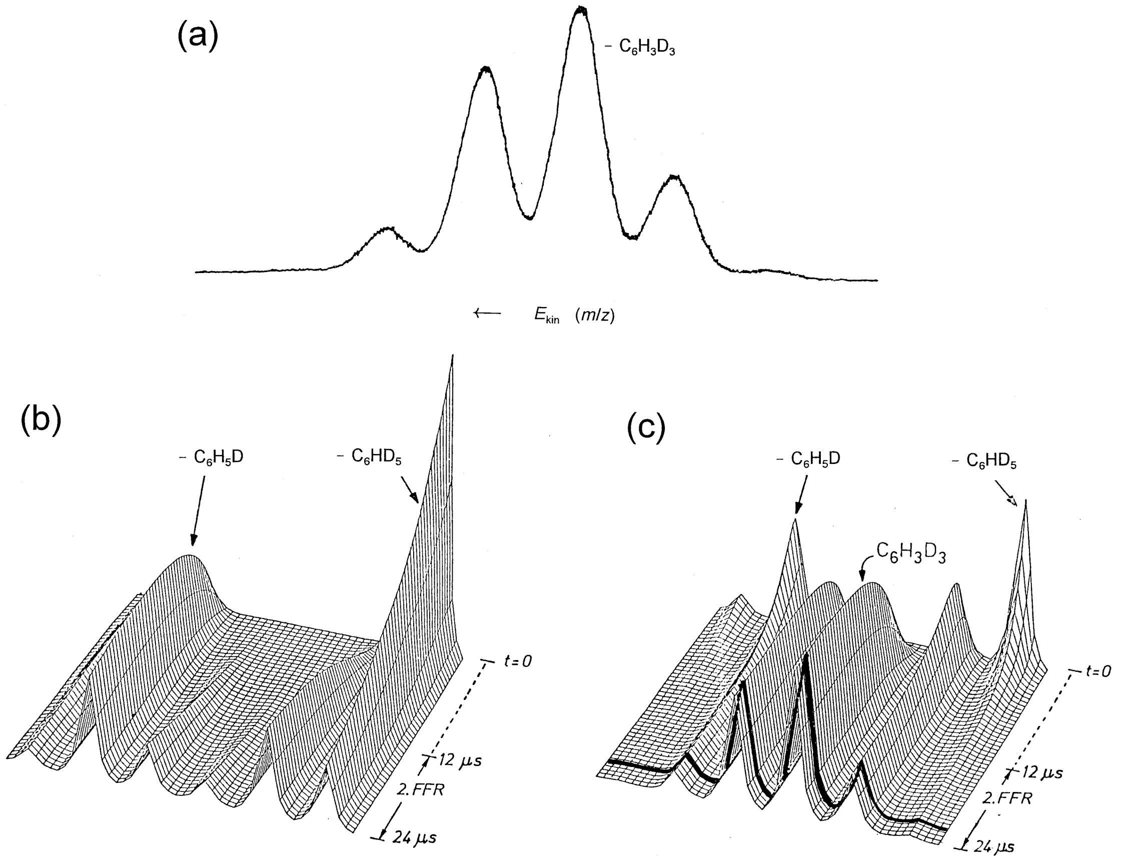


Fig. 8. Lifetime dependence of the relative abundances of the benzene isotopomers lost from ions **9a**. (a) Experimental pattern (MIKE spectrum); (b) calculated for $k_H = k_D = 1 \times 10^5$ s^{-1} and $k_f = 5 \times 10^4$ s^{-1} and found to be too slow to fit the experimental pattern; (b) calculated for $k_H = k_D = 1 \times 10^6$ s^{-1} and $k_f = 5 \times 10^4$ s^{-1} and found to fit the experimental pattern. [Taken from 44].

proton and deuteron transfer are assumed to be $k_H = 5 \times 10^5$ s^{-1} and $k_H = 1 \times 10^5$ s^{-1}. Thus, in this case, the isomerization reactions compete with the fragmentation reaction ($k_H/k_f \approx 10$ and $k_D/k_f \approx 2$) and the kinetic isotope effect $k_H/k_D \approx 5$ is clearly reflected by the concave abundance pattern (Fig. 9).

9. Complex cases of scrambling in apparently simply ionic species

As shown above, there are many cases where isotope exchange leads to complete scrambling, i.e. to the statistical interchange between atoms within a given part (or in the whole) of a molecular entity. The cases where the scrambling can be recognized clearly as being en route to the total equilibration of these atoms, as shown in the previous section, are relatively rare. One reason for this is that the simulation of the "slow" scrambling process requires the assumption of a concrete mechanistic model, such as the interannular proton transfer in ions **41a**, and it is often not easy to develop a reasonable and simple mechanism as a basis for the simulation. In contrast, many ions that exhibit "partial scrambling" undergo a set of competing isomerization processes, that is, two or several different rearrangement mechanisms compete to various extents within the ions' lifetime. This kind of situation is often very difficult (or impossible) to rationalize and conceivable mechanistic models can hardly be proven by labeling experiments. In this

