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Aromatic Alkylation by Gaseous Me_3C^+ Ions. Kinetic Role of Deprotonation of Intermediate Arenium Ions

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Abstract: The alkylation of *m*-xylene by Me_3C^+ ions has been studied in the gas phase with the aim of assessing the kinetic role of proton transfer from intermediate arenium ions. Hydrogen kinetic isotope effects (KIEs) emerging from the reaction of *m*-xylene-*4-d* and of *m*-xylene/*m*-xylene-d_{10} mixtures have been exploited as mechanistic probes. The Me_3C substitution at the 4-position displays a base-strength-dependent KIE related to rate-determining deprotonation of arenium intermediates. The Me_3C^+ reaction at the 5-position is instead characterized by a base-independent KIE due to 1,2-hydrogen shift to form a highly stable isomeric arenium ion. When the latter species originates from *m*-xylene-*4-d*, its neutralization involves an intramolecular competition of proton vs deuteron abstraction, manifesting a net primary KIE. Factors affecting its magnitude and base-strength dependence are discussed.

Introduction

Much effort has been devoted to the problem of ascertaining the multistep character of electrophilic aromatic substitution reactions occurring in the gas phase, a medium where charged reagents are free from complicating environmental effects due to specific catalyst, solvent, and counterion interactions. A benchmark system has been found in the alkylation reaction by gaseous Me_3C^+ ions, where the mild character of the electrophile allows reaction steps other than the chemically featureless collisional encounter of the reactants to become kinetically relevant.[1] The bulk $i\text{-}C_4H_{10}$ gas, from which Me_3C^+ can be generated by ionization/dissociation and ensuing ion–molecule reactions, is a fairly inert medium as far as solvation of cationic species is concerned and provides a "neutral" background to the ionic reactivity pattern of interest. The primary ionization of the bulk gas may be triggered by an electron beam in the ion source of a mass spectrometer or, alternatively, by secondary electrons in the interaction of γ-radiation with matter, as occurs in the γ-radiolysis of isobutane. The use of the radiolytic technique,[2] operating at pressures up to 1 atm, copes with an inherent problem of gas-phase studies of ion–molecule reactions, namely, the fast removal of the electrostatic energy deposited into the collisional complex from the ion–molecule encounter.[3] The excited complex may experience a comparatively efficient thermalization allowed by the short time lapse (ca. 10^{-10} s at 1 atm) between unreactive collisions with the bath gas, thus making a direct comparison with kinetic processes in solution possible.

A recent study on the *tert*-butylation of benzene and toluene[4] has ascertained the role of the primary ipso σ-complex I in the overall pattern of the electrophilic substitution reaction depicted in Scheme 1 ($E^+ = Me_3C^+$). Depending on X, ion I may undergo a more or less rapid isomerization by proton shifts whose rate has been estimated using selectively deuterated substrates. Whereas several examples of electrophilic aromatic substitutions by gaseous cations display a reactivity pattern consistent with rate-determining formation of the encounter complex (k_c) and relatively few show intermolecular selectivities arising from rate determining electrophilic attack (k_E), only the rate of the Me_3C^+ substitution is known to be affected, in some instances, by the rate of deprotonation of σ-complex intermediates which may or may not compete with intramolecular H-shift. We decided to investigate this process further, seeking a system where side isomerization pathways would play a minor role and using the H/D kinetic isotope effect (KIE) as a mechanistic probe.[5] The goal was to assess the kinetic role of deprotonation of arenium ions, besides gaining a deeper understanding of the fundamental process of proton transfer from gaseous ions in nearly thermal equilibrium with their environment.

Experimental Section

Materials. The gaseous reagents ($i\text{-}C_4H_{10}$ and O_2) were research grade gases with stated purity ≥ 99.95 mol %. Substrates (*m*-xylene and *m*-xylene-d_{10}) and bases (amines, nitriles, carbonyl compounds, alcohols, etc.) were commercially available from Aldrich Chimica S.r.l. or Fluka Chemie A.G. *m*-Xylene-*4-d* was prepared, purified, and analyzed for its deuterium content (65 ± 2%) according to the same procedure already described for the preparation of selectively deuterated toluenes.[4]

General Procedure of Radiolytic Experiments. Gaseous mixtures were prepared by standard vacuum line procedures. The bulk $i\text{-}C_4H_{10}/O_2$ components were admitted in carefully outgassed 135-mL Pyrex vessels containing weighed amounts of liquid substrates and additives into breakable glass ampules. The latter were broken and their contents let free to evaporate, forming a homogeneous mixture in the sealed vessel, which was exposed to irradiation from a ^{60}Co source in a 220 Gammacell (Nuclear Canada Ltd) at the dose rate of 2×10^4 Gy h^{-1} and an irradiation temperature of 40 °C. The total dose ranged from 1×10^4 to 2×10^4 Gy, which yielded less than 1% substrate conversion into products under typical reaction conditions, i.e. in the presence of ca. 5 Torr of added base. The radiolytic product mixture was recovered by washing the walls of the vessel with ethyl acetate, introduced through a gas-tight septum, ensuring condensation of all gaseous components by means of repeated freeze–thaw cycles from liquid nitrogen temperature to room temperature.

[⊗] Abstract published in *Advance ACS Abstracts*, May 15, 1994.

