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Gas-Phase H/D Exchange between Arenium Ions and Selected Bases. The Site of Protonation of Simple Aromatics

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Abstract: H/D exchange between arenium ions bearing various substituents (Y = Et, Me_2CH, CF_3, CF_3CO, NO_2, Me_3Si) on a perdeuterated ring and bases having at least one H atom at the active site are described. A radiolytic technique operating at atmospheric pressure and allowing the recovery of neutral end products was used. The exchange depends on features of both the base (structure, proton affinity) and the arenium ion. The elementary step for back proton transfer from the protonated base to the neutral arene has been studied by NMR analysis of the H distribution within YC_6D_4H. The protonation was found to involve the most basic ring positions: ortho/para for alkyl substituents (Y = Et, Me_2CH) and ortho/meta for electron-withdrawing substituents (Y = CF_3, CF_3CO, NO_2).

Introduction

The exchange of acidic hydrogen for deuterium results from proton-transfer reactions that regenerate the reactants. Therefore the reaction is approximately thermoneutral, if allowance is made for a change in the isotopic content. Exchange reactions have been extensively studied in solution, providing information, for example, on the kinetic acidities of weak carbon acids.[1] They have also been the topic of several gas-phase studies aimed at evaluating the number of sites that may be involved in proton transfer within a gaseous species[2] and at differentiating isomers.[3] H/D exchange reactions have recently gained renewed interest as a probe of biomolecule structure.[4]

A working model for the mechanism of the exchange reaction on a positive ion can be represented by a four-step process (Scheme 1),[5] where [MD^+ AH], [M ADH^+], and [MH^+ AD] represent ion−neutral complexes. Steps a and d describe the formation and separation of ion−neutral complexes, and steps b and c are hydron transfers (the term "hydron" is used throughout the paper to indicate H^+ and D^+ collectively).

Scheme 1

$$MD^+ + AH \rightleftharpoons [MD^+\ AH] \qquad (a)$$

$$[MD^+\ AH] \rightleftharpoons [M\ ADH^+] \qquad (b)$$

$$[M\ ADH^+] \rightleftharpoons [MH^+\ AD] \qquad (c)$$

$$[MH^+\ AD] \rightarrow MH^+ + AD \qquad (d)$$

In the present study MD^+ is a deuterated arenium ion. These species are known to undergo H/D exchange in the presence of a neutral that has a proper proton affinity (PA) and an exchangeable hydrogen at the active site.[6] The MH^+ product ion from Scheme 1 may react further if one more deuterium is present at the protonated site or if multiple D-bearing sites may be protonated. Thus, the parent benzenium ion, $C_6D_7^+$, may exchange up to all seven D's. The scheme becomes more complex when the neutral partner, AH, possesses two or more H atoms at equivalent basic sites because multiple exchange processes may occur between the partners within the ion−neutral complex.

The exchange process of Scheme 1 may be described also from an alternative point of view. Step b shows the formation within the ion−neutral complex of the base M together with a relatively mild Brønsted acid, ADH^+. Typically, AH and M should not differ in proton affinity (PA) by more than 20−25 kcal mol^{-1} in order for H/D exchange to be observed.[2c,5] Thus, the subsequent H^+ transfer step c deals with a closely thermoneutral proton transfer to the neutral aromatic ring of M. From

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this perspective, we have used the exchange sequence of Scheme 1 to investigate the site to which a proton transfers. The idea of using a selected reagent ion, generated within an ion−neutral complex from the ionic precursor of the neutral substrate, is not new in gas-phase ion chemistry. A novel application of this concept has recently been reported, involving the formation of an alkylating species inside a long-lived ion−neutral complex formed upon collision of an arenium ion with an olefin that ultimately undergoes a "Crafts−Friedel" reaction.[7] Much effort has been devoted to assessing the site of protonation in gaseous aromatics. This problem has been addressed by various mass spectrometric techniques, which usually suffer from the limited ability to resolve unambiguously the protonation site on the aromatic ring.[8] This kind of information has been sought by computational methods, estimating the relative stability of the isomers of protonated aromatics. We have used an experimental kinetic approach to the problem, based on a radiolytic technique that allows the recovery of the neutral products from ion−molecule reactions occurring in the pressure range from a few Torr to several atmospheres.[9] The neutral products may be analyzed by H NMR, allowing detailed structural characterization. This approach has successfully been exploited in the evaluation of both the extent and the site of protonation of toluene by gaseous Brønsted acids.[10] In particular, H NMR analysis revealed that strong acids such as CH_5^+ and $C_2H_5^+$ protonate the aromatic carbons of toluene-d_8 in an almost statistical way. Here we focus on evaluating the protonation site of substituted benzenes by mild Brønsted acids, such as those generated within the ion−neutral complexes of Scheme 1.