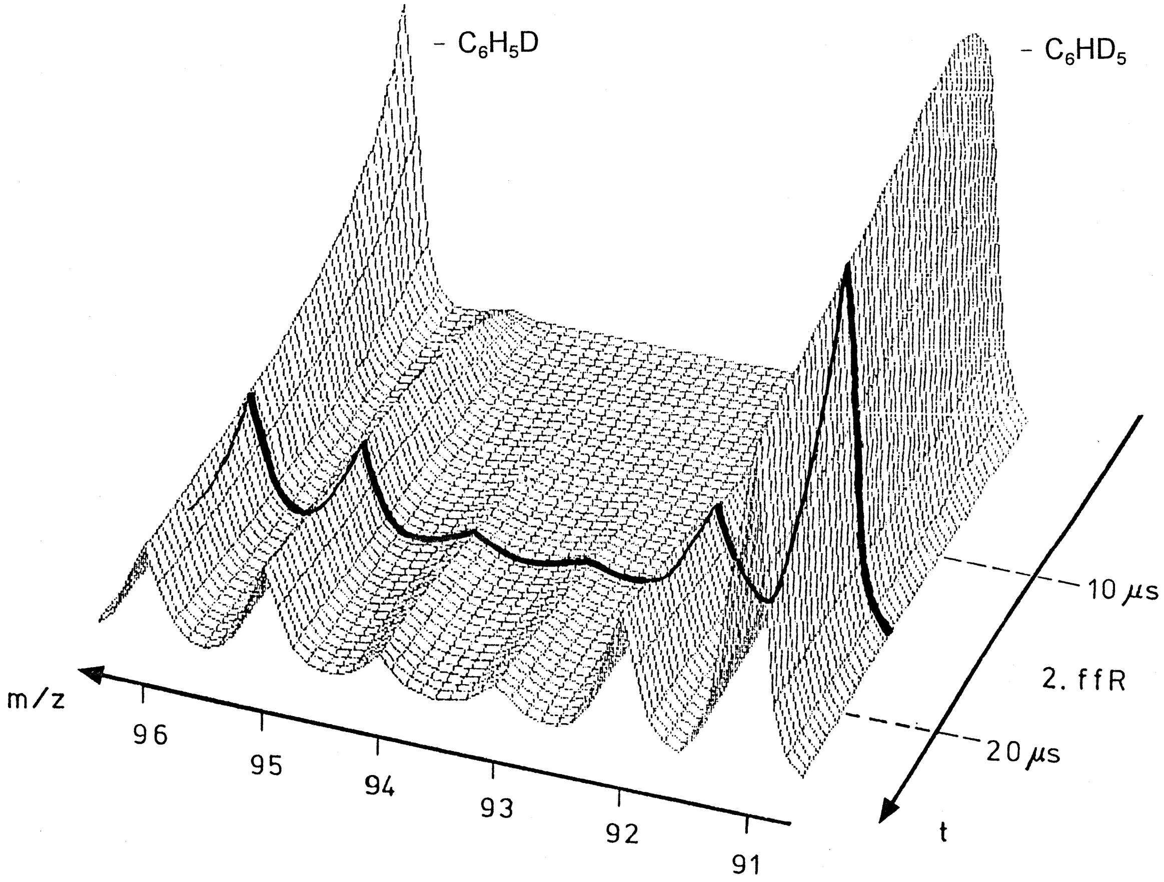
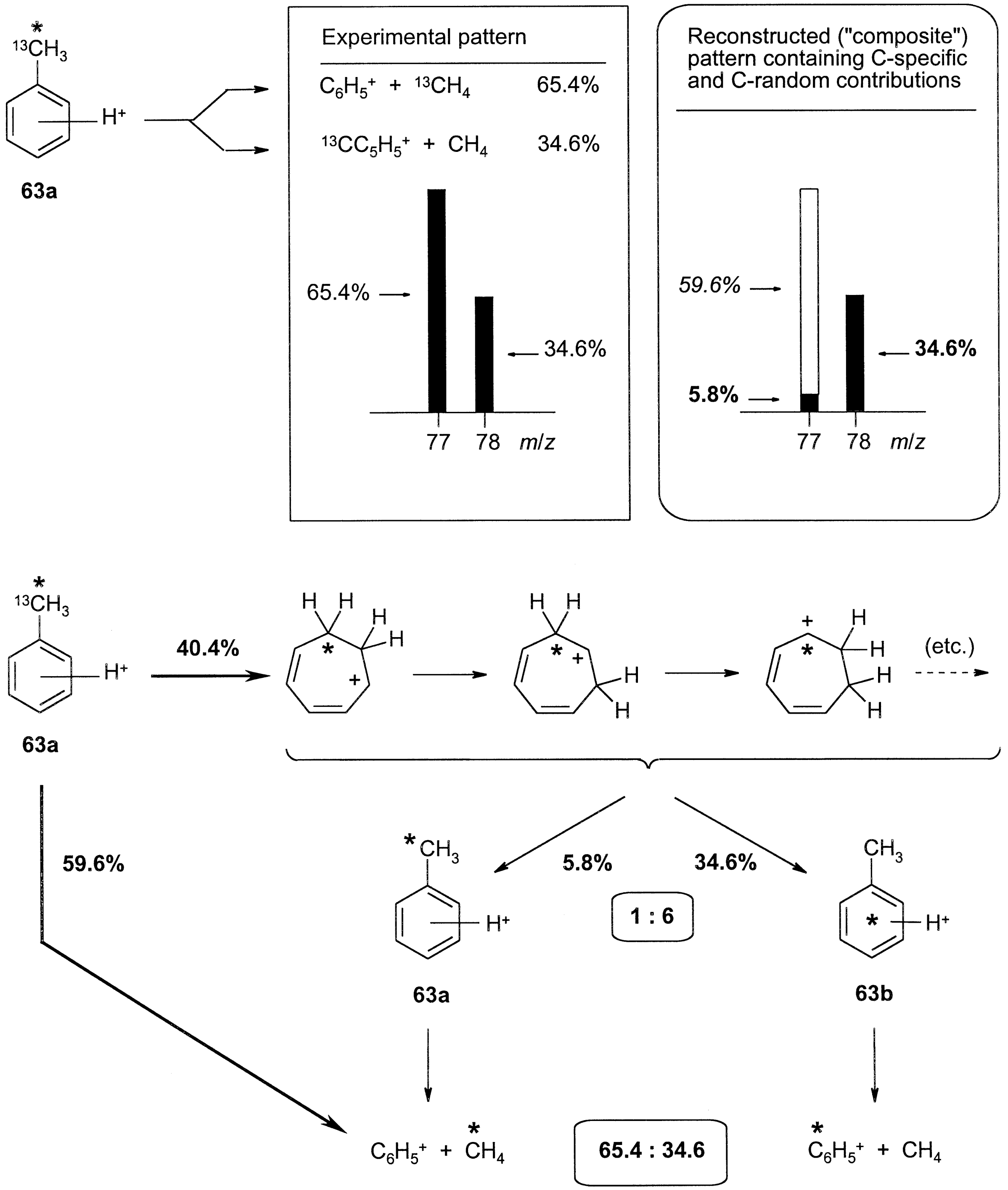


Fig. 9. Lifetime dependence of the relative abundances of the benzene isotopomers lost from ions **41a**, calculated for $k_H = 5 \times 10^5\ s^{-1}$, $k_D = 1 \times 10^5\ s^{-1}$ and $k_f = 8 \times 10^4\ s^{-1}$ and found to fit the experimental pattern (bold line). [Taken from 73].

