−16.472 me, on the average, for each H atom. The average Δq_H = −4.772 me value, while not giving a true reflection of the individual CH bonds, is sufficient for the correct evaluation of the total gain in stability of the CH part. Each of the four CH bonds formed by C-1 and C-4 is (in this "average" calculation) 1.584 × 0.247 ± 4.772 × 0.632 = 3.407 kcal/mol more stable than the ethane CH bond, and each of the other eight CH bonds has gained 2.443 × 0.247 + 4.772 × 0.632 = 3.169 kcal/mol. The total stabilization is, hence, 12.63 (CC bonds) + 42.58 kcal/mol (CH bonds) with respect to the ethane bonds.

For the chair form of cyclohexane, we obtain from δ 21.8 (ppm from ethane) that $\Delta q_C = -3.227$, giving a stabilization of 2 × 0.488 × 3.227 = 3.150 kcal/mol for each CC bond. The "average" charge on the H atoms being now −15.937 me and, thus, Δq_H = −4.237 me, each CH bond is stabilized by 4.237 × 0.632 + 3.227 × 0.247 = 3.475 kcal/mol. The total gain in stability is, hence, 18.90 (CC bonds) + 41.70 kcal/mol (CH bonds) relative to the ethane bonds.

Finally, comparing now the boat and chair forms, it is deduced that the 12 CH bonds are more stable in the boat conformer by 0.88 kcal/mol but that the carbon skeleton of chair cyclohexane is more stable than that of the boat form by 6.27 kcal/mol, giving a total difference in stability of 5.39 kcal/mol favoring the chair conformer. This result agrees with the measured energy increment (5.39 kcal/mol) between the *trans-anti-trans-* and *trans-syn-trans*-perhydroanthracenes,[35] which differ only because of the center boat in the former compound, and with the difference in $\Delta E_a{}^{*\text{bonds}}$, 5.23 kcal/mol, calculated from their ^{13}C spectra[14] by using eq 33.

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[35] The thermochemical data are extracted from ref 15. The ^{13}C NMR shifts are from ref 34.

Gas-Phase Ion/Molecule Isotope-Exchange Reactions: Methodology for Counting Hydrogen Atoms in Specific Organic Structural Environments by Chemical Ionization Mass Spectrometry

Donald F. Hunt* and Satinder K. Sethi

Contribution from the Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901.

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Abstract: Ion/molecule reactions are described which facilitate exchange of hydrogens for deuteriums in a variety of different chemical environments. Aromatic hydrogens in alkylbenzenes, oxygenated benzenes, *m*-toluidine, *m*-phenylenediamine, thiophene, and several polycyclic aromatic hydrocarbons and metallocenes are exchanged under positive ion CI conditions by using either D_2O, EtOD, or ND_3 as the reagent gas. Aromatic hydrogens, benzylic hydrogens, and hydrogens on carbon adjacent to carbonyl groups suffer exchange under negative ion CI conditions in ND_3, D_2O, and EtOD, respectively. A possible mechanism for the exchange process is discussed.

Introduction

Solution methods of exchanging hydrogen for deuterium in organic molecules have been widely used in structural studies involving mass spectrometry.[1,2] Hunt and co-workers[3] developed a simplified procedure for replacing acidic hydrogens with deuterium under CI conditions by using deuterium oxide as the reagent gas. Hydrogens bonded to heteroatoms in alcohols, phenols, carboxylic acids, amines, amides, and mercaptans were shown to undergo rapid exchange for deuterium during the lifetime of the sample in the CI ion source. Isotope-exchange reactions were also shown to facilitate differentiation of primary, secondary, and tertiary amines when either ND_3[4] or MeOD[5] was used as the CI reagent. Hydrogen–deuterium exchange under GC conditions has been accomplished on column by using either neutral or basic carbowax pretreated with deuterium oxide.[6]

Exchange of aromatic hydrogens in the gas phase was first reported by Beauchamp and co-workers.[7] Using ion cyclotron resonance (ICR) spectroscopy, they observed sequential replacement of hydrogen by deuterium during reaction of protonated benzene ions with D_2O. Several substituted benzene derivatives also incorporated deuterium under ICR conditions but the rate of the isotope exchange reaction showed a strong dependence on the structure of the sample. All four ring hydrogens in the *o*- and *p*-difluorobenzenes exchanged deuterium rapidly whereas only slow incorporation of a single deuterium occurred in the *m*-difluorobenzene isomer. No exchange of aromatic hydrogens was observed in benzene derivatives with strong electron-donating or electron-withdrawing substituents. Many of these compounds protonate on the substituent and it was concluded that ring protonation was a necessary condition for the hydrogen deuterium isotope exchange to occur. Martinson and Buttrill came to the same conclusion on the basis of a CI study of protonated benzene derivatives with D_2O as the reagent gas.[8]