Experimental Section

Materials. C_3H_8, CH_4, CF_4, CO, C_2H_4, O_2, and SF_6 were research-grade gases from Matheson Gas Products Inc. with a stated purity in excess of 99.95 mol %. Benzene-d_6 and toluene-d_8 with isotopic purity of >99.96% were purchased from Aldrich. A high isotopic purity is required to allow a meaningful determination of the H content within products arising from H/D exchange processes, originating from the deuterated substrates. Since the exchange is not extensive under typical conditions, one must subtract the background H content without affecting the significance of the measured H incorporation. The NMR solvents, $(CD_3)_2CO$ and CD_2Cl_2, were purchased from Cambridge Isotope Laboratories, Inc. Methyl nitrate[11] and 2,2,2-trifluoroacetophenone-d_5[12] were prepared according to conventional methods. All other compounds used as additives, as standards, or as reagents for the synthesis of standards were obtained from commercial sources.

Procedure. The gaseous samples were prepared according to a well-established procedure. In a typical experiment, a few milligrams of benzene-d_6 or toluene-d_8 was weighed and sealed into fragile glass ampules, which were introduced into a 1-L Pyrex vessel. The vessel was outgassed, filled with the selected gases, and sealed. The ampule was cracked open inside the reaction vessel. Following thorough mixing of all components, the vessel was irradiated at 37 °C in a 220 Gammacell (Nuclear Canada Ltd.) at the dose rate of ca. 5×10^3 Gy h^{-1} for 3−5 h. The radiolytic products were extracted by freezing the vessel in liquid nitrogen and injecting 0.4 mL of deuterated solvent under airtight conditions. The solution of the radiolytic products was analyzed by GC−MS using a Hewlett-Packard 5890 series II gas chromatograph in line with a quadrupole mass spectrometer HP 5989B. The capillary columns and gas chromatographic conditions were the following: (i) a 50-m long, 0.20-mm-i.d. fused silica capillary column, coated with a 0.5-μm cross-linked methylsilicone film (HP PONA column), operated isothermally at 60 °C for 5 min and then heated at the rate of 3 deg min^{-1} to 75 °C and subsequently at 16 deg min^{-1} to 240 °C; (ii) a 30-m long, 0.20-mm-i.d. bonded-phase capillary column, coated with a 0.2-μm poly(ethylene glycol) film (Supelcowax 10M from Supelco Co.), operated at 35 °C for 5 min and then heated at the rate of 8 deg min^{-1} to 60 °C and subsequently at 16 deg min^{-1} to 220 °C.

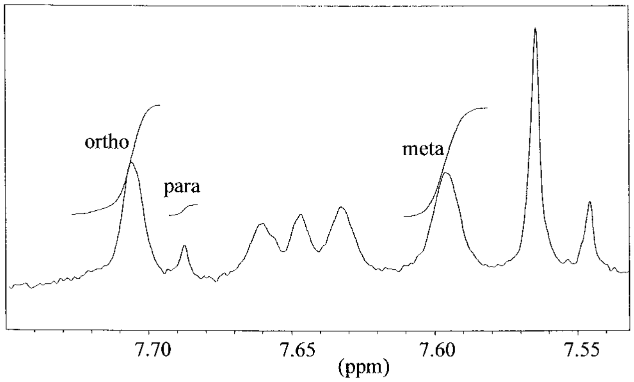

Figure 1. NMR spectrum of the aromatic protons of $CF_3C_6D_4H$ in the $(CD_3)_2CO$ solution of the radiolytic products from a gaseous mixture of benzene-d_6 (2.3 Torr), H_2O (1.6 Torr), CF_4 (610 Torr), and O_2 (10 Torr).

The GC−MS analysis yielded information not only on the chemical identity of the radiolytic products but also on their isotopic content. By starting from the perdeuterated substrates, benzene-d_6 or toluene-d_8, radiolytic products were expected to incorporate H on the aromatic ring to varying extents, to be determined from the individual experiments. To this end, the mass spectrum of the unlabeled standard of each radiolytic product was examined to search for diagnostic fragment ions. To yield meaningful information, the selected fragment ion should retain the constituents of the aromatic ring and not be accompanied by other ions differing by one mass unit. In some cases, the search was unsuccessful in the EI mass spectrum and GC−MS analyses were performed under chemical ionization (CI) in methane where the ion formed by addition of $C_2H_5^+$ behaved satisfactorily. The solutions of the radiolytic products were first analyzed in the full scan mode to identify the radiolytic products and evaluate their absolute and relative yields by using the internal standard calibration method. Subsequent GC−MS runs were performed in the selected ion monitoring mode to increase the sensitivity in the quantitation of the diagnostic peaks for the H incorporation. Whenever appropriate, corrections for the ^{13}C contribution of an adjacent peak were effected.