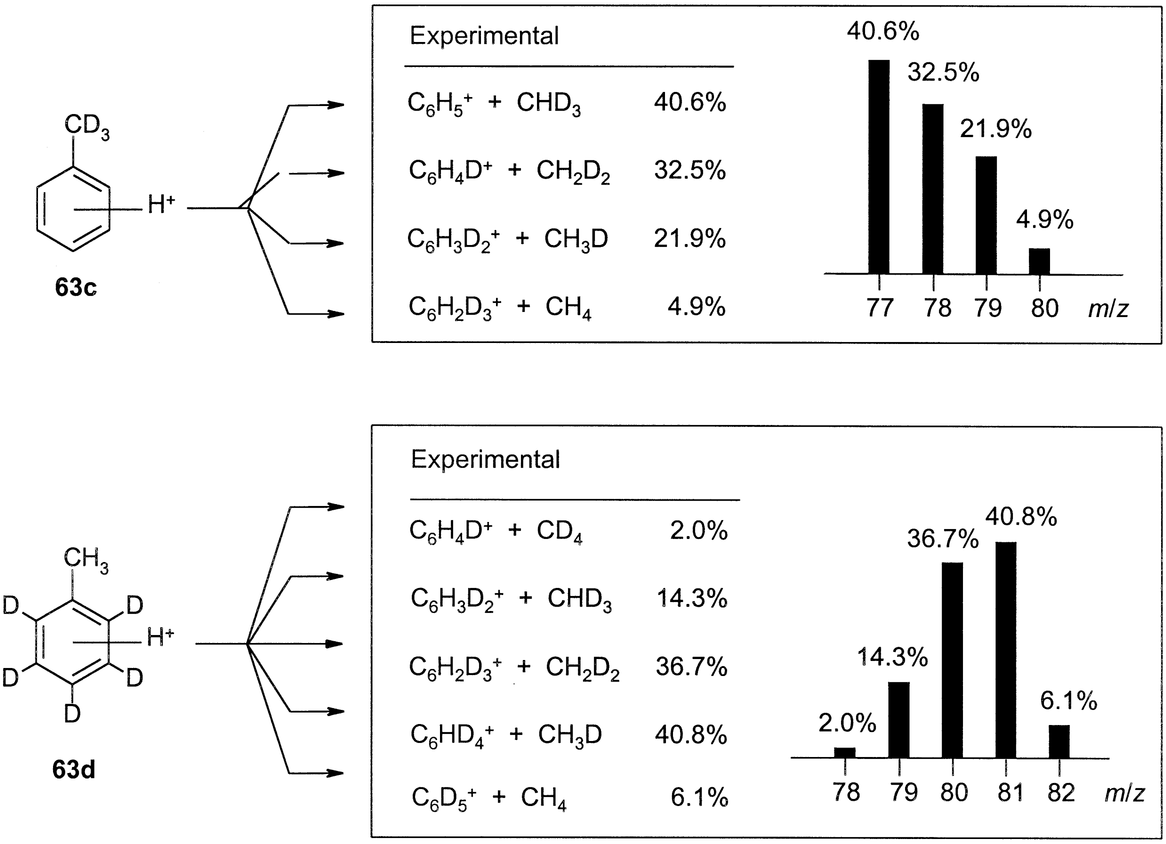
section, some cases are presented where relatively simple ions, viz. protonated and ionized methylbenzenes, undergo incomplete scrambling prior to fragmentation but where the origin of this effect can be traced to "fractional" behaviour, that is, one fraction of the ions suffer "complete scrambling", another one react by slow hydrogen exchange, and still another one dissociate under retention of the original constitutents, i.e. they behave specific.

9.1. Methane loss from toluenium ions: Anything else than simple

To demonstrate this kind of composite scrambling behavior, we first refer back to protonated alkylbenzenes. Ironically, the unimolecular fragmentation of the smallest alkylbenzenium ions, protonated toluene, and protonated xylenes, in contrast to the higher protonated congeners, represent good examples. This complex situation is illustrated in detail in Schemes 21–24 on the basis of a ^{13}C and deuterium labeling study [39a] on the methane loss from metastable toluenium ions (**63**), generated from ionized 1-methyldihydrobenzoic acids (cf. Scheme 2). As shown in Scheme 21, [α-^{13}C]-labeled ions **63a** lose only 65.4% of the methane under retention of the label in the neutral fragment. The other minor fraction of ions **63a** retains the label in the ionic fragment due to reversible ring expansion to dihydrotropylium ions. This process, which has been suggested by Williams and Hvistendahl [91,92] to precede the dihydrogen loss from **63** and studied by us more recently in further