Recently Stewart et al. have shown that M − 1$^-$ ions from esters, olefins, acetylenes, allenes, and toluene undergo hydrogen–deuterium exchange when allowed to react with D_2O under flowing afterglow conditions.[9] In a later paper from the same group, M

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$- 1^-$ ions from ketones and aldehydes were shown to suffer exchange with deuterated alcohols.[10] Earlier presentations from our laboratory indicated that $M - 1^-$ ions from carbonyl compounds would incorporate deuterium under CI conditions in EtOD but not in D_2O.[11] Use of ND_3 was reported to facilitate exchange of ring hydrogens in $M - 1^-$ ions from aromatic compounds.[11] Replacement of benzylic hydrogens by deuterium in the $M - 1^-$ ions from alkylbenzenes was demonstrated in D_2O but not EtOD.[11] A mechanism to explain the gas-phase ion/molecule isotope-exchange data was also presented.[11]

Here we summarize the results of all our studies on positive ion and negative ion gas-phase ion/molecule isotope-exchange reactions. An analytical method which facilitates the use of mass spectrometry for counting the number of hydrogens in several specific structural environments within an organic sample is also described.

Experimental Section

General Data. All spectra were recorded on either a Finnigan Model 3200 quadrupole mass spectrometer modified for PPINICI[12] (pulsed positive ion negative ion chemical ionization) or on an AEI MS-902 double-focusing magnetic sector instrument equipped with a dual CI/EI ion source manufactured by Scientific Research Instruments Corp.[13] Operating parameters for the Finnigan Instrument have been described previously.[12] Primary ionization of the CI reagent gas on the AEI MS-902 mass spectrometer is accomplished by using a 500-eV beam of electrons from a heated rhenium filament. Pressures of reagent gas and sample were maintained at 0.5–1.0 torr and $<10^{-3}$ torr, respectively. Other operating parameters include an accelerating potential of 8 kV, an analyzer pressure of 3×10^{-7} torr, and an ion-source temperature of 100–200 °C. Samples entered the ion source via either a heated direct insertion probe or a leak from a liquid inlet system. Most experiments were performed at ion-source temperatures of 90 or 175 °C although the temperature was varied between 80 and 200 °C in order to find the optimum conditions for the ion/molecule exchange reactions.

Reagent Gases and CI Reactant Ions. Nitrous oxide (98.5%) was obtained from Matheson Gas Products Inc., East Rutherford, NJ. D_2O (98.5 + atom% D), CH_3OD (99.5 + atom% D), EtOD (99.5 + atoms% D), and n-C_3H_7OD (98.0 + atom% D) were purchased from Aldrich Chemical Co., Milwaukee, WI. ND_3 (99.0 + atom% D), CH_3ND_2 (98.0 + atom% D), and CF_3CD_2OD (98.0 + atom% D) were obtained from Merck and Co., St. Louis, MO. Reactant ions for positive ion CI are produced by electron ionization of the reagent gas followed by ion/molecule reactions of the resulting radical cations with a second molecule of the neutral reagent gas as shown in eq 1 and 2. Reaction 2 is

$$MH + e^- \rightarrow MH^{+\cdot} + 2e^- \qquad (1)$$

$$MH^{+\cdot} + MH \rightarrow MH_2^+ + M\cdot \qquad (2)$$

exothermic for all of the reagent gases, ROD (R = D, CH_3–, C_2H_5–, C_3H_7–, CF_3CD_2–), ND_3, and CH_3NH_2.[14] Cluster ions of the type $ROD_2^+(ROD)_n$, where n = 1–4, and $CH_3ND_3^+(CH_3ND_2)_n$, where n = 1–3, are also present in appreciable quantities. Reagent ion spectra of deuterated alcohols also contain ions of the type $R_2OD^+(ROD)_n$ (n = 0–1), formed by loss of D_2O from the cluster ions $ROD_2^+(ROD)_n$ (n = 1, 2).