H NMR Analysis. The solutions of the radiolytic products in the deuterated solvent were examined by H NMR to determine the H content on the aromatic ring positions of the product arenes. The H NMR spectra were performed on a Bruker AMX 500 instrument with a H probe operating at 500.13 MHz. The deuterium signal of the solvent was used as the lock. The chemical shifts are given in ppm (δ) with reference to TMS as internal standard. All the spectra have been performed using a sweep width of 6000 Hz, 25° flip angle, and a repetition time of 9 s. Typically, 4000 scans were averaged. Apodizations were used to improve DFT spectra. They can be used to improve resolution or sensitivity but not both simultaneously. Examples are shown in Figure 1, where sensitivity was privileged at the cost of broadened peaks, and Figure 2, where the resolution was

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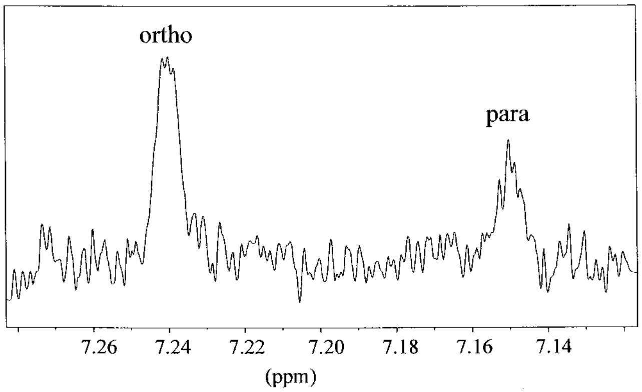

Figure 2. NMR spectrum of the aromatic protons of $Me_2CHC_6D_4H$ in $(CD_3)_2CO$. $Me_2CHC_6D_4H$ (together with $Me_2CHC_6D_5$) was isolated by preparative GC from the radiolytic products from a gaseous mixture of benzene-d_6 (2.1 Torr), H_2O (1.2 Torr), C_3H_8 (630 Torr), and O_2 (10 Torr).

Table 1. NMR Data on the Aromatic Proton in Otherwise Perdeuterated Arenes

compd	δ (ppm)			$^4J_{HD}$	
YC_6D_4H	ortho	meta	para	(Hz)	solvent
Y = Me_2CH	7.240 (t)	7.275 (m)	7.150 (m)	1.1	$(CD_3)_2CO$
Y = NO_2	8.256 (t)	7.693 (m)	7.845 (m)	1.0	$(CD_3)_2CO$
Y = CF_3	7.720 (t)	7.610 (m)	7.680 (m)	1.1	$(CD_3)_2CO$
Y = CF_3CO	7.986 (t)	7.486 (m)	7.653 (m)	1.1	CD_2Cl_2

improved at the expense of a decreased signal/noise ratio. Prior to NMR analysis of the radiolytic products, standard compounds were examined to ascertain the chemical shift and absorption pattern of the aromatic hydrogen into otherwise perdeuterated arenes under the prevailing instrumental conditions. The collected data are listed in Table 1. In several systems the NMR signals of the aromatic protons in the radiolytic products emerged clearly from the analysis of the crude solutions without further workup. Figure 1 shows the signals of the aromatic protons of $PhCF_3$ in the crude solution of the radiolytic products. However, in most cases, the results were checked on the isolated aromatic product after separation from the radiolytic mixture by preparative GC, using the following columns: (i) bentone 34-diisodecylphthalate (1:1 on Chromosorb W, 5 m, 70 °C); (ii) SE 30 silicone oil (3% on Supelcoport, 4 m, 80 °C). Care was exercised to check the possible occurrence of H enrichment upon GC separation, which was never observed. The GC separation was accompanied by partial loss of the minute amounts of the arene products formed, so that once the signal pattern (chemical shifts and relative intensities) of the product of interest was unambiguously identified, it was preferable to work on the crude solutions to determine the H content on each ring position by integration of the corresponding NMR signals. Figure 2 presents a typical spectrum of the aromatic protons of $PhCHMe_2$ isolated from a radiolytic experiment.

PA Determination. The PA value of CFH_2CH_2OH was evaluated in the present study, by studying the equilibrium for the proton-transfer reactions $C_2FH_6O^+ + B \rightarrow C_2FH_5O + BH^+$ in the cell of a Bruker Apex 47e FT-ICR mass spectrometer at 300 K. $EtNO_2$ and MeOH were used as reference bases (B) of known PA.[13] The entropy change of the proton-transfer equilibrium was assumed to be negligible.

Table 2. H Incorporation in the Alkylated Products from the Gas-Phase Reaction of Benzene-d_6 with Radiolytically Formed Me_2CH^+ Ions

system composition[a]		extent of H incorporation within the aromatic ring of $Me_2CHC_6D_5$ (%)[b]
C_6D_6 (Torr)	additives (Torr, PA/kcal mol^{-1})[c]	
1.7	C_2H_4, 2.0 (163)	18
3.0	H_2O, 1.4 (167)	17
4.3[d]	H_2O, 1.2 (167)	18
2.0	H_2O, 5.3 (167)	17
2.1	CF_2HCH_2OH,1.8 (176)	32
2.5	CCl_3CH_2OH,1.6 (177)	18
2.1	MeOH, 0.6 (182)	13
2.0	MeOH, 0.9 (182)	13
2.2	MeOH, 1.9 (182)	12
2.6	CFH_2CH_2OH,1.8 (183)[e]	10
2.1	*n*-C_3H_7OH, 1.1 (191)	7
0.8	*n*-C_3H_7OH, 2.0 (191)	7
2.2	c-$C_6H_{10}O$, 1.0 (201)	6
2.2	Et_3N, 1.5 (232)	5

[a] All systems contained C_3H_8 (580−700 Torr) and O_2 (10 Torr). [b] % values refer to the fraction of $Me_2CHC_6D_4H$ with respect to the overall ($Me_2CHC_6D_4H + Me_2CHC_6D_5$) products formed, as determined by mass spectrometry. [c] The PA values are taken from ref 13, unless stated otherwise. [d] The C_3H_8 pressure was ca. 4 atm. [e] This work.