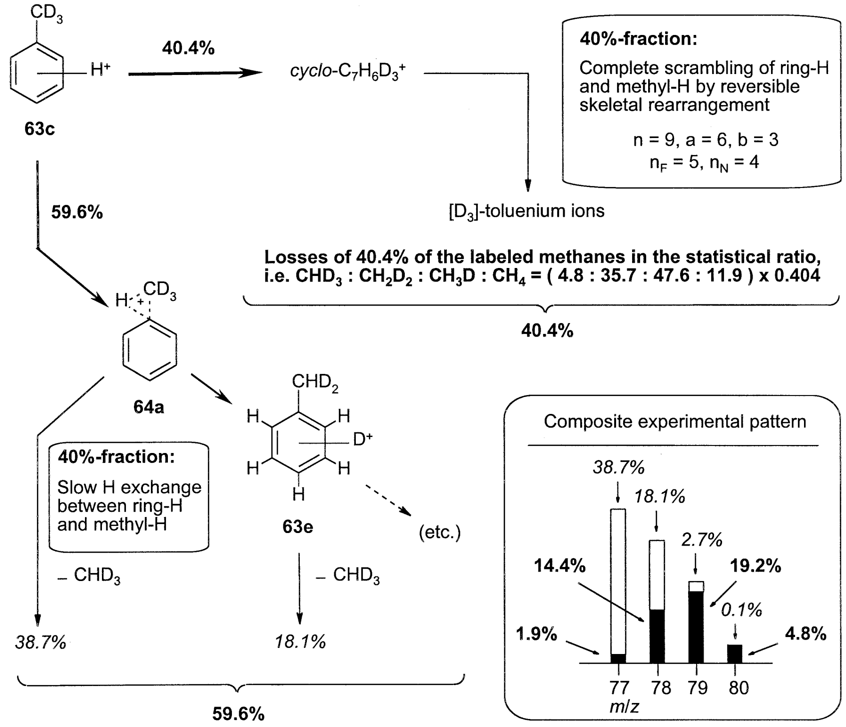
Scheme 21. Observed (top left) loss of methane isotopomers from long-lived [α-^{13}C]-labeled toluenium ions **63a**. The "composite" spectrum (top right) is in agreement with the fragmentation of **63a** in two fractions as shown in the scheme.



Scheme 22. Observed loss of methane isotopomers from long-lived [α,α,α-D_3]-labeled toluenium ions **63c** and [ring-D_5]-labeled ions **63d**.

detail [39,93–95], may be assumed to not only randomize the seven carbon atoms but also the nine hydrogen atoms. Importantly, the observed $^{12}CH_4$ loss reflects only the fraction (6/7) of the ring expanding/recontracting ions **63a** which react via isotopomers **63b**, while a remaining fraction of the ions (1/7) regenerate toluenium ions **63a** from which $^{13}CH_4$ is expelled. Thus, only $65.4 - (1/7 \times 34.6) = 59.4\%$ ($\approx 60\% \ \Sigma$) of the $^{12}CH_4$ loss observed represents the fraction of ions **63a** undergoing carbon-specific methane loss.

The deuterium-labeled toluenium ions **63c** and **63d** eliminate four and five methane isotopomers in ratios which neither reflect a specific nor a statistical behaviour (Scheme 22). However, with the result of the carbon-labeling experiment at hand, the two obviously complex pattern for the $C(H,D)_4$ losses can be analyzed and reveal some interesting additional insight. In the case of the [methyl-D_3] isotopomer **63c**, the 40%-fraction of the ions which undergo carbon and hydrogen randomization contributes to the overall pattern as shown by the black bars in Scheme 23. The losses of CH_4 and CH_3D found experimentally can be attributed almost exclusively to the fragmentation of this fraction of ions **63c**. However, the CHD_3 loss from **63c** is clearly less specific than anticipated from the C-specific $^{13}CH_4$ loss from **63a**, only 39% of the deuterium label being completely retained in the neutral fragment. There is a slow and incomplete exchange between the hydrogen atoms of the ring and the methyl group by way of the methonium-type intermediates **64a** leading to isotopomers **63e** (Scheme 23). Thus, the labeling data of toluenium ions **63c** reveal that a major fraction (~39%) of the

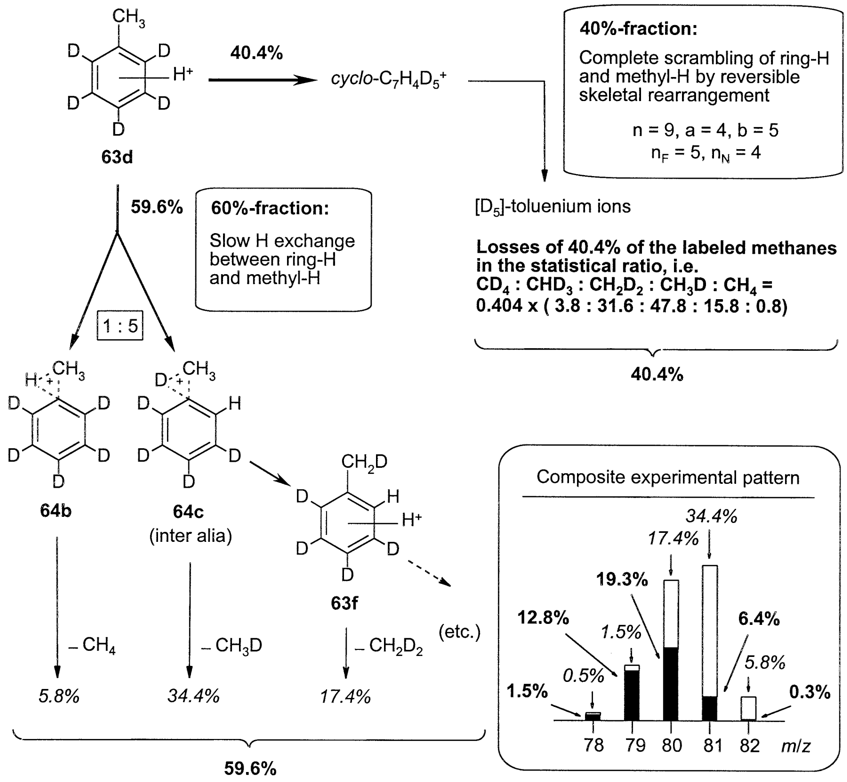


Scheme 23. Reconstruction of the observed spectrum for ions **63c** by underlaying the observed pattern with the 40%-contribution (black bars) of the completely scrambled fractions of ions (see text).

methane lost comprises specifically all of the original constituents of the methyl group and that a minor fraction (~21%) comprises the original carbon atom but more than one single hydrogen atom from the ring—besides the fraction of ~40% of random methane loss.