Reagent ions for negative ion CI are produced from deuterium oxide and deuterated alcohols by a two-step sequence involving dissociative electron capture of nitrous oxide followed by reaction of the resulting oxygen radical anion with either deuterium oxide or deuterated alcohol to produce the desired Brønsted base.[15]

$$N_2O + e^- \rightarrow O^{-\cdot} + N_2 \qquad (3)$$

$$O^{-\cdot} + ROD \rightarrow RO^- + DO\cdot \qquad (4)$$

Cluster ions of the type $(D_2O)_nOD^-$ (n = 1–3) and $(ROD)_nRO^-$ (n = 1–2) are also formed in appreciable abundance from deuterium oxide and deuterated alcohols, respectively. Optimum reagent ion abundances were obtained by metering nitrous oxide into deuterium oxide or deuterated alcohol at 0.5–1.0 torr until the intensities of the desired signals maximized. This was usually the case when the mixture composition was ROD/N_2O = 10/1. Dissociative electron attachment on ND_3 was used to produce ND_2^- and the cluster ions $(ND_3)_nND_2^-$ (n = 1–2) (see eq 5).[16]

$$ND_3 + e^- \rightarrow ND_2^- + D\cdot \qquad (5)$$

Chemicals. All samples were obtained from either the Aldrich Chemical Co., Milwaukee, WI, or from Chemical Sample Co., Columbus, OH. Deuterated steroids were obtained as a gift from Professor O. R. Rodig of the University of Virginia.

Results

Positive Ion CI Data. Gas-phase ion/molecule isotope-exchange data obtained under positive ion CI conditions are presented in Table I. Note that ion abundances in Tables I and II have not been corrected for contributions due to ^{13}C isotopes. Names corresponding to the number designations given to compounds discussed in this and the following section can be found in the two tables.

When deuterium oxide is employed as the CI reagent, the dominant ion in the spectra of benzene (**1**), toluene (**2**), o-xylene (**3**), and p-xylene (**4**) occurs at a m/z ratio corresponding to d_nMD^+ in which all aromatic hydrogens have been exchanged for deuterium. m-Xylene (**5**) and mesitylene (**6**) also suffer exchange of aromatic hydrogens but at a rate that is slow compared to that observed for compounds **1**–**4**. The most abundant ion in the spectra of **5** and **6** is d_0MD^+. Negligible exchange of aromatic hydrogens is observed in deuterium oxide for all the aromatic compounds containing amino, hydroxy, alkoxy, acetyl, and nitrile substituents, the polyaromatic hydrocarbons, and the metallocenes in Table I.

When D_2O (PA_{H_2O} = 170 kcal)[17] is replaced by the more basic reagent EtOD (PA_{EtOH} = 186 kcal),[17] the rate of exchange for the aromatic protons in m-xylene (**5**) and mesitylene (**6**) increases substantially. The dominant ion in the spectra of **5** and **6** now occurs at a m/z ratio corresponding to d_nMD^+ in which all of the aromatic hydrogens have undergone exchange for deuterium. Use of EtOD as the CI reagent also facilitates exchange of the aromatic hydrogens in the oxygenated benzene derivatives (**7**–**15**). The MD^+ ions from all of these compounds, except **14**, appear to incorporate deuterium at all carbon atoms ortho and para to electron-donating substituents in the molecules. Only one aromatic hydrogen suffers exchange in resorcinol (**14**). Of the polyaromatic hydrocarbons and thiophenes (Table I) that were studied with deuterated alcohols as reagent gases, only pyrene (**31**) and anthracene (**29**) fail to incorporate deuterium. Replacement of aromatic hydrogen by deuterium in the MD^+ ion of 1,3,5-trimethoxybenzene (**16**), the amino benzenes, benzonitrile (**24**), acetophenone (**25**), and ferrocene (**35**) still fails with EtOD as the reagent.

Several of the above compounds, however, do incorporate deuterium when the more basic molecule (ND_3) is used as the CI reagent. Slow exchange of aromatic hydrogens in ND_3 is observed with **16**, m-toluidine (**20**), m-phenylenediamine (**23**), and the two ferrocene derivatives **35** and **38**. Naphthalene (**26**), phenanthrene (**28**), and chrysene (**32**), compounds that incorporate deuterium in EtOD, now afford spectra containing only M^+ ions when the reagent gas is switched to ND_3.

Molecules that fail to undergo ion/molecule isotope exchange of aromatic hydrogens in either D_2O, EtOD, or ND_3 include aniline (**17**), o-toluidine (**18**), p-toluidine (**19**), o-phenylenediamine[5,8] (**21**), p-phenylenediamine (**22**).[5,8] Ruthenocene (**39**) and the two ferrocene derivatives **36** and **37** also fail to incorporate deuterium when ND_3 is used as the reagent gas.