Table 3. H Incorporation in the Alkylated Products from the Gas-Phase Reaction of Toluene-d_8 with Radiolytically Formed Me_2CH^+ Ions

system composition[a]		extent of H incorporation within the aromatic ring of $Me_2CHC_6D_4CD_3$ (%)[c] (*ortho*/*meta*/*para*)		
$CD_3C_6D_5$ (Torr)	additives (Torr, PA/kcal mol^{-1})[b]			
2.4	CF_3CH_2OH, 2.1 (169)	8	9	9
2.2	CF_2HCH_2OH, 1.9 (176)	11	6	12
2.6	CCl_3CH_2OH, 1.9 (177)	10	9	10
2.6	$MeNO_2$, 2.5 (179)	2	3	2
2.5	MeOH, 1.9 (182)	12	23	12
2.6	CFH_2CH_2OH, 1.9 (183)[d]	12	11	12
1.8	EtOH, 0.9 (188)	6	11	6
2.1	*t*-C_4H_9OH, 0.9 (194)	4	3	5
2.6	c-$C_5H_{10}NH$, 2.3 (226)	4	3	3
2.2	Et_3N, 1.9 (232)	3	2	3

[a] See note *a* in Table 2. [b] See note *c* in Table 2. [c] % values refer to the fraction of $Me_2CHC_6D_3HCD_3$ with respect to the overall ($Me_2CHC_6D_3HCD_3 + Me_2CHC_6D_4CD_3$) products formed, as determined by mass spectrometry. [d] See note *e in* Table 2.

Results

H-Incorporation in the Aromatic Products. The aromatic substitution products from the perdeuterated substrates are listed in Tables 2−4, which report on isopropylation reactions and on substitutions by various Y groups. Typically, the composition of a radiolytic system includes a bulk gas or mixture of gases, from which the reagent ion, Y^+ or NY^+, is produced by γ-irradiation, and O_2, used as scavenger of radical species that might interfere with the ionic products of interest. The perdeuterated substrate and a basic additive are present as minor components. The substitution products account for the major reaction product(s) of the reagent ion. The product yields (not reported in Tables 2−4) approach the values expected from (i) the known radiochemical yield of the reagent ion from γ-radiolysis of the bulk neutral gas[14] and (ii) the mole fraction of the substrate that competes for the reagent ion with other basic additives. All reagent ions are known to give aromatic substitution products according to well-established sequences of ionic reactions.[9,15] The relevant new data listed in Tables 2−4 concern the extent of H incorporation on the aromatic ring of the substitution products, evaluated from the integration of

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Table 4. H Incorporation in the Substitution Products from the Gas-Phase Reaction of Benzene-d_6 and Toluene-d_8 (C_6D_5X, X = D, CD_3) with Charged Electrophiles

system composition (Torr)^a				extent of H incorporation within the aromatic ring of YC_6D_4X (%)^b		
C_6D_5X (X)	bulk gas	additives (PA/kcal mol^{-1})^c	reactant ion (Y)	(*ortho*/*meta*/*para*, when X = CD_3)		
D, 2.0	CH_4, 700	H_2O, 1.0 (167)	Et^+ (Et)		16	
CD_3, 2.6	CH_4, 640	CF_2HCH_2OH, 1.9 (176)	Et^+ (Et)	12	11	17
CD_3, 0.6	CH_4, 605	MeOH, 7.4 (182)	Et^+ (Et)	34	50	42
D, 3.9	CH_4, 605; $MeONO_2$, 8.5	H_2O, 0.9 (167)	$MeONO_2H^+$ (NO_2)		2.9	
D, 2.1	CH_4, 620; Me_4Si, 20	NH_3, 1.0 (204)	Me_3Si^+ (Me_3Si)		1.0	
D, 2.2	CH_4, 620; Me_4Si, 20	c-$C_5H_{10}NH$, 1.0 (226)	Me_3Si^+ (Me_3Si)		0.5	
D, 2.9	CH_4, 575; Me_4Si, 20	Et_3N, 0.7 (232)	Me_3Si^+ (Me_3Si)		0.9	
D, 3.9	CF_4, 400; CO, 200	H_2O, 2.0 (167)	CF_3CO^+ (CF_3CO)		1.5	
D, 3.7	CF_4, 650	C_2H_2, 5 (155)	CF_3^+ (CF_3)		0.5	
D, 1.8	CF_4, 645	C_2H_4, 2.0 (163)	CF_3^+ (CF_3)		4.4	
D, 2.3	CF_4, 610	H_2O, 1.6 (167)	CF_3^+ (CF_3)		2.7	
D, 2.3	CF_4, 590	c-$C_6H_{10}O$, 1.0 (201)	CF_3^+ (CF_3)		1.8	
D, 1.9	CF_4, 635	Et_3N, 1.7 (232)	CF_3^+ (CF_3)		1.4	
CD_3, 2.4	CF_4, 590	H_2O, 1.6 (167)	CF_3^+ (CF_3)	1.2	5.7	2.9
CD_3, 1.8	CF_4, 590	Et_3N, 1.6 (232)	CF_3^+ (CF_3)	0.5	0.8	1.0