The data obtained for the toluenium ions **63d** confirm this analysis and allow us to still recognize another (and well known) facet. In this case, the 40%-fraction of the randomised ions represent almost exclusively the low-mass portion of the overall pattern, as shown again by the black bars in Scheme 24. Also, the major contribution of the C-specific methanes appear as CH_3D containing a single deuterium atom from the ring, accompanied by about half that much of CH_2D_2 bearing two of these. Methonium ion **64c** and toluenium isotopomer **63f** are formed as intermediates here. In addition, however, CH_3D loss is accompanied with CH_4 loss in a ratio of roughly 5 : 1, as evident from the high-mass end of the experimental pattern (Scheme 24). Although some tighter corrections are required for a strict treatment of the data, this portion of the methane elimination from ions **63d** clearly reflects the complete "H_1D_5" scrambling by proton ring walk within protonated phenyl group. Thus, besides the consistency of the three fractions discussed above (~40 : 39 : 21), the ubiquitous intraannular proton exchange has also been recognised in the "background" of this composite scrambling system.

In total, protonated toluene isomerizes in a fractional manner: One portion of $C_7H_9^+$ ions (~40% Σ) undergoes complete equilibration of all carbon and all hydrogen atoms prior to elimination of methane, whereas another fraction (~60% Σ) loses methane without carbon scrambling but after a slow exchange between the hydrogen atoms of the ring and the methyl group. Of the latter ions, a sub-fraction of (~2/3 × 60% Σ = 40% Σ) eliminates methane containing the original methyl hydrogen atoms and one of the six hydrogen from the protonated ring, in the

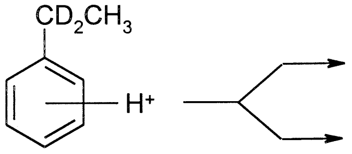


Scheme 24. Reconstruction of the observed spectrum for ions **63d** by underlaying the observed pattern with a 40%-contribution (black bars) of the completely scrambled fractions of ions (see scheme and text).

statistical ratio reflecting the fast intraannular proton ring walk. The remaining subfraction (~1/3 × 60% Σ = 20% Σ) of the "C-specific" ions undergoes, in addition, a slow and therefore incomplete exchange between the hydrogen atoms at the protonated ring and the methyl group [96].

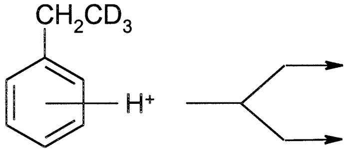
9.2. Ethene loss from ethylbenzenium ions

A minute extension of the smallest protonated alkylbenzene gives rise to two cases. Protonated ethylbenzene **65** eliminates almost exclusively ethene but the hydrogen rearrangement from the ethyl group to the ring, generating the $C_6H_7^+$ fragment ion (**3**), is again accompanied by slow and incomplete hydrogen scrambling. However, scrambling does not occur between the alkyl group and the ring, in contrast to toluenium ions **63**, but within the ethyl group itself. Leung and Harrison [97] demonstrated that dissociation of short-lived isotopomers **65a** and **65b** generated by CI(CH_4) involves rearrangement of 21% of the methylene- and 79% of the methyl-H atoms with an isotope effect of $k_H/k_D = 1.76$, as calculated from the data shown in Scheme 25 by using the approach mentioned earlier for ions **5** (cf. Scheme 3) [98]. Audier et al. [99] found that metastable ions **65a** and **65b** behave identically after CI(H_2O) [100]. Higher simple alkylbenzenium ions behave similarly in that they undergo hydride shift within the side chains but, in addition, mostly incomplete proton exchange between the aliphatic moiety and the aromatic ring. In all cases, including ethylbenzenium ions **65**, the intermediacy of ion/molecule complexes have been invoked [31,101–106] to explain both scrambling processes. However, protonated ethylbenzene **65** is special, because formation of the complex $[C_2H_5^+$



65a

Experimental	unstable ions CI(CH_4), ref. [97]	metastable ions CI(H_2O), ref. [99]
$C_6H_7^+$ + $C_2H_2D_2$	86.7%	86%
$C_6H_6D^+$ + CH_3D	13.3%	14%



65b

Experimental	unstable ions CI(CH_4), ref. [97]	metastable ions CI(H_2O), ref. [99]
$C_6H_7^+$ + C_2HD_3	31.8%	31%
$C_6H_6D^+$ + CH_2D_2	68.2%	69%

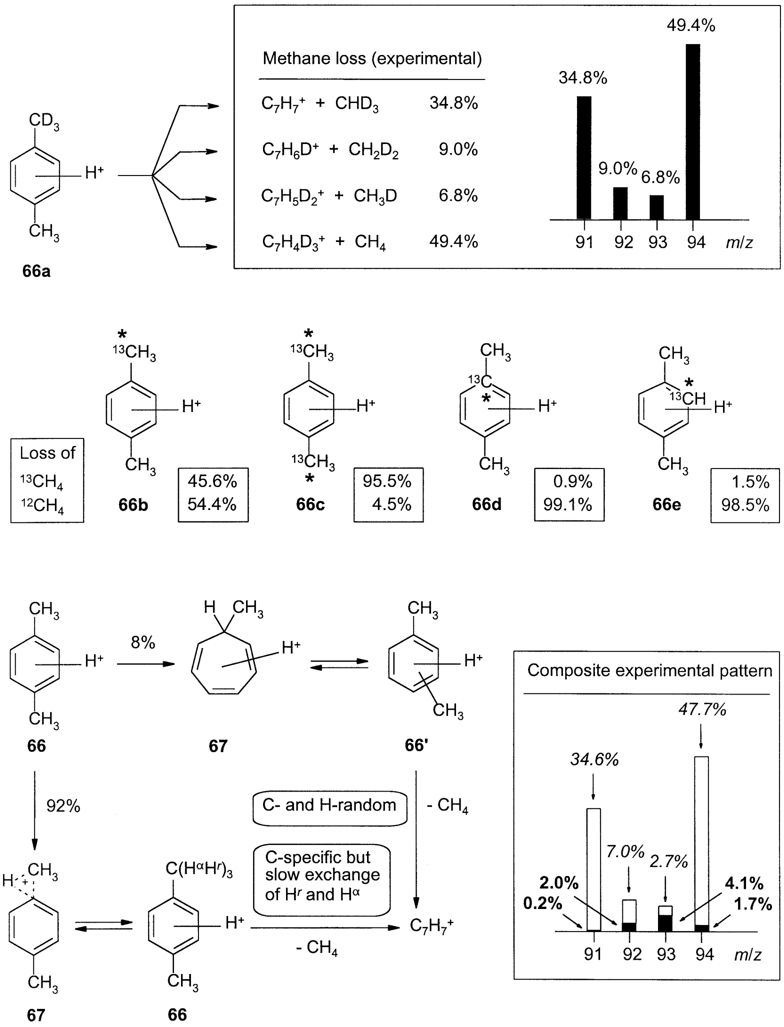
Scheme 25. Loss of ethene from short-lived and long-lived [α,α-D_2]- and [α,α,α-D_3]-labeled ethylbenzenium ions **65a** and **65b**.