Negative Ion CI Data. Gas-phase ion/molecule isotope-exchange data obtained under negative ion CI conditions are presented in Table II. When OD^- and D_2O are employed as the

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[14] Values of ΔH in eq 2 for the different reagent gases are as follows: D_2O, ΔH = −29.8 kcal; CH_3OD, ΔH = −18.9 kcal; ND_3, ΔH = −21.4 kcal.

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CI reactant and reagent gas, respectively, the dominant ion in the spectra of the alkylbenzenes (**40–43**) occurs at a *m/z* ratio corresponding to $d_nM - 1^-$ in which all of the benzylic hydrogens have been exchanged for deuterium. Proton abstraction from these compounds does not occur with the weaker base EtO^-.

Use of D_2O as the reagent gas also facilitates partial exchange of hydrogens on carbon atoms adjacent to the carbonyl group of simple ketones, but the rate of deuterium incorporation is slow and the exchange process is quite inefficient under CI conditions. If D_2O is replaced by the stronger acid EtOD, however, the rate of exchange for hydrogen on carbon adjacent to carbonyl groups increases substantially. All of the unconjugated carbonyl compounds in Table II except **50**, **52**, and **68–70** now afford spectra in which the most abundant ion corresponds to $d_nM - 1^-$ with all enolizable hydrogens exchanged for deuterium. Spectra of the diesters (**68–70**) are unique in that the only ion observed corresponds to $M - 1 - MeOH^-$. The preganan-3,20-dione (**52**) is already deuterated and suffers partial back-exchange of all seven remaining enolizable deuteriums in the $M - D^-$ ion when ethanol-d_0 is used as the CI reagent gas. In **50** proton abstraction occurs preferentially at the phenolic oxygen. Incomplete exchange of enolizable hydrogen is observed in the $M - 1^-$ ion from conjugated carbonyl compounds **55**, **56**, **57**, **58**, and **59**. The rate of exchange of enolizable hydrogen in β-dicarbonyl compounds **64** and **65** increases substantially when the reagent gas is changed from EtOD to the stronger acid CF_3CH_2OD.

Abstraction of aromatic hydrogen is accomplished with ND_2^-, a stronger base than EtO^-. The resulting $M - 1^-$ ions from benzene (**74**), naphthalene (**75**), anthracene (**76**), and phenanthrene (**77**) undergo rapid exchange for deuterium in ND_3. Pyrene (**78**), chrysene (**79**), and benzo[*a*]pyrene (**80**) incorporate deuterium at a slower rate, but all aromatic hydrogens suffer at least partial exchange. Use of ND_3 also facilitates exchange of all hydrogens in the four organometallic compounds ferrocene (**81**), ferrocene carboxaldehyde (**82**), phenylferrocene (**83**), and (toluene)chromium tricarbonyl (**84**). In contrast to **84**, toluene (**40**) itself only suffers partial replacement of benzylic hydrogens in ND_3.

Discussion

Mechanism of the Ion/Molecule Isotope-Exchange Reaction. At 0.5–1.0 torr each sample ion and reagent ion suffer up to a few hundred collisions with neutrals before exiting the CI ion source.[18] In contrast multiple collisions between a given sample molecule and the reagent ion population are highly improbable. Sample concentration is usually less than 0.1–1.0% that of the reagent gas, 10^{16} molecules/cm^3, and the total ion population is only 10^{10} ions/cm^3. Thus incorporation of deuterium into a sample ion must occur during the lifetime of an ion/molecule complex formed as a result of collision between the deuterium-labeled reagent gas and the sample ion. Dissociation of this complex to labeled sample ion and a neutral molecule followed by formation of additional sample ion reagent molecule complexes is allowed under the experimental conditions. In contrast, if the complex dissociates to neutral sample and reagent ion, then the labeled sample molecule will exit the ion source before it suffers a second ionizing collision and thus be lost.