[a] All systems contained O_2 (10 Torr). [b] % values refer to the fraction of YC_6D_3HX with respect to the overall (YC_6D_3HX + YC_6D_4X) products formed, as determined by mass spectrometry. [c] See note *c* in Table 2.

the GC−MS profiles of diagnostic ions and corrected for the background content due to incomplete deuteration of the substrate. Despite a specific search, no evidence was obtained for the formation of substitution products incorporating *two* H's. The isopropylation products have been the most thoroughly examined. The data collected in Tables 2 and 3 allow some generalizations regarding the dependence of the extent of H incorporation in the alkylated products on the features of the additive. In particular, to observe appreciable H incorporation, the additive should have a labile H atom and an appropriate PA. The additive becomes decreasingly effective when its PA is higher or lower than the optimum value. The highest values of H incorporation depend on the structure of the alkylation product. Thus, in the case of $Me_2CHC_6D_5$ formed from benzene-d_6, the most effective additive appears to be CF_2HCH_2OH, whereas the isomeric $Me_2CHC_6D_4CD_3$ products from toluene-d_8 undergo the highest extent of H incorporation in the presence of methanol, showing a somewhat different behavior depending on their isomeric structure. As the PA of the additive is increased (for example, by using strongly basic amines), the H incorporation reduces to very low values, irrespective of whether the amine is tertiary or possesses an exchangeable H at the basic nitrogen atom. Experiments performed at a total pressure of 4 atm showed a negligible effect of the pressure of the bulk gas. In a similar way, changing the concentration of the additive by a factor of 3 did not affect significantly the results.

Table 4 summarizes the results regarding the H incorporation in the substitution products from the reaction of benzene-d_6 and toluene-d_8 with various ionic electrophiles. These data do not lend themselves to broad generalizations because they derive from few examples of different reactions run under different conditions. However, it is worth pointing out certain features. Even though the ethylation products formed in CH_4 have not been extensively studied, they nevertheless appear to behave similarly to the higher homologues from the isopropylation reaction, in that the extent of H incorporation depends on the PA of the additive. Other electrophiles, i.e., CF_3CO^+, CF_3^+, Me_3Si^+, and the nitrating ion $MeONO_2H^+$, lead to a relatively minor H incorporation, though a smaller variety of additives was investigated than in the isopropylation reaction. Y groups such as CF_3CO, CF_3, and NO_2 are characterized by the presence of highly electronegative atoms. Finally, the formation of silylated arenes from Me_3Si^+ requires the presence of basic amines, thus limiting the effective choice of additives.

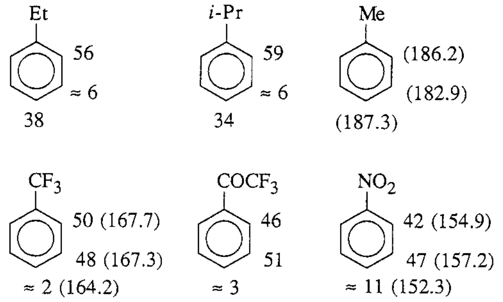

Figure 3. Experimental distribution of H incorporation and theoretical site-specific PA's (in parentheses). The PA's for the ring positions of toluene were calculated by the MP2(fc)/6-31G**//HF6-31G* + ZPE (HF/6-31G*) model (ref 16a−c). The PA's of nitrobenzene were obtained by 4-31G calculations on the isodesmic reaction $NO_2{-}C_6H_6^+ + C_6H_6 \rightarrow NO_2{-}C_6H_5 + C_6H_7^+$ (ref 16d). Site-specific PA's of α,α,α-trifluototoluene were obtained by MP2(fc)/6-31G*//HF/6-31G* + ZPE (HF/6-31G*) calculations (ref 17).

H Distribution in the Arene Products (YC_6D_4H). The positional distribution of H on the aromatic ring of the substitution products determined by H NMR is summarized in Figure 3. The five YC_6D_4H arenes that were examined may be divided in two groups. When Y is an alkyl group, the overall H incorporation in the presence of H_2O as the additive is ca. 18% (Tables 2 and 4). The H NMR analysis affords a reliable evaluation of the positional distribution of H with an uncertainty of only ±3%. In both products (Y = Et and Me_2CH) the ortho and para positions are strongly favored. In the case of Y = CF_3CO, CF_3, and NO_2, the H incorporation that was obtained in the presence of H_2O is much smaller (Table 4) and the positional distribution of H is affected by a greater uncertainty of about ±6%. However, despite the problems associated with the determination of very low levels of H enrichment, it clearly emerges that the major fraction of H incorporation takes place at the ortho and meta ring positions.