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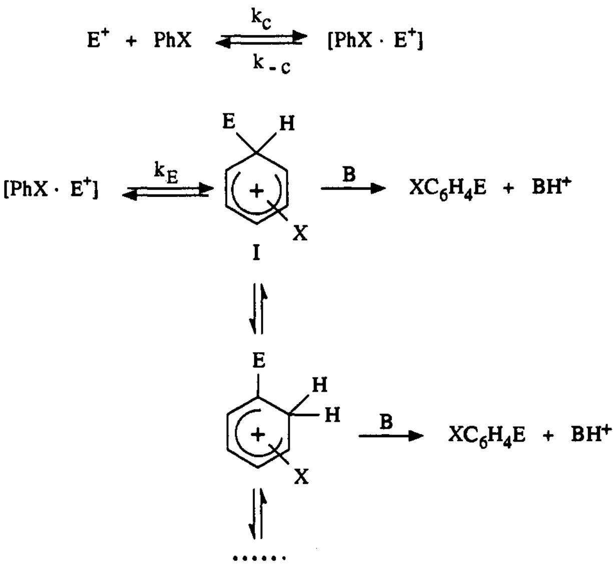
Scheme 1



Product distributions, yields, and deuterium contents were obtained by GLC-MS analysis on a Hewlett-Packard 5890 gas chromatograph in line with a HP 5970B mass selective detector. The following capillary columns were used: (i) a 50-m-long, 0.2-mm-i.d. fused silica column coated with a 0.5-μm cross-linked methylsilicone film (PONA column from Hewlett-Packard); (ii) a 30-m-long, 0.2-mm-i.d. fused silica column coated with a 0.2-μm film of cross-linked polyethylene glycol (Supelcowax 10 column from Supelco Co.).

The product distributions were obtained from the integrated areas of isomeric products. Absolute yields were calculated from the ratio of products and substrate areas checked against a calibration curve for varying ratios of standard compounds. The deuterated to unlabeled product ratios were obtained from the integrated areas of the corresponding well-resolved chromatographic peaks in the experiments involving competitive *tert*-butylation of *m*-xylene and *m*-xylene-d_{10}. The deuterium content in the *tert*-butylation products of *m*-xylene-*4*-*d* was derived from the relative abundancies of $[M-CH_3]^+$ fragment ions at *m*/*z* 147 and *m*/*z* 148 in the elution peak summing the unlabeled and singly deuterated product.

Table 1. Gas-Phase Reaction of Me_3C^+ Ions with *m*-Xylene and *m*-Xylene-d_{10} Mixtures

		product distribution (%)[c]		k_H/k_D[d]	
added base[a] (Torr)	PA (base)[b] (kcal mol^{-1})	1,3,*4*[e]	1,3,*5*[e]	1,3,*4*[e]	1,3,*5*[e]
Et_3N (2.2)	232	73	27	0.8	1.2
pyridine (2.4)	221	85	15	0.9	1.4
c-hexanone (4.5)	201	84	16	1.1	1.3
mesitylene (4.3)[f]	201	24*	76*	1.9	1.4
PhCHO (5.1)	200	66*	34*	2.1	1.2
Me_2CO (0.88)	197	66	34	1.5	1.1
Me_2CO (4.7)	197	77	23	1.5	1.3
Me_2CO (9.3)	197	79	21	1.6	1.2
Me_2CO (4.9)[g]	197	9	91	1.8	1.1
Me_2CO (5.3)[h]	197	87	13	1.5	1.2
[f]	196[i]	17	83	1.5	1.3
n-PrCN (3.8)	194	67	33	1.9	1.4
EtCN (4.5)	193	60*	40*	2.1	1.2
p-$CF_3C_6H_4CHO$ (4.3)	192	58	42	2.2	nd[j]
HCO_2Me (4.8)	188	44	56	1.6	1.3
MeOH (9.1)[f]	182	82	18	1.2	1.3

[a] All gaseous systems contain comparable amounts of *m*-xylene and *m*-xylene-d_{10} (0.7–1.5 Torr), *i*-C_4H_{10} (630–710 Torr, unless stated otherwise), and O_2 (10 Torr) as thermal radical scavenger. [b] Taken from ref 6. [c] Standard deviation of duplicate experiments ±3%. Isomeric distributions are approximately equal for the deuterated and undeuterated products except in cases indicated by an asterisk, where the deuterated products are shifted in favor of a higher fraction (>10%) of 1,3,*5* isomer with respect to the unlabeled products.

$$^{d}\,k_H/k_D = \frac{[1,3,4(5)]}{[1,3,4(5)\text{-}d_9]}\,\frac{[m\text{-xylene-}d_{10}]}{[m\text{-xylene}]}$$

[e] *tert*-Butylated position italicized. [f] In these experiments the 1,3,*5*-d_9 product is accompanied by approximately 10% singly exchanged 1,3,*5*-d_8 product. In the MeOH experiment there is also a 5% fraction of 1,3,*4*-d_8. The same is found with *t*-BuOH as the base. [g] Experiment run at 120 °C instead of the usual 40 °C. [h] In this experiment the *i*-C_4H_{10} pressure was 2660 Torr. [i] PA of *m*-xylene. [j] Not determined.

Table 2. Gas-Phase Reaction of Me_3C^+ Ions with *m*-Xylene-*4*-*d*

		isomer distribution (%)		D-content (%)[c]		k_H/k_D[d]	
added base[a] (Torr)	PA (base)[b] (kcal mol^{-1})	1,3,*4*	1,3,*5*	1,3,*4*	1,3,*5*	1,3,*4*	1,3,*5*
(*i*-Pr)$_2$NEt (0.5)	235	32	68	60	80	1.5	1.5
(*i*-Pr)$_2$NEt (4.6)	235	52	48	60	78	1.5	1.3
Et_3N (2.6)	232	73	27	55	75	1.2	1.0
pyridine (3.0)	221	83	17	54	75	1.2	1.0
PhCOMe (5.5)	205	62	38	57	84	1.3	2.1
c-hexanone (4.5)	201	83	17	56	83	1.3	1.9
mesitylene (4.7)	201	20	80	63	83	1.7	1.9
PhCHO (3.9)	200	72	28	58	85	1.4	2.3
Me_2CO (1.3)	197	68	32	63	83	1.7	1.9
Me_2CO (4.3)	197	77	23	62	84	1.6	2.1
	196	16	84	58	79	1.4	1.4
PhCN (1.5)	196	63	37	69	87	2.2	2.8
t-BuOH (4.5)	194	81	19	58	84	1.4	2.1
EtCN (4.1)	193	64	36	68	88	2.1	3.2

[a] All gaseous systems contained *m*-xylene-*4*-*d* (1.4–2.6 Torr), *i*-C_4H_{10} (690–710 Torr), and O_2 (10 Torr). [b] Taken from ref 6. [c] D-content is normalized to the hypothesis of starting from 100% deuterated substrate. [d] $k_H/k_D = [1,3,4\text{-}d]/[1,3,4]$ and $k_H/k_D = 1/2\{([1,3,5\text{-}d]/[1,3,5]) - 1\}$, respectively.