To explain the data obtained from the ion/molecule isotope-exchange reactions run under negative ion CI conditions, we propose a mechanism consistent with the above restrictions which involves the series of steps shown in eq 6 and 7. An energy diagram for the exchange process between the acetone $M - 1^-$ anion and both D_2O and EtOD is shown in Figure 1.

$$HRH + R'O^- \rightarrow {}^*HR^- + R'OH^* \xrightarrow{ROD} HR^- + ROD^* \tag{6}$$

$$\begin{aligned} HR^- + DOR' &\rightleftharpoons HR^-\cdots D\text{-}OR' \rightleftharpoons HR\text{-}D\cdots{}^-OR' \rightleftharpoons \\ HR\text{-}D\cdots\cdots{}^-OR' &\rightleftharpoons DR\text{-}H\cdots\cdots{}^-OR' \rightleftharpoons HR\text{-}D\cdots{}^-OR' \rightleftharpoons \\ &DR^-\cdots H\text{-}OR' \rightleftharpoons DR^- + HOR' \end{aligned} \tag{7}$$

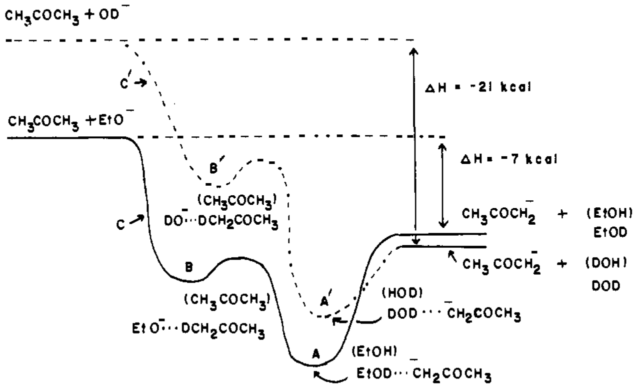

Figure 1. Energy diagram for the ion/molecule isotope-exchange reactions involving the acetone $M - 1^-$ ion and both D_2O and EtOD.

When the proton affinity of the reagent anion is greater than that of the sample anion, eq 6 is exothermic as written and the liberated energy is partitioned between the two products HR^- and the neutral reagent gas molecule. Subsequent collisions with neutral molecules in the CI source remove the excess energy from the vibrationally excited $^*HR^-$ ion. Encounters of this type also lead to formation of cluster ions containing a molecule of deuterium-labeled reagent gas and the sample anion (eq 7). Ion dipole, ion-induced dipole, charge delocalization, and/or formation of strong hydrogen bonds provide the driving force for this initial solvation of the HR^- ions. High-pressure equilibrium measurements on the association of H_2O with I^- and OH^- show an enthalpy change of −10 and −25 kcal, respectively (see eq 8 and 9).[19]

$$I^- + H_2O \rightarrow I(H_2O)^- \quad \Delta H = -10 \text{ kcal} \tag{8}$$

$$OH^- + H_2O \rightarrow (H_2O)OH^- \quad \Delta H = -25 \text{ kcal} \tag{9}$$

Solvation of the delocalized anions generated in the present work should be much less exothermic than solvation of OH^-. In the absence of experimental data we make the assumption that the enthalpy change for solvation of the ions in this study should be about the same as that observed for I^-, −10 to −15 kcal. Thus, at the instant of their formation the cluster ions in Figure 1 exist in a vibrationally excited state.[20] Part of the energy released in their production can be used to surmount the activation barrier leading to the less stable solvated species B in Figure 1 and to a structure C in Figure 1 in which the deuterium bond is weakened sufficiently to permit rotation of the sample molecule and formation of a new hydrogen bond. Participants in an ion/molecule complex are known to suffer a number of collisions before the complex dissociates. At the temperature and pressure employed in the present study collisional stabilization of the cluster ion involving a third body is not observed and the solvated species returns along the reaction pathway ($C \rightarrow B \rightarrow A \rightarrow d_1M - 1^-$) and dissociates to produce the isotopically enriched sample anion.

We noted earlier that the extent of deuterium incorporation into a sample decreases as the proton affinity difference between the reactant and sample anions increases. Incorporation of deuterium into the $M - 1^-$ anion of acetone is rapid in EtOD but slow in D_2O. Increasing the strength of the base employed to ionize the sample alters the energetics of the exchange pathway in several ways. Formation of the cluster ions (A and A′ in Figure 1) containing the $M - 1^-$ anion of acetone and a molecule of reagent gas is expected to be less exothermic with D_2O than with the stronger acid EtOD. In addition as the exothermicity of the forward deuteron-transfer reaction increases, the structure of the less stable hydrogen-bonded cluster (B and B′ in Figure 1) becomes more like that of the reactants and, therefore, moves up on the energy scale of the diagram. Thus as the exothermicity of the

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Table I. Ion Molecule Isotope Exchange Data Obtained under Positive Ion CI Conditions