Discussion

Because this work was focused on the behavior of arenes and arenium ions with respect to hydron-transfer reactions, well-

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known routes to the formation of gaseous arenium ions have been explored. Direct protonation of a Y-substituted benzene or toluene, the most straightforward approach to Y-substituted arenium ions, is complicated by the possible occurrence of proton transfer not only to the ring carbons but also to the Y substituent. When Y is the thermodynamically favored protonation site, arenium ions might never be obtained by this route. Alternatively, arenium ions can be formed as the charged intermediates of the electrophilic aromatic substitution reaction by gaseous cations generated in dense gases by a radiolytic methodology.[9,15] To this end, charged electrophiles have been selected corresponding to Y^+ (Et^+, Me_2CH^+, CF_3^+, CF_3CO^+, Me_3Si^+) or to cationic species able to deliver Y^+ to an aromatic ring ($MeONO_2H^+$). These ionic reagents are known to be formed as the major ionic species from the interaction of γ-radiation with a selected gas or gaseous mixture at atmospheric pressure. In the gaseous environment of the radiolytic systems, the reagent ions are thermalized by several unreactive collisions before a reactive encounter with the aromatic substrate takes place. The charged intermediate, a Y-substituted arenium ion, may in turn dissipate any excess energy content deriving from the exothermic formation process by collisions with the bulk gas at atmospheric pressure. The ground state Y-substituted arenium ion thus created undergoes unimolecular and bimolecular reactions, which have been studied in detail. The Y-substituted arenium ion primarily formed corresponds to an ipso-protonated Y-substituted arene, which is known to evolve by relatively fast 1,2-hydron shifts to more stable isomers.[18] This unimolecular rearrangement may compete with the hydron transfer to a base, which may be purposely added or be the aromatic substrate itself. The latter situation may be relevant in those cases where the entering Y group decreases the basicity of the aromatic ring by an electron-withdrawing effect, so that hydron transfer from the Y-substituted arenium ion to the starting substrate is an exothermic process.[17] Finally, upon collision with a suitable neutral molecule, the Y-substituted arenium ion may engage into a reversible hydron transfer sequence that regenerates the reactants and would occur unnoticed unless appropriate deuterium labeling is used. It is on this last process that the following discussion is centered.

H/D Exchange within [Arenium Ion Neutral] Complexes. The incorporation of H into the aromatic ring of the products from the electrophilic substitution of benzene-d_6 or toluene-d_8, which depends on the features of an added neutral, provides strong evidence that in the radiolytic systems at atmospheric pressure H/D exchange takes place, which resembles the well-known H/D exchange detected by various mass spectrometric techniques.[6] This statement is substantiated by several analogies emerging from inspection of Table 2. Consider the reaction of a single electrophile, Me_2CH^+ generated in propane, with benzene-d_6 or toluene-d_8 in the presence of comparable concentrations of additives. The PA of the additive affects the extent of H incorporation. For example, in the isopropylation of benzene-d_6, an increased fraction of H on the aromatic ring is found when the PA of the additive increases from the value of 163 kcal mol^{-1} (ethylene) to 176 kcal mol^{-1} (CF_2HCH_2OH).[13] The increase would be steeper if a statistical correction were made for the different number of exchangeable H's on the additive: two for H_2O, four for C_2H_4, and only one for CF_2HCH_2OH. A further increase in the basicity of the additive has a detrimental effect on the efficiency of H/D exchange. It may be argued that the series includes additives that greatly differ in structure. The efficiency of isotope exchange reactions is known for example to increase, the greater the dipole moment of AH.[5,6c] However, the same trend is observed in the meta isomer from the isopropylation of toluene-d_8 performed in the presence of a series of alcohols, though in this case the most pronounced H incorporation is found in the presence of MeOH (PA = 182 kcal mol^{-1}). Both series of isopropylation reactions show that H/D exchange is most effective when the PA difference between the isopropylation product (isopropylbenzene, PA = 192 kcal mol^{-1}; *m*-isopropyltoluene, PA ≈ 196 kcal mol^{-1}) and the exchange reagent is ca. 15 kcal mol^{-1}. As previously reported, isotope exchange does not occur when there are no H atoms at the site of proton transfer in the neutral molecule.[4-6] Thus, the effect of $MeNO_2$, used in the place of an alcohol of similar basicity, is to reduce the H incorporation to the background levels that are observed when a highly basic tertiary amine like Et_3N ensures fast and irreversible deprotonation of the arenium intermediate. The residual H incorporation is ascribed to the presence of unavoidable traces of water in the radiolytic systems. It follows from these observations that the H/D exchange process requires the presence of an H atom at the basic site of the additive in order to occur, but its extent depends on the balance of at least two factors. Within the framework of Scheme 1, step b will be increasingly favored as AH becomes more basic. However, to obtain exhange products, step c must occur, as well. Step c becomes progressively less favored as the PA of AH increases, to the point of diminishing in the face of competing reactions. For example, dissociation to M and AHD^+ may occur, activated by collision with a molecule of the bulk gas. The involvement of a second molecule of AH is rejected on the basis of the negligible effect on the H incorporation of varying concentrations of AH, which might otherwise be expected to affect the formation of termolecular complexes. Finally, the generally accepted energy profile for H/D exchange reactions (Figure 4) predicts that exchange within a single collision event is limited by the thermalization provided by frequent unreactive collisions with the bulk gas at atmospheric pressure. The ion−neutral complexes may dissipate their excess energy to the point of becoming unable to surmount the energy barrier separating them.