Results

Tables 1 and 2 summarize the results from the gas-phase reaction of Me_3C^+ with *m*-xylene and *m*-xylene-d_{10} mixtures and with *m*-xylene-*4*-*d*, respectively. As already reported, the *tert*-butylation of *m*-xylene by gaseous Me_3C^+ ions gives substitution products at the 4- and 5-position (henceforth denoted as 1,3,*4* and 1,3,*5*) with radiochemical yields typically around $G_M \approx 0.05$ μmol J^{-1} in the present systems, which are indicative of an overall highly efficient reaction. In fact, nearly all experiments were run in the presence of added bases of different strength, all of them able, however, to act as a sink for the reactant Me_3C^+ ion by either deprotonating it[6] or binding to it to form adduct or cluster ions.[7] The bases used markedly influence the 1,3,*4* vs 1,3,*5* product distribution, which is sensitive to their concentration, proton affinity (PA), and structural features. Bases of increasing PA favor the formation of 1,3,*4*, which is highest in the case of pyridine and cyclohexanone. Exceptions in this general trend are (i) the bulky (*i*-Pr)$_2$NEt, less effective in inhibiting the formation of 1,3,*5* than its high PA would predict; (ii) the alcohols, *t*-BuOH and MeOH, which still favor the formation of 1,3,*4* in spite of their relatively low PA; and (iii) the aromatics, mesitylene and the substrate itself, the least effective in yielding the 1,3,*4* isomer. Increasing base concentration, Me_2CO from 0.88 to 9.3 Torr (Table 1) or (*i*-Pr)$_2$NEt from 0.5 to 4.6 Torr (Table 2), brings about an increased fraction of 1,3,*4*. At constant base concentration, ca. 5 Torr of Me_2CO, the relative amount of 1,3,*5* increases at higher temperature and lower pressure.

The data of major interest in this work concern the differential reactivity of isotopically different substrates or reaction sites. The competitive *tert*-butylation of *m*-xylene/*m*-xylene-d_{10} mixtures yields unlabeled and deuterated products in ratios which are normalized by the ratio of corresponding reactants concen-

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(6) Unless otherwise stated, all thermodynamic data are taken from the following: Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, N. G. *J. Phys. Chem. Ref. Data* **1988**, 17, Suppl. 1.

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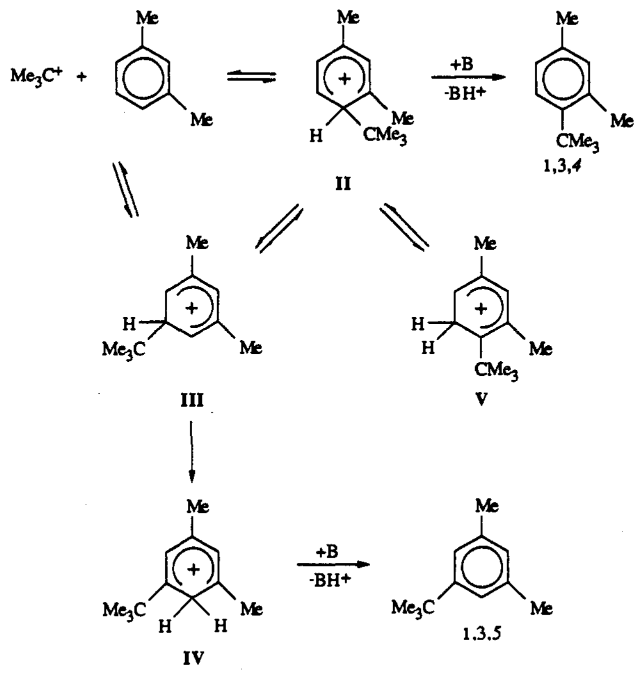
tration and given as k_H/k_D values in Table 1. The 1,3,*4* and 1,3,*5* products display markedly different sets of k_H/k_D values. The 1,3,*5* isomer shows an approximately constant $k_H/k_D \approx 1.3 \pm 0.1$ in the whole range of base strength and base concentration investigated. The 1,3,*4* product exhibits k_H/k_D close to unity in the case of strong bases such as pyridine and cyclohexanone and a trend of increasing k_H/k_D for weaker bases up to a value of ca. 2, though no distinct pattern is clearly discernible. Rather, the k_H/k_D values seem to depend even on the chemical features of the base, since bases of almost equal PA (e.g. cyclohexanone and PhCHO) may give different values (1.1 and 2.1, respectively). A 10-fold variation of Me_2CO concentration or an increase of the bulk *i*-C_4H_{10} pressure up to 3.5 atm does not affect k_H/k_D. A certain increase is instead observed at the higher temperature of 120 °C.

The deuterium contents of the 1,3,*4* and 1,3,*5* products from the reaction of *m*-xylene-*4-d* are reported in Table 2, after correction for incomplete deuteration of the starting substrate. In doing so, one assumes that the percent fraction of undeuterated substrate would give an equal percent fraction of undeuterated products. These data allowed us to derive $k_H/k_D = [1,3,4\text{-}d]/[1,3,4]$ and $k_H/k_D = 1/2\{([1,3,5\text{-}d]/[1,3,5]) - 1\}$ for the formation of the 1,3,*4* and 1,3,*5* isomer, respectively (see the Discussion section). Both isomers are sensitive to variation of base strength and structure in a trend analogous to that displayed by the 1,3,*4* product from the intermolecular competition of *m*-xylene and *m*-xylene-d_{10}. In the high PA range, a certain positive deviation emerges for the bulky $(i\text{-}Pr)_2NEt$ which shows k_H/k_D values distinctly greater than unity, in contrast to other somewhat less basic amines, i.e. Et_3N and pyridine. In the presence of bases of lower PA, k_H/k_D ratios exhibit higher values, which are also sensitive to base structure. For example, lower k_H/k_D values are observed in the presence of *t*-BuOH than in the presence of either PhCN or EtCN, nitriles of comparable PA with respect to the alcohol.