C_6H_6] is endothermic with respect to dissociation and thus too short-lived to allow complete hydrogen scrambling within the ethyl cation [99].

9.3. Methane and ethene loss from xylenium ions

Protonated xylenes, e.g. **66**, exhibit more complicated behavior than ion **65**, akin to the toluenium ions **63** discussed above. In a recent study, we have complemented earlier insights [39b] into the scrambling scenario of para-xylenium ions **63** obtained from deuterium labeling with extended ^{13}C-labeling [41]. Loss of methane from the [methyl-D_3] isotopomers **66a** is again associated with incomplete H/D scrambling and mechanistic explanations are extremely difficult (Scheme 26). Again, it appears that several fractions of ions exhibit different types of scrambling to different extents, although the overall scrambling is reduced as compared to ions **63**. This follows from the fragmentation of four ^{13}C-labeled isotopomers **66b**-**66e** which helps to understand the fragmentation of the [D_3]-labeled isotopomer **66a**.

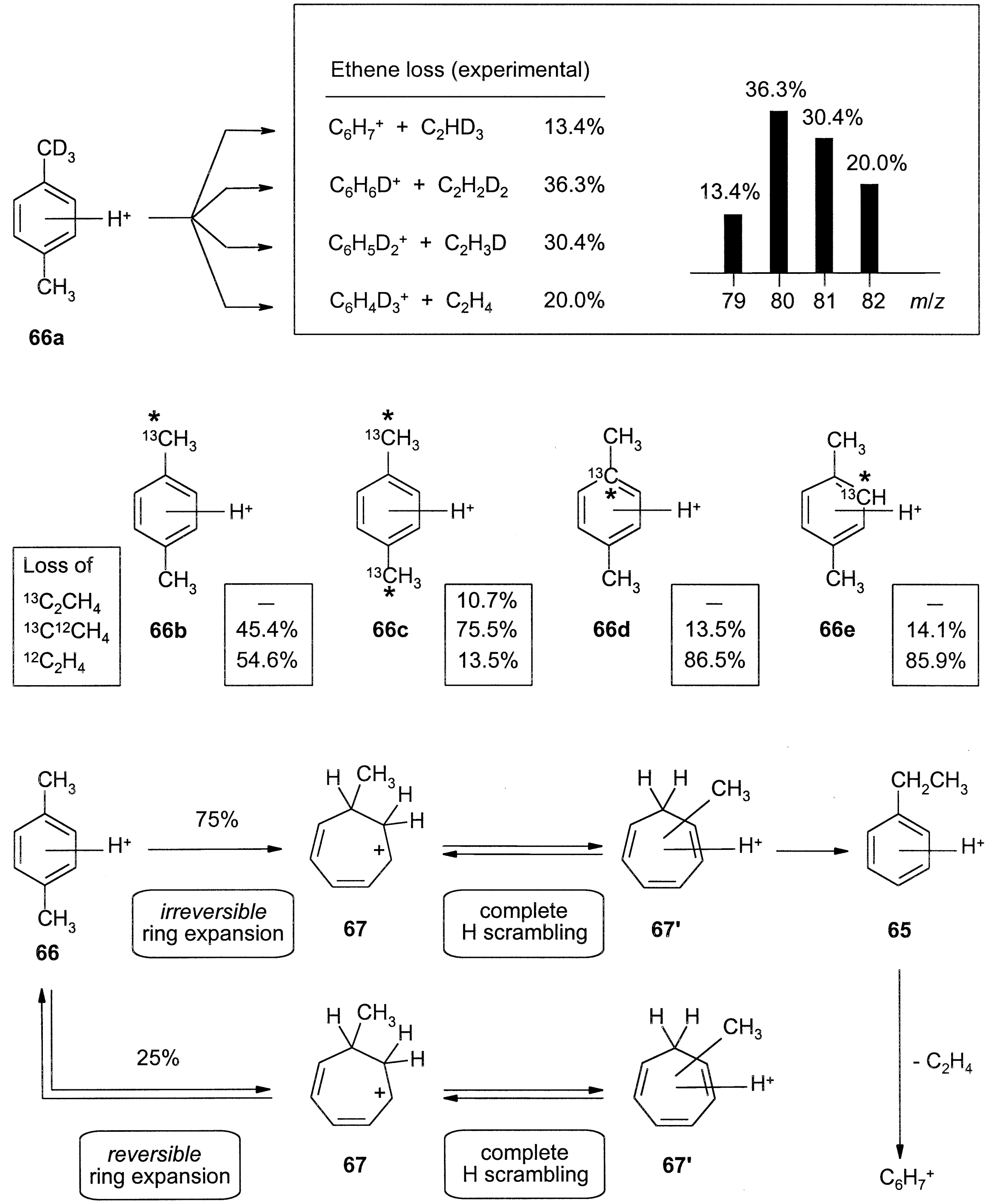
As suggested from the loss of C(H,D)$_4$ from **66a**, the ^{13}C-labeled isotopomers **66b** and **66c** indicate that the loss of methane involves the constituents of the methyl groups to a higher extent as that found for the toluenium ions. Nevertheless, some 5% of the carbon are lost as methane originates from the ring (cf. **66c**) and, complementarily, the two [ring-^{13}C]-labeled isotopomers **66d** and **66e** expel a small but significant fraction ($\sim$1%) of $^{13}CH_4$. Extensive model calculation based on the insights into the isomerization of toluenium ions **63** have led us to conclude that, in the case of ions **66**, a relatively small fraction (8%) of the xylenium ions undergo complete C- and H-scrambling by reversible ring expansion/contraction via ions **67** (Scheme 26), whereas 92% of the ions expel methane C-specifically but after slow and incomplete hydrogen exchange between the ring and the methyl groups. In fact, the statistical distribution of C(H,D)$_4$ amounting to a 8%-fraction ions **66a** fits well the inner part of the experimental pattern of this isotopomer (see *m/z* 93 composite pattern in Scheme 26). A ratio of [CH_2D_2] : [CHD_3] = 7.0 : 34.6 $\approx$ 0.20