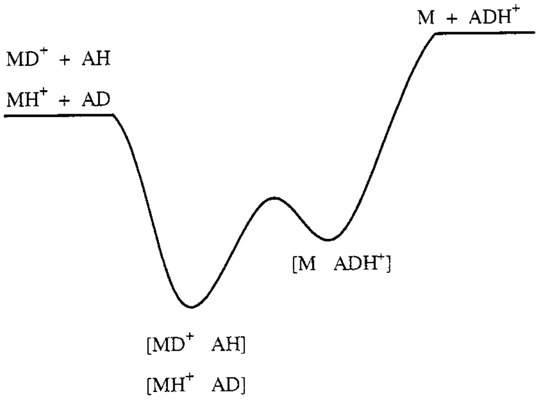

Figure 4. Potential energy profile for H/D exchange.

Specific features of the arenium ion affect the progress of the H/D exchange. An additional methyl group on isopropylbenzenium ions alters the efficiency of the exchange reagent.

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Different alkyl groups exert similar effects on the basicity of an aromatic ring;[13] hence, it was expected (and found) that the ethylation products of benzene-d_6 and toluene-d_8 showed comparable behavior regarding the extent of H incorporation as the isopropylated ones.

The presence of a few other exemplary substituents on the arenium ion (Y = Me_3Si, NO_2, CF_3, CF_3CO) decreases the extent of H incorporation markedly with respect to the alkylated arenium ions (Y = Me_2CH, Et), though these cases have been less thoroughly investigated. The thermodynamically favored site of protonation of substituted benzenes bearing strongly electron-withdrawing substitutents is known to be the Y group. This notion is well established for Y = CF_3[17] and NO_2[16d] and can be reasonably extended to Y = $COCF_3$. Thus, it is conceivable that most of the corresponding arenium ions will undergo an irreversible deuteron transfer to form $[YC_6D_5\ ADH^+]$ complexes that further evolve into Y-protonated species, as exemplified by step f in Scheme 2.

Scheme 2

$$[YC_6D_6^+\ AH] \rightleftharpoons [YC_6D_5\ ADH^+] \tag{e}$$

$$[YC_6D_5\ ADH^+] \rightleftharpoons [C_6D_5YH^+\ AD] \tag{f}$$

$$[C_6D_5YH^+\ AD] \xrightarrow{B} C_6D_5Y + BH^+ + AD$$

This competitive route prevents any H/D exchange since a hydron on the Y substituent lacks any driving force for migration to the less basic aromatic ring and is bound to be removed by a base. In a minor fraction of back hydron transfer events, however, a proton may move to the least disfavored aromatic carbons, yielding a detectable amount of ring H incorporation. This conclusion derives from the detectable dependence of the extent of H incorporation on the presence of various additives in the trifluoromethylation reaction. In particular, a distinct fraction of H incorporation is observed in the presence of C_2H_4 and H_2O. At the same time, basic compounds devoid of exchangeable H's suppress the H incorporation to background levels.

The negligible H incorporation displayed by trimethylsilylbenzene is traced to a different origin. It is known that the presence of a Me_3Si group on the aromatic ring strongly enhances the basicity of the ipso carbon.[19] Therefore this site will be the only one that may be involved in back and forth transfer of a hydron that will finally be removed by the base. In this case it cannot be verified whether a hydron-transfer process does indeed occur within the $[Me_3SiC_6D_6^+\ AH]$ complex by the present experimental technique. Further, the formation of neutral silylated products from the gas-phase reaction of Me_3Si^+ requires the presence of a strong nitrogen base, whereas neutrals containing oxygen (such as alcohols) react with silylated arenium ions by nucleophilic attack at silicon. The absence of any significant H incorporation within $Me_3SiC_6D_5$ thus confirms the known reactivity behavior of silylated arenium ions.[20]