Discussion

***tert*-Butylation of *m*-Xylene at the 4-Position. Rate-Determining Proton Transfer.** Me_3C^+ is endowed with a relatively mild electrophilic character and significant steric bulk.[1,8] These two features account for its peculiar reactivity toward arenes. The high $k_{\text{benzene}}/k_{\text{toluene}}$ ratio, ca. 50 at room temperature, may seem at odds with its unreactivity toward *p*-xylene and mesytilene, unless one takes into account the factors hindering an ortho relationship of the Me_3C group with methyl groups.[1a–d] Me_3C^+ does react with *m*-xylene according to the pattern depicted in Scheme 2. The kinetically favored attack at the 4-position leads to intermediate II, which benefits from the electron-releasing effect of two ortho/para methyl groups. Deprotonation of II by the base B yields the 1,3,*4* isomer, which involves an ortho relationship with only one methyl group. However, if a longer lifetime is allowed to II, e.g. at lower base concentrations or lower PA of the base, factors that generally decrease the deprotonation rate, an apparent isomerization takes place, either intramolecular or via back-dissociation to the reactants, ultimately leading to 1,3,*5*, via intermediate IV, by far the most stable among the possible isomeric arenium ions. Ion II may conceivably undergo a second isomerization process, namely, II → V. A similar 1,2-hydrogen shift reportedly follows Me_3C^+ attack at the para position of toluene[4] (Scheme 1, X = *p*-Me, $E^+ = Me_3C^+$), estimated to be a nearly thermoneutral process. The same does not hold for II → V, both for electronic reasons, since two ortho/para methyl groups in II are replaced by only one alkyl group ortho to the tetrahedral carbon in V, and on steric grounds, owing to the unfavorable coplanar relationship of the ortho methyl and *tert*-butyl groups in V.[9] In fact, the reverse process, V → II, would rather occur, as shown by the enhanced rate of de-*tert*-butylation of *o*-*tert*-butyltoluene with respect to *p*-*tert*-butyltoluene, upon attack by gaseous cations.[10] On this basis, the 1,3,*4* isomer is exclusively formed by deprotonation of intermediate II, which in turn is formed in a reversible step, as demonstrated in the alkylation of toluene. This suggests that the *tert*-butylation of *m*-xylene at the 4-position provides a model system whereby to test the kinetic role of the deprotonation step in the overall electrophilic substitution of aromatics by gaseous cations. As the radiolytic technique used relies on the recovery and the analysis of neutral end products, the appearance of hydrogen KIE from competition experiments involving *m*-xylene and *m*-xylene-d_{10} was checked. The results listed in Table 1 are drawn vs the PA of the added base, used at constant concentration, in the graph of Figure 1. Whereas the thermodynamics of the proton transfer from II to B are not known since an experimental PA value of the *tert*-butylated position of 1,3,*4* is not available, we may assume it to lie in the proximity of that of *m*-xylene,[11] traced as a vertical line in the graph. In its neighborhood, k_H/k_D reaches values ≥2, which level off to ca. 1 in the presence of strongly basic amines. Qualitatively, such behavior argues in favor of a rate-determining hydron transfer from II to B, possibly damped by competing reactions, as shown in Scheme 3, an excerpt from Scheme 2, which illustrates the reaction of Me_3C^+ at the 4-position of *m*-xylene in a representative, if simplified, way. According to Scheme 3, the overall k_H/k_D ratio in the competitive reaction of perdeuterated and unlabeled *m*-xylene is given by eq 1, obtained by applying to II the steady-state approximation.

Scheme 2



$$\frac{k_H}{k_D} = \frac{k_B^{\,H}}{k_B^{\,D}}\,\frac{k_1^{\,H}}{k_1^{\,D}}\,\frac{k_{-1}^{\,D} + k_B^{\,D}[B]}{k_{-1}^{\,H} + k_B^{\,H}[B]} \tag{1}$$

The k_B^H/k_B^D ratio, i.e. the KIE relative to hydron transfer from II to B, is coupled to two additional factors. The first one, $k_1^H/$

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(8) Taylor, R. *Electrophilic Aromatic Substitution*; Wiley: New York, 1990.

(9) Pearson, H. *J. Chem. Soc. Chem. Commun.* **1975**, 912.

(10) (a) Cacace, F.; Crestoni, M. E.; de Petris, G.; Fornarini, S.; Grandinetti, F. *Can. J. Chem.* **1988**, *66*, 3099. (b) Sen Sharma, D. K.; Ikuta, S.; Kebarle, P. *Can. J. Chem.* **1982**, *60*, 2325. (c) Munson, M. S. B.; Field, F. H. *J. Am. Chem. Soc.* **1979**, *89*, 1047. (d) Harrison, A. J.; Lin, P. H.; Leung, H. W. *Adv. Mass Spectrom.* **1978**, *7*, 1394.

(11) The PA of the t-butylated position of 1,3,*4* is probably higher than that of the 4-position of *m*-xylene due to steric strain from the coplanar ortho methyl and *tert*-butyl groups, which is somewhat relieved upon protonation at the t-butylated carbon.

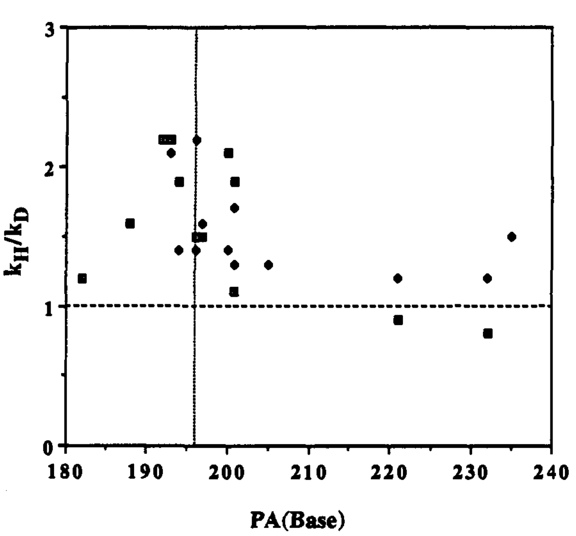


Figure 1. k_H/k_D values relative to Me_3C substitution at the 4-position of *m*-xylene/*m*-xylene-d_{10} mixtures (square centered points) or *m*-xylene-*4-d* (diamond points) drawn against the PA of added base.