				% total sample ion current^a										
compd	no.	gas	mol wt	M^+	MD^+	d_1MD^+	d_2MD^+	d_3MD^+	d_4MD^+	d_5MD^+	d_6MD^+	d_7MD^+	d_8MD^+	other, *m/z* (%)
benzene	1	D_2O^b	78	44.4	2.8			2.8	5.7	5.6	38.7			
		$EtOD^c$		100										
toluene	2	D_2O^b	92	11.1	4.4	4.4	4.4	6.7	13.3	51.1				91 (4.6)
		$EtOD^c$		56.2	6.2									91 (28.0), 93 (8.6)
o-xylene	3	D_2O^b	106	7.7	7.7	7.7	9.2	16.9	47.7					105 (3.1)
		$EtOD^c$		14.2	4.8	4.8	9.5	23.8	33.3					105 (7.1), 107 (2.5)
p-xylene	4	D_2O^b	106	8.5	6.4	4.3	4.3	12.8	57.5					105 (6.3)
		$EtOD^c$		24.3	4.0	4.0	5.4	16.2	31.1					105 (12.2), 107 (2.7)
m-xylene	5	D_2O^b	106	6.3	46.9	25.0	10.9	6.3	3.1					105 (1.7)
		$EtOD^c$		6.2	3.2	3.2	6.3	33.3	43.8					105 (2.0), 107 (2.0)
mesitylene	6	D_2O^b	120	2.9	45.1	21.6	18.6	11.8						
		$EtOD^c$		4.2	7.1	23.2	21.2	42.1						119 (1.1), 121 (1.1)
phenol^d	7	D_2O^b	94		2.6	80.3	14.8	1.6	0.7					
		$EtOD^c$				20.0	16.0	24.0	26.0	10.0	4.0			
anisole	8	D_2O^b	108		89.3	10.7								
		$EtOD^c$		4.4	18.5	26.8	25.5	22.8	2.0					
o-cresol^d	9	$EtOD^c$	108	9.0	6.1	15.3	24.0	27.4	6.2	3.0				109 (9.0)
p-cresol^d	10	$EtOD^c$	108	6.0	6.0	14.0	20.0	20.0	14.0	12.0				109 (8.0)
m-cresol^d	11	$EtOD^c$	108	3.2	4.4	19.7	24.1	24.1	20.5					109 (4.0)
hydroquinone^d	12	D_2O^b	110	7.1	5.7	2.9	65.7	12.9	5.7					
		$EtOD^c$					25.0	19.4	16.6	19.4	19.6			
catechol^d	13	$EtOD^c$	110	1.2	27.4	8.7	18.6	15.3	14.1	8.6	3.6			111 (2.5)
resorcinol^d	14	D_2O^b	110		2.1	3.1	46.3	4.2						132 (2.1), 133 (3.1), 134 (35.9), 135 (3.2)
		$EtOD^c$			4.6	14.0	43.9	18.7	1.0					159 (1.0), 160 (2.8), 161 (11.2), 162 (2.8)
1,3,5-trihydroxybenzene^d	15	$EtOD^c$	126					16.1	16.1	30.4	37.4			
		$ND_3{}^c$							7.1	21.4	71.5			
1,3,5-trimethoxybenzene	16	$EtOD^c$	168	3.8	77.9	7.8								169 (10.5)
		$ND_3{}^c$		1.0	60.8	31.4	5.3	1.0						169 (0.5)
aniline^d	17	D_2O^c	93				94.0	6.0						
		$EtOD^c$					94.0	6.0						
		$ND_3{}^c$					30.7	2.0						95 (67.3)
o-toluidine^d	18	D_2O^c	107				93.2	6.8						
		$EtOD^c$				12.8	81.2	6.0						
		$ND_3{}^c$					93.1	6.9						
p-toluidine^d	19	D_2O^c	107				93.0	7.0						
		$EtOD^c$				6.0	88.0	6.0						
		$ND_3{}^c$					93.0	7.0						
m-toluidine^d	20	D_2O^c	107				93.2	6.8						
		$EtOD^c$				13.9	80.1	6.0						
		$ND_3{}^c$					43.8	34.3	16.2	5.7				
o-phenylenediamine	21	$EtOD^c$	108				3.6	26.4	48.7	2.8				160 (4.3), 161 (14.2)
		$ND_3{}^c$						3.6	52.7	2.6				133 (1.8), 134 (38.4), 135 (0.9)