Positional Selectivity of the Gas-Phase Protonation of Substituted Benzenes. A fundamental problem in gas-phase ion chemistry concerns the protonation site within molecules possessing two or more basic sites. Mass spectrometric studies have used different approaches to the problem, which have been successfully applied to a number of very simple species.[21] Alternatively, the study of thermodynamic parameters for proton-transfer equilibria has yielded indirect information on the relative stability of isomeric protonated species that may be further characterized by the reactivity of suitably labeled models. Finally, theoretical calculations may provide information on the relative stability of isomeric species, though their reliability decreases with increasing size of the species. The H NMR analysis of H incorporation in the ortho, meta, and para positions has allowed the first direct experimental determination of the ring sites undergoing protonation within a few gaseous arenes. It may in fact be noticed that the elementary step leading to H incorporation is a proton-transfer event from ADH^+ to YC_6D_5 within the noncovalent complex $[YC_6D_5\ ADH^+]$, the same complex that would be obtained by collision of ADH^+ with YC_6D_5. The protonation of YC_6D_5 by ADH^+ is only slightly exothermic, starting from the free reagents. Therefore we expect ADH^+ to behave as a mild and selective Brønsted acid. It may be also emphasized that $[YC_6D_5\ ADH^+]$ complexes cannot be unambiguously generated by other routes. Ionic Brønsted acids that may be formed by the radiolytic technique are either too strong or behave as Lewis acids or tend to form clusters with their neutral precursor.

In the absence of specific activation barriers, selective Brønsted acids should protonate the thermodynamically favored sites. This expectation is fulfilled by the experimental H distribution reported in Figure 3, compared with the calculated site-specific PA's (in parentheses). The effect of an alkyl group on the benzene ring increases the basicity of the ortho and para carbon atoms, as predicted by calculations where the methyl group is used as a model. Both ethyl- and isopropylbenzene are protonated on the ortho/para positions in a closely statistical ratio. The ortho/para selectivity that characterizes this H incorporation is among the highest ever observed in the reaction of a gaseous charged electrophile with an alkylbenzene. The Y substituent in the second row of Figure 3 is an electron-withdrawing group deactivating the ring with respect to electrophilic attack and is generally less deactivating in the meta position.[22] The similar extent of H incorporation on both the ortho and meta positions is a novel finding. It fits, however, into the pattern of calculated PA's for the ring positions of nitrobenzene and α,α,α-trifluorotoluene, which predict that the ortho and meta positions have a comparable basicity, distinctly greater than that of the para position. Protonation at the ortho position may benefit from the interaction between the ortho hydrogens on the tetrahedral carbon and the electronegative atoms on the substituent.[17]

In discussing the H/D exchange process within $[YC_6D_5\ ADH^+]$ complexes, it was implicitly assumed that the complexes undergo mutual rotation of their components, allowed by their significant lifetime. Therefore, ADH^+ is free to migrate and attack any position. Several experimental studies have shown that gaseous [arene cation] complexes, where the cation is an alkyl cation, have significant lifetimes indeed.[23] The mobility of the *tert*-butyl cation within $[t\text{-}C_4H_9^+\ Ar(CH_2)_nAr]$ has been reported,[24] and the intermediacy of "loose" ion−neutral com-

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plexes has been demonstrated by a stereochemical probe based on the use of chiral reagents.[23b] An alternative mechanism for the site-specific H/D exchange is, however, conceivable. A rapidly equilibrating (by 1,2-D^+ shifts) mixture of ortho, meta, and para $YC_6D_6^+$ ions may form a "structured" complex with AH. D^+ transfer from the tetrahedral carbon yields ADH^+, which subsequently releases a proton to the same carbon.[25] In this alternative pathway ADH^+ remains near the unique ring carbon that undergoes both reaction steps. In most cases this site-specific model appears unlikely, in view of the growing evidence on related [arene cation] complexes. It may, though, be possibly involved in the H/D exchange of arenium ions bearing electron-withdrawing substituents, where thorough sampling of the potential basic sites of the neutral arene by ADH^+ should rather favor protonation of the substituent.

Conclusions

The protonation of arenes has been studied under minimally perturbed conditions, between the partners of an ion−neutral complex, using a H/D exchange process as mechanistic tool. The addition or transfer reaction of Y^+ to benzene-d_6 or toluene-d_8 has been used to form Y-substituted deuterated arenium ions. The ion−neutral complex of the arenium ion with a base may evolve by different routes, depending on the relative PA of the base and the neutral arene. A relatively strong base abstracts a deuteron, forming the Y-substituted arene irreversibly, whereas no reaction occurs with a weak base. In intermediate situations, where deuteron transfer to the base is allowed within the ion−neutral complex but the dissociation of the protonated base and neutral arene is thermodynamically forbidden, a back hydron transfer may occur, resulting in H/D exchange if the base has one or more other H's on the basic atom. Under the conditions of the radiolytic technique (which ensure the complete thermalization of the charged reagent), the most extensive H/D exchange in alkylbenzenes has been observed when the PA of the base and the arene differ by about 15 kcal mol^{-1}. The back proton transfer from the exchange reagent to the arene within the ion−neutral complex yields Y-subtituted products incorporating a H atom into an otherwise perdeuterated aromatic ring. The positional H distribution obtained by H NMR analysis of the aromatic products affords the first direct determination of the kinetic site of protonation of gaseous aromatics. It is thus confirmed that alkyl groups exert a marked ortho/para orienting effect, whereas strongly electron-withdrawing groups such as NO_2 and CF_3 display a comparable extent of ortho as well as meta H incorporation. The site selectivity of proton transfer was found to parallel the site-specific PA's calculated by theoretical approaches.

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