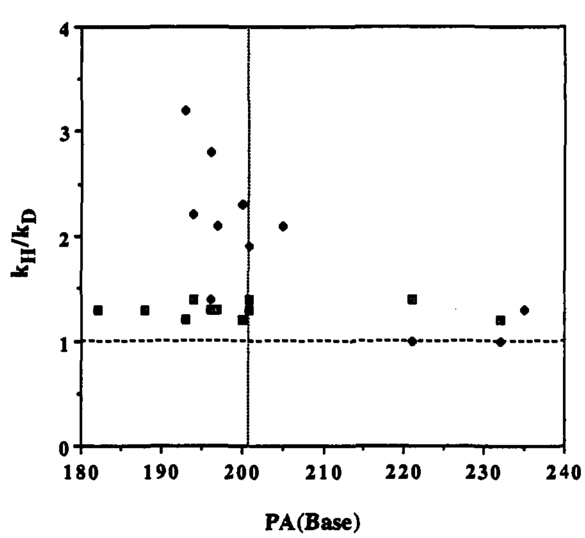
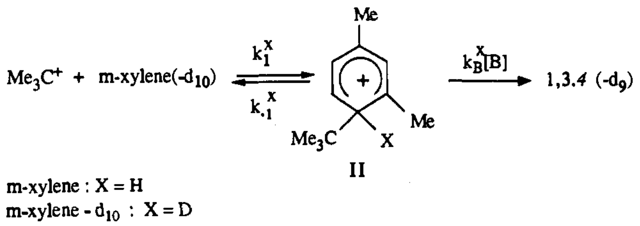


Figure 2. k_H/k_D values relative to Me_3C substitution at the 5-position of *m*-xylene/*m*-xylene-d_{10} mixtures (square-centered points) or *m*-xylene-*4-d* (diamond points) drawn against the PA of added base.

Scheme 3



k_1^D, includes secondary KIEs due to the differences in isotopic substitution between the two competing substrates. Inter alia, it may involve contributions from an α-KIE due to the change of hybridization at the reaction site and from a "steric" KIE due to the incoming Me_3C group adjacent to a CD_3 or CH_3 group.[5a] The second factor $[(k_{-1}^D + k_B^D[B])/(k_{-1}^H + k_B^H[B])]$ ranges from k_{-1}^D/k_{-1}^H to k_B^D/k_B^H, depending on the relative magnitude of k_{-1}^X and $k_B^X[B]$. In the latter case, the deprotonation step is no longer rate determining. Such a situation is likely to prevail in the presence of strong bases, i.e. Et_3N and pyridine, which anyway should give a k_B^H/k_B^D approaching unity, in view of the large exothermicity of hydron transfer.[5] In the intermediate PA range, eq 1 predicts that k_H/k_D be a function of [B], which has been investigated using Me_2CO as the base B. The absence of any variation of k_H/k_D with $[Me_2CO]$ changes spanning a factor of 10 may arise from $k_{-1} \gg k_B[B]$, and hence $k_H/k_D = (K_1^H/K_1^D)(k_B^H/k_B^D)$, where $K_1 = k_1/k_{-1}$. The alternative possibility of $k_{-1} \ll k_B[B]$, leading to $k_H/k_D = k_1^H/k_1^D$, is inconsistent with the dependence of k_H/k_D on the base strength and with its highest values, ca. 2, suggestive of a primary KIE. It follows from these arguments that the k_H/k_D ratios reflect the primary KIE of hydron transfer (k_B^H/k_B^D) multiplied by the K_1^H/K_1^D ratio, which might significantly affect the observed values. An alternative way to study KIEs unaffected by the burden of multiple secondary contributions both to hydron transfer and to the preceding and the parallel steps in the complex reaction scheme relies on the use of *m*-xylene-*4-d*. Its reaction with Me_3C^+ at either the deuterated or unlabeled 4- and 6-position is described in Scheme 4, which uses the same simplifying assumptions adopted in Scheme 3, and obeys eq 2.

$$\frac{k_H}{k_D} = \frac{k_B'^H}{k_B'^D}\,\frac{k_1'^H}{k_1'^D}\,\frac{k_{-1}'^D + k_B'^D[B]}{k_{-1}'^H + k_B'^H[B]} \qquad (2)$$

As shown in Figure 1, the k_H/k_D trend is similar to the intermolecular competition of *m*-xylene/*m*-xylene-d_{10}, though only in one case (B = EtCN) do the two data superimpose. It may be inferred that the observed k_H/k_D values include a major contribution from a primary KIE related to the deprotonation of the arenium ion II, consistent with the observation of a significant k_H/k_D in the case of B = $(i\text{-Pr})_2NEt$, a highly basic, sterically hindered amine. In fact, steric effects are known to lower the reaction efficiencies of proton removal from *tert*-butylated arenium ions,[12] and steric hindrance to deprotonation is related to comparably higher KIE.[13]

***tert*-Butylation of *m*-Xylene at the 5-Position. Rate-Determining 1,2-Hydrogen Shift and Product-Determining Hydron Transfer.** The k_H/k_D values for the formation of 1,3,*5* and 1,3,*5*-d_9 from the competitive reaction of *m*-xylene and *m*-xylene-d_{10} reveal a completely different pattern from that observed in the formation of 1,3,*4* and 1,3,*4*-d_9, when plotted against the PA of added base (square points, Figure 2). The nearly constant k_H/k_D ratios with changing base strength indicate that hydron transfer to external bases does not affect the reaction kinetics. In marked contrast with the intermolecular competition of isotopically different substrates, the formation of 1,3,*5* and 1,3,*5*-*d* from *m*-xylene-*4-d* exhibits significant base-strength dependence, which is bound to arise from hydron transfer to B. The combined information on the different trend of isotopic product ratios vs PA of base can be explained as follows, within the framework of Scheme 5, another excerpt of Scheme 2. Me_3C^+ attack at the 5-position leads to the formation of the σ-complex III, not significantly stabilized by the two meta methyl groups and hence prone to exothermically evolve via a 1,2-hydrogen shift into IV, stabilized by three ortho/para alkyl groups. A steady-state treatment of III in this two-step process yields eq 3.