Scheme 26. Observed pattern for the loss of methane from [α,α,α-D_3]-labeled xylenium ions **66a** (top) and from the four ^{13}C-labeled isotopomers **66b-66d** (middle). Reconstruction of the observed spectrum for ions **66a** by underlaying the observed pattern with a 8%-contribution (black bars) of the completely scrambled fractions of ions (see scheme and text).

indicates the extent of slow H^r/H^α exchange with regards to one methyl group, again a lesser extent than in the toluenium ions (cf. Scheme 23, $[CH_2D_2]$: $[CHD_3] = 18.1 : 38.7 \approx 0.47$.

Finally, it has to be noted that long-lived xylenium ions **66** also eliminate ethene [39b]. It is obvious that this process requires the intermediacy of ethylbenzenium ions **65** from which ethene is expelled eventually, and methyldihydrotropylium ions **67** represent again the logical intermediates for the isomerization **66** → **65** [92,94]. As may be expected for the ethene loss channel, hydrogen scrambling was found to be more extensive than for methane loss (Scheme 27 vs. Scheme 26). In fact, the fragmentation of the deuterium-labeled isotopomer **66a** indicates incomplete scrambling and results from different fractions of ions undergoing different isomerization processes. However, investigation of the four [^{13}C]-labeled isotopomers **66b–66e** has allowed us to develope a scrambling model for ethene loss from **66** [41]. It appears that the major part (75%) of the xylenium ions **66** suffers irreversible ring-expansion to protonated



Scheme 27. Observed pattern for the loss of ethene from [α,α,α-D_3]-labeled xylenium ions **66a** (top) and from the four ^{13}C-labeled isotopomers **66b**-**66d** (middle). The scheme indicates the fractional behaviour of the ions (see text).

methylcycloheptatriene **67** with associated complete hydrogen scrambling (**67**$\rightleftharpoons$**67′**, Scheme 27). This leaves the second methyl group unaffected prior to ring contraction to ethylbenzenium ions **65**. The minor fraction of ions **66** (25%) undergoes reversible ring expansion/contraction, giving rise to complete hydrogen and carbon scrambling prior to (irreversible) formation of ions **65**. Extensive calculations suggest that slight modifications of this model are possible but that we must account for at least two sets of ions with differently extensive scrambling behavior [41].

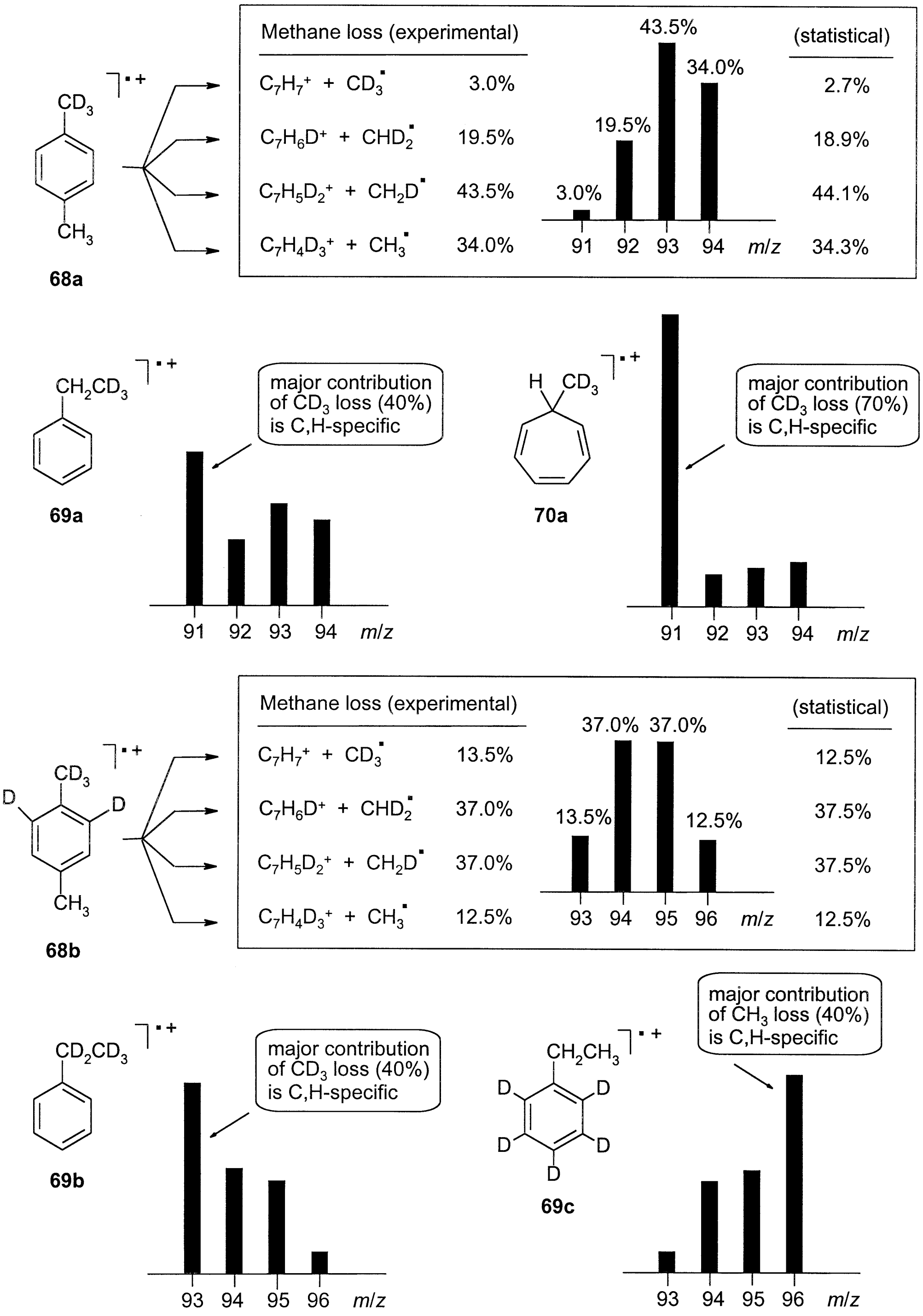
9.4. Back to the "roots": Methyl loss from the radical cations of xylene