p-phenylene-diamine[d]	**22**	EtOD[c]	108				4.7	23.8	50.0	4.7				160 (4.7), 161 (12.1)
		ND_3[c]						2.2	62.2	2.2				133 (2.2), 134 (29.0), 135 (2.2)
m-phenylene-diamine[d]	**23**	EtOD[c]	108				4.1	21.8	36.4	10.6	2.5			160 (5.9), 161 (13.5), 162 (4.1), 163 (1.1)
		ND_3[c]					8.4	24.7	31.6	26.8	6.5			134 (2.0)
benzonitirle	**24**	MeOD[b]	103		9.9									138 (31.0), 139 (2.4), 171 (52.1), 172 (4.6)
		D_2O[c]		7.5	29.0	2.5								125 (57.0), 145 (4.0)
acctophenone	**25**	MeOD	120		32.1	1.8								155 (53.6), 156 (3.6), 188 (8.9)
naphthalene	**26**	EtOD[b]	128	44.1	3.6	2.5	3.2	6.8	5.4	3.6	4.3	6.8	14.3	129 (5.4)
		EtOD[c]		17.0	3.8	4.8	5.8	6.8	7.7	8.7	8.7	11.6	21.3	129 (3.8)
		ND_3[c]		90.0										129 (10.0)
2,3-dimethyl-naphthalene	**27**	EtOD[b]	156	28.8	8.0	10.4	16.2	15.0	10.4	4.8	2.4			157 (4.0)
		EtOD[c]		20.9	5.7	10.5	17.0	19.1	15.4	6.6	2.9			157 (1.9)
phenanthrene	**28**	EtOD[c]	178	16.5	4.5	6.8	7.7	7.7	7.7	8.0	8.7	8.7	8.0	d_9MD^+ (6.8), $d_{10}MD^+$ (4.9), 179 (4.0)
		ND_3[c]		89.0										179 (11.0)
anthracene	**29**	EtOD[c]	178	3.6	78.6	14.3								179 (3.5)
		ND_3[c]		7.1	52.8	28.6	11.5							
		$MeND_2$[c]		81.1										176 (5.4), 179 (13.5)
9,10-dimethyl-anthracene	**30**	ND_3[c]	206		84.8	15.2								
pyrene ($C_{16}H_{10}$)	**31**	EtOD[c]	202	7.6	71.4	15.3								203 (5.7)
		ND_3[c]		13.6	43.9	26.4	10.2	3.4						203 (2.5)
chrysene ($C_{18}H_{12}$)	**32**	EtOD[c]	228	8.7	33.9	25.7	14.7	6.8	2.9					229 (7.3)
		PrOD[c]		13.6	18.1	16.8	15.6	10.7	7.2	4.8	4.8	2.4		229 (6.0)
		ND_3[c]		62.3										225 (15.1), 227 (4.5), 229 (13.6), 230 (4.5)
thiophene	**33**	MeOD[c]	84	33.1	5.3	10.5	33.3	10.8	3.5					85 (3.5)
2,5-dimethyl-thiophene	**34**	MeOD[c]	112	12.5	71.0	10.0	5.0							113 (1.5)
ferrocene	**35**	PrOD[c]	186	24.5	52.6	12.4								187 (10.5)
		ND_3[c]		13.6	39.4	23.3	10.9	6.1	1.4	1.8				187 (4.0)
hydroxymethyl-ferrocene	**36**	ND_3[c]	216											199 (87.2), 200 (12.8)
ferrocene-carboxaldehyde	**37**	ND_3[c]	214	3.4	35.6	3.8								215 (1.7), 234 (3.5), 235 (3.4), 236 (43.1), 237 (5.5)
vinylferrocene	**38**	ND_3[c]	212	7.1	69.8	15.5	3.8							213 (3.8)
ruthenocene	**39**	ND_3[c]	232	39.2	60.8									

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[a] Ion abundances are not corrected for contributions due to ^{13}C isotopes. [b] Data recorded on a Finnigan Model 3200 quadrupole mass spectrometer at the optimal ion-source temperature for exchange, 90 °C, as read on a thermocouple gage. [c] Data recorded on an AEI MS-902 double-focusing magnetic sector mass spectrometer at the optimal ion-source temperature, 175 °C, as read on a thermocouple gage. [d] Data include contributions from ion molecule isotope exchange of hydrogen for deuterium on heteroatoms in the molecule.