$$k_{\text{overall}} = \frac{k_2 k_{\text{shift}}}{k_{-2} + k_{\text{shift}}} \qquad (3)$$

If the competitive alkylation of *m*-xylene and *m*-xylene-d_{10} is considered, one should estimate the effect of isotopic substitution on all three individual rate constants appearing in eq 3. In view of the extremely favorable thermodynamics for the formation of IV, an alternative pathway may also be conceived, namely, that the Me_3C^+ attack might involve "concerted" hydrogen migration (k_3), in which case the k_3 rate constant would include a primary

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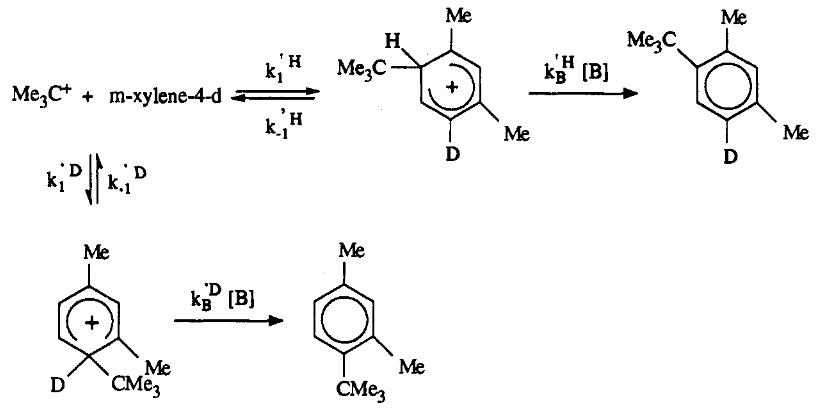
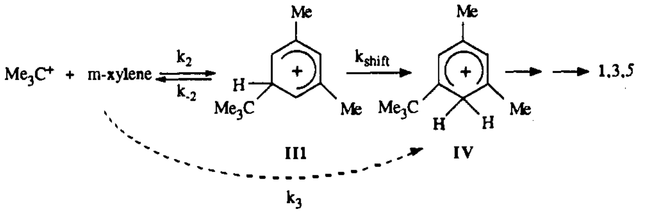
(12) (a) Büker, H.-H.; Grützmacher, H.-F. *Int. J. Mass Spectrom. Ion Processes* **1991**, *109*, 95. (b) Meot-Ner (Mautner), M.; Smith, S. C. *J. Am. Chem. Soc.* **1991**, *113*, 862. (c) Houriet, R.; Rolli, E. *New J. Chem.* **1987**, *11*, 221.

(13) Jasinski, J. M.; Brauman, J. I. *J. Am. Chem. Soc.* **1980**, *102*, 2906.

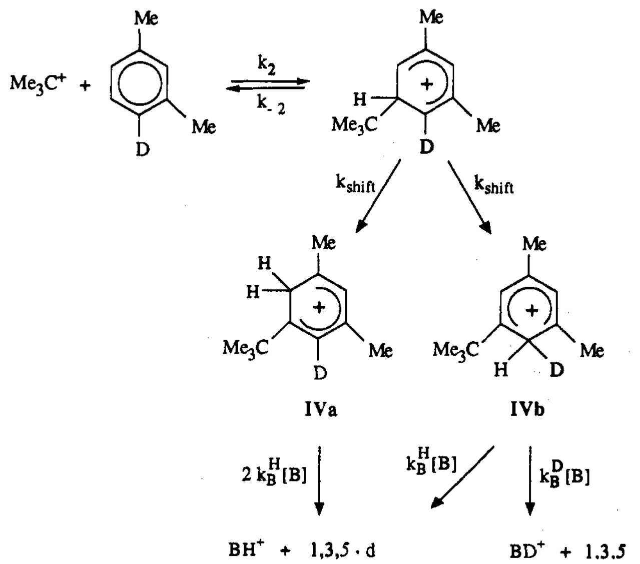
Scheme 4



Scheme 5



Scheme 6



KIE component. While the present data can not solve this ambiguity, the major contribution to the $k_H/k_D \approx 1.3$ value should anyway be regarded as due to a primary KIE in the stepwise or concerted 1,2-hydrogen shift. This stems from the significant KIE observed for 1,2-hydrogen-shift processes in the arenium ion from para-*tert*-butylation of toluene.[4] A quite similar situation emerged as well from the *tert*-butylation of benzene/benzene-d_6 mixtures.

With respect to the intermolecular competition between *m*-xylene and *m*-xylene-d_{10}, the reaction of *m*-xylene-*4-d* points out a different feature of the *tert*-butylation at position 5. In fact, the deuterated to unlabeled product ratio now displays a significant *dependence* on the base strength, unveiling the kinetic role of a reactive event which follows the rate-determining step, i.e. the deprotonation of IV. Within the reasonable assumption that the k_{shift} rate constants leading to IVa and IVb (Scheme 6) be equal (their formation should be affected by a negligible α-KIE),[14] the ratio of the deuterated to unlabeled 1,3,5 product is described by eq 4, which gives the $k_H/k_D = k_B{}^H/k_B{}^D$ values reported in Table 2 and plotted in Figure 2 (diamond points). At variance with the overall k_H/k_D values observed in the formation of 1,3,*4*, here the k_H/k_D values represent net primary KIEs for proton abstraction by the bases B. Such values should not be directly compared to those corresponding to deprotonation of II since the acidity of II and IV will be in general different and their deprotonation by a given base shows a different sensitivity to isotopic substitution.[5] The PA of 1,3,*5* should be close to that of mesytilene, drawn as a vertical line in Figure 2. One may notice that the diamond points in Figure 2 display a pattern similar to that observed in Figure 1, which confirms that the k_H/k_D data related to the formation of 1,3,*4* include a major contribution from the primary KIE of the deprotonation step.