The observation that scrambling ions behave "composite" is quite common, although often not recognized, and its origins lie certainly in the multidimensionality of energy hypersurfaces and diverging dynamics of isomers with respect to mutual interconversion and competing fragmentation. Several attempts have been made to understand this in more detail, including early investigations of the radical cations of toluene and cycloheptatriene by Venema et al. [107] and by Howe and Baldwin et al. [42,43], mentioned in the first section of this article. To close the loop and, at the same time, demonstrate the similarity of closely related and nevertheless chemically quite different ionic species undergoing hydrogen and carbon scrambling, we add some insights into the behavior of ionized xylene, ethylbenzene, and methylcycloheptatriene, i.e. the radical cations **68**, **69** and **70** (Scheme 28). This system deserves particular notice because of the fact that it has been investigated and modeled with respect to its energetic and kinetic parameters [108,109].

At variance from the protonated xylenes such as **66**, long-lived xylene radical cations **68** fragment after virtually complete scrambling, as illustrated for the $C_8H_7D_3$ isotopomer **68a** and the $C_8H_5D_5$ isotopomer **68b** in Scheme 28 [108]. Calculations have shown that, due to the particularly deep potential well of **68** and thus its high density of states at the level of internal energies of the metastable ions, this isomer represents a "kinetic trap" within the overall $C_8H_{10}^{\cdot+}$ hypersurface. In contrast, ionized ethylbenzene **69** and, even more so, ionized methylcycloheptatriene **70**, exhibit a fractional scrambling behavior: A fraction of ~60% of the metastable ions' population of the [D_3]-labeled ions **69a** and of the two [D_5]-labeled ions **69b** and **69c** lose the four $C(H,D)_3^{\cdot}$ isotopomers in the statistical ratio, whereas a fraction of ~40% undergoes specific methyl loss (Scheme 28). In the case of ionized methylcycloheptatriene **70a**, about 30% of the ions exhibit nearly complete randomization but 70% dissociate specifically. ^{13}C-labeling of a methyl group in ions **68** and of the methyl groups in ions **69** and **70** clearly corroborates this analysis [109].

10. Conclusion

Scrambling reactions in organic ions are ubiquitous. They occur in radical cations and even-electron ions, which have been discussed in quite some detail here, and also in negative ions, which have been mentioned here only indirectly in the case of an ylid structure hidden in a phosphonium ion (cf. Scheme 26). This article has spanned the various facets of atom scrambling, including complete proton, hydrogen, and methyl group equilibration, slow hydrogen exchange, kinetic simulation, and composite scrambling behavior. A tutorial on the combinatorics of randomized ionic systems has also been included, and it is the author‘s hope that fascination with scrambling phenomena in gaseous ions remains vivid, as this type of degenerate chemical reaction is not limited to organic mass spectrometry but occurs in solution chemistry as well albeit often less conveniently detectable than in a mass spectrometer. In any case, achievements from the past five decades on the field of mass spectrometry has offered us a rich variety and quite deep insights in this part of ion chemistry, and it is hoped that the next five decades will bring us even more.



Methane loss (experimental)		(statistical)
$C_7H_7^+ + CD_3^•$	3.0%	2.7%
$C_7H_6D^+ + CHD_2^•$	19.5%	18.9%
$C_7H_5D_2^+ + CH_2D^•$	43.5%	44.1%
$C_7H_4D_3^+ + CH_3^•$	34.0%	34.3%

major contribution of CD_3 loss (40%) is C,H-specific

major contribution of CD_3 loss (70%) is C,H-specific

Methane loss (experimental)		(statistical)
$C_7H_7^+ + CD_3^•$	13.5%	12.5%
$C_7H_6D^+ + CHD_2^•$	37.0%	37.5%
$C_7H_5D_2^+ + CH_2D^•$	37.0%	37.5%
$C_7H_4D_3^+ + CH_3^•$	12.5%	12.5%

major contribution of CD_3 loss (40%) is C,H-specific

major contribution of CH_3 loss (40%) is C,H-specific

Scheme 28. Statistical H/D scrambling observed through the loss of $C(H,D)_3^•$ radicals from [α,α,α-D_3]- and [α,α,α,*o*,*o*-D_5]-labeled xylene radical cations **68a** and **68b**, as contrasted to the factional behavior of the isomeric radical cations of labeled ethylbenzene (**69a-69c**) and cycloheptatriene (**70a**). The C,H-specific losses represent the major parts of the assigned peaks (arrows). The contributions due to the fractions that have undergone complete scrambling are not underlaid in these cases.

Acknowledgements

To recognize a scrambling process in gaseous organic ions and assess its extent of progression and maybe its perfect completeness has always been great pleasure to me. I thank my inspirators and students and many colleagues worldwide who have shared this pleasure with me over the years. The names of many of them have been mentioned in this review, and some of them have become friends. I express my apologies to those whose inspiring contributions have not been mentioned herein. I thank J.J. Veith and F.I. Runge (Technische Universität Darmstadt) and H.-F. Grützmacher and D. Kirchhoff (Universität Bielefeld) for kindly agreeing in my mentioning some of their yet incompletely published work in this review.

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