$$\frac{[1,3,5\text{-}d]}{[1,3,5]} = 2\frac{k_B{}^H}{k_B{}^D} + 1 \qquad (4)$$

Primary KIE in Hydron Transfer from Gaseous Arenium Ions. Once it is recognized that the [1,3,*5*-*d*]/[1,3,*5*] product ratio from the *tert*-butylation of *m*-xylene-*4-d* is directly related to the $k_B{}^H/k_B{}^D$ ratio for hydron removal from IV, one may discuss the magnitude of such primary KIEs reported in the right-hand column of Table 2 and in Figure 2 as diamond points. The $k_B{}^H/k_B{}^D = 1$ value obtained for the deprotonation of IV by Et_3N and pyridine conforms to the expectation that highly exothermic proton transfer (by ca. 31 and 20 kcal mol^{-1}, respectively) shows vanishing KIE. This experimental finding substantiates previous assumptions concerning primary KIE for the deprotonation of gaseous *tert*-butylarenium ions by strong bases.[4] The behavior of $k_B{}^H/k_B{}^D$ for bases of PA closer to that of 1,3,*5* does not appear to be a simple function of PA(B), as indicated by the scattered points in Figure 2. What could be expected for the KIE affecting the deprotonation of IV, a cationic carbon acid, would have been a bell-shaped curve similar to the textbook example concerning proton abstraction in solution from neutral carbon acids, e.g. nitroalkanes and keto compounds, showing a maximum $k_H/k_D \approx 8$, in correspondence to thermoneutral proton transfer.[5a,b] Several reasons, however, militate against a straightforward relationship between the gas-phase and the solution trend of a finely tuned kinetic feature such as KIE. In the absence of the mediating influence of the solvent, structure-specific interactions in the encounter ion–molecule complex play an important role in the gas phase. In this respect, it may be noted that bases belonging to the same class and having a similar PA give closer k_H/k_D values, e.g. ca. 2 in the case of carbonyl compounds and ca. 3 in the case of nitriles. In a highly dilute and apolar medium such as i-C_4H_{10} gas at atmospheric pressure, the intermediate arenium ions conceivably form long-lived collision complexes with any available polar molecule including the added base. The same probably holds also for the ion–molecule complex following hydron

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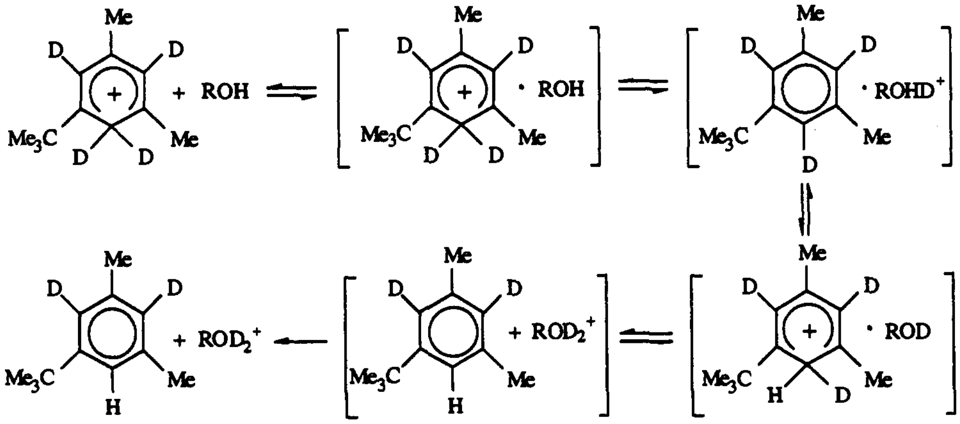
[14] Reference 8, p 33.

Scheme 7

$$\text{arene H}^+ + \text{B} \xrightleftharpoons{\text{encounter}} \underset{\text{VI}}{[\text{arene H}^+ \cdot \text{B}]} \xrightleftharpoons[\text{transfer}]{\text{proton}} \underset{\text{VII}}{[\text{arene} \cdot \text{BH}^+]} \xrightarrow{\text{separation}} \text{arene} + \text{BH}^+$$

Scheme 8

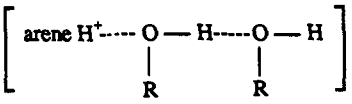


transfer, i.e. [$BH^+ \cdot$arene]. Multiple hydron transfer may occur within such complexes (Scheme 7), as is well documented by mass spectrometric studies, showing ring hydrogen exchange reactions of arenium ions in the presence of D_2O.[15] Hydron transfer may be reversible within the complex also in the presence of only one hydron to be transferred between the arene and the base, though, in this case, it would not give rise to isotopic exchange. The net effect may be a lowering of the intrinsic k_H/k_D ratios in a kind of "internal return" effect. In other words, hydron transfer to the external base is no longer a slow step with respect to diffusional separation of the product pair.[16] The end result is a diminished k_H/k_D, which may ultimately reduce to the equilibrium isotope effect for the hydron transfer between the arenium ion and the base within the ion–molecule complexes VI and VII.

A hint of such ion–polar molecule interactions and of multiple reactive events within encounter complexes comes from the experiments run in the presence of alcohols which differ from the other bases used for the presence of an exchangeable proton at the reaction center. The reaction of *m*-xylene-d_{10} in the presence of MeOH and *t*-BuOH yields 1,3,5-d_9 together with a ca. 10% fraction of 1,3,5-d_8, which is indicative of the exchange process depicted in Scheme 8. Thus, at least the alcohols give rise to some extent of "internal return" effect. The reaction in the presence of alcohols spurs another consideration. Given the endothermicity of the process (approximately 7 kcal mol^{-1}), the rate of proton removal from IV by *t*-BuOH should be quite slow (ca. 10^3 s^{-1} at 300 K, based on reaction enthalpy alone). Yet, *t*-BuOH appears to effectively interact with the arenium ions, for example, it prevents isomerization of II to IV to about the same extent as pyridine. Such apparent contradictions point once again to the kinetic role of ion–molecule complexes. Electrostatic stabilization and collisional quenching may allow the [arene $H^+ \cdot$*t*-BuOH] complex a sufficiently long lifetime to encounter a second *t*-BuOH molecule. By way of the ensuing ternary complex, proton transfer may progress to diffusional separation of the products, gaining the enthalpic contribution relative to formation of the proton-bound dimer [*t*-$BuOH_2^+ \cdot$*t*-BuOH] (Scheme 9).[17] In this process the thermodynamic requirements of the elementary proton-transfer step are not simply related to the PA difference between isolated bases nor to the enthalpy difference for the processes occurring within the encounter complex (e.g. VI → VII), being affected by the assistance of a second base molecule and the formation of the proton-bound dimer of the base. These considerations may apply to varying extents to other bases besides the alcohols, especially if PA differences referred to the isolated bases predict an endothermic proton transfer. In conclusion, since net PA differences do not measure the reaction enthalpy for the elementary proton-transfer step, the PA scale of Figures 1 and 2 will not be linearly related to it. The apparently easier proton transfer from arenium ions to alcohols with respect to other bases may be traced to the possibility that the first, but not the latter, may react within the ternary collision complex by a hydrogen-bonded transition state (VIII), thereby lowering the activation energy and leading directly to the thermodynamically most favored proton-bound dimer.

Scheme 9

$$\begin{tikzcd}
\text{arene H}^+ + \text{1-BuOH} \arrow[r, shift left] & \arrow[l, shift left] [\text{arene H}^+ \cdot \text{1-BuOH}] \arrow[r, shift left, "\text{1-BuOH}"] & \arrow[l, shift left] [\text{arene H}^+ \cdot (\text{1-BuOH})_2] \arrow[d, shift left] \\
\text{arene} + [\text{1-BuOH}_2^+ \cdot \text{1-BuOH}] & [\text{arene} \cdot \text{1-BuOH}_2^+ \cdot \text{1-BuOH}] \arrow[l] & \arrow[u, shift left]
\end{tikzcd}$$



$$\left[\text{arene H}^+ \cdots\cdots \underset{\text{R}}{\underset{|}{\text{O}}} — \text{H} \cdots\cdots \underset{\text{R}}{\underset{|}{\text{O}}} — \text{H}\right]$$

VIII

A further reason which should discourage one from drawing hasty comparisons between KIE trends in solution and in the gas phase, at least in the low-pressure range accessible to mass spectrometric studies, lies in the different energy profile of the proton-transfer reaction (Scheme 7). In the gaseous systems at low pressure, Brauman's double-well potential model predicts that the proton-transfer event (VI → VII) may occur within a collision complex VI excited by the electrostatic energy gained by the ion–molecule

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interaction.[18] This fact makes it extremely difficult to define the temperature at which the reaction occurs and a KIE is manifested. In the present radiolytic experiments at ca. 1 atm, collisional frequency with the bulk i-C_4H_{10} gas may be sufficiently high (ca. 10^{-10} s^{-1}) to ensure thermalization of VI, as suggested by the invariance of the observed k_H/k_D from the *m*-xylene/*m*-xylene-d_{10} reaction with a 3.5-fold change of i-C_4H_{10} pressure.

In conclusion, the detailed mechanism of proton transfer in an atmospheric pressure gaseous environment and the different factors which may affect the corresponding primary KIE deserve further investigation, though the study of the Me_3C^+ reaction with *m*-xylene has opened intriguing perspectives.

Conclusions

The Me_3C^+ reaction with *m*-xylene has provided a model to test the detailed multistep mechanism of electrophilic aromatic substitution reactions in the gas phase, especially with regard to the final deprotonation step of arenium intermediates. This may become rate determining in those cases where decomposition of the arenium ion, either by reverting to the reactants or by any intervention of gaseous nucleophiles, occurs faster than or approximately as fast as evolution to products by proton removal. Such a condition is satisfied by the arenium ion produced from Me_3C^+ attack at the 4-position of *m*-xylene, where steric encumbrance of the ortho methyl group favors back-dissociation and steric hindrance to deprotonation lowers the rate of proton abstraction. The use of KIE as a mechanistic tool has in fact revealed a primary, base-dependent effect, confirming a stepwise mechanism and manifesting a rate-determining proton transfer. The pattern of k_H/k_D vs PA (base) relative to the formation of 1,3,*4* and 1,3,*4*-d_9 from the competitive reaction of *m*-xylene and *m*-xylene-d_{10} and from the competition of the deuterated vs unlabeled site of *m*-xylene-*4-d* is qualitatively similar to that observed for the primary KIE for the deprotonation of IVb, which follows from attack at the 5-position of *m*-xylene-*4-d*. On the contrary, the overall reaction sequence leading to the substitution product at the 5-position is characterized by a base-independent KIE of 1.3, resulting from the reaction of *m*-xylene/*m*-xylene-d_{10}, ascribed to 1,2-hydrogen shift from the attacked 5-carbon to an adjacent ring site.

Thus, besides the intrinsic mechanistic interest associated with the study of the electrophilic aromatic substitution in the gas phase, the present study has demonstrated KIEs involved in the fundamental process of proton transfer in an atmospheric pressure environment, best suited for an investigation of subtle reactivity differences such as those due to isotopic substitution. The determination of the factors affecting KIEs in bimolecular ion–molecule reactions crucially depends on the attainment of thermal equilibrium with the environment by excited intermediate complexes, and not unexpectedly, few data are available to date from mass spectrometric studies in low-pressure regimes ($1-10^{-8}$ Torr).[19]

Acknowledgment. We are grateful to Prof. F. Cacace for his active interest and helpful discussions. The work was supported by the Italian Ministero dell'Università e della Ricerca Scientifica e Tecnologica.

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