Table II. Ion Molecule Isotope-Exchange Data Obtained under Negative Ion CI Conditions

compd	no.	gas	mol wt	% total sample ion current^a										
				$M-1^-$	d_1M-1^-	d_2M-1^-	d_3M-1^-	d_4M-1^-	d_5M-1^-	d_6M-1^-	d_7M-1^-	d_8M-1^-	d_9M-1^-	other, *m/z* (%)
toluene	40	ND_3^b	92	35.3	33.4	31.3								
		D_2O^b		15.0	20.0	65.0								
		EtOD^b												
o-xylene	41	D_2O^b	106	8.5	6.5	9.0	9.0	12.0	55.0					
		EtOD^b												
mesitylene	42	D_2O^b	120	5.6	9.1	12.4	7.9	7.9	9.1	9.1	11.3	27.6		
		EtOD^b												
triphenylmethane	43	D_2O^b	244	100.0										
2-decanone	44	D_2O^c	156	65.5	21.8	8.7	4.0							
		EtOD^b		2.8	2.8	5.6	16.7	72.2						
4-decanone	45	D_2O^c	156	89.7	10.3									
		EtOD^b		5.3	7.9	18.4	68.4							
acetophenone	46	D_2O^c	120	85.7	14.3									
		EtOD^b		18.0	31.9	50.1								
5α-androstan-17-one	47	MeOD^b	274	33.9	49.1	13.5	3.5							
pregnenolone	48	EtOD^b	316		11.7	15.6	23.4	38.9	7.8	2.6				
estrone-3-methyl ether	49	MeOD^b	284	31.5	49.1	14.0	5.4							
estrone	50	MeOD^b	270	79.0	17.3	3.7								
5-androstan-3,17-dione	51	EtOD^b	288	2.5	5.4	11.2	14.6	19.6	39.2					293 (7.5)
5α-pregnan-3,20-dione-*2,2,4,4,17,21,21,21*-d_8^d	52	EtOH^{b,d}	324	12.3	15.4	16.8	14.2	12.5	10.2	7.0	7.0	4.6		
cyclobutanone	53	EtOD^b	70	3.7	4.9	12.4	79.0							
1-hexen-5-one	54	EtOD^b	98	2.3	4.5	6.8	18.2	68.2						
2-cyclohexen-1-one	55	EtOD^b	96	80.6	18.6	1.1								
3-methyl-2-cyclohexen-1-one	56	EtOD^b	110	76.2	18.8	5.0								
trans-4-phenyl-3-buten-2-one	57	EtOD^b	146	32.0	46.0	16.1	5.9							
6-methoxy-1-tetralone	58	EtOD^b	176	19.4	20.3	21.3	34.3	4.7						
4-androsten-3,17-dione	59	EtOD^b	286	53.8	30.0	7.3	1.9							284 (1.9), 283 (3.2), 282 (0.6), 281 (1.3)
1-androsten-3-one-*2,4,4*-d_3	60	EtOH^b	275	51.8	29.6	2.0								274 (13.1), 275 (3.5)
n-butyraldehyde	61	EtOD^b	72	26.0	74.0									
ethyl butyrate	62	EtOD^b	116	9.1	90.9									
methyl crotonate	63	EtOD^b	100	95.0	5.0									
acetylacetone	64	EtOD^b	100	60.4	39.6									
		CF_3CD_2OD		28.6	71.4									
diethyl malonate	65	EtOD^b	160	88.4	11.6									
		$CF_3CD_2OD^b$		55.0	45.0									
diethyl succinate	66	EtOD^b	174	8.7	9.8	16.3	65.2							
diethyl glutarate	67	EtOD^b	188	6.2	6.2	4.4	3.7							87 (3.1), 88 (12.4), 89 (52.8), 159 (11.2)
dimethyl adipate	68	EtOD^b	174											113 (5.8), 141 (62.8), 142 (24.9), 143 (6.5)
dimethyl pimelate	69	EtOD^b	188											155 (57.0), 156 (38.4), 157 (4.6)
dimethyl suberate	70	EtOD^b	202											169 (54.3), 170 (33.7), 171 (12.0)
dimethyl azeleate	71	EtOD^b	216	2.6	4.9	18.0	46.0							183 (1.1), 184 (3.4), 185 (15.0), 201 (9.0)

diethyl sebacate	72	EtOD^b	258	5.2	5.3	10.9	78.6							
dimethyl 1,4-cyclohexane dicarboxylate	73	EtOD^b	200	5.5	50.0									214 (33.3), 228 (11.2)
		MeOD^b		12.0	88.0									
benzene	74	$ND_3{}^b$	78	12.0	12.0	12.0	12.0	20.0	32.0					
naphthalene	75	$ND_3{}^b$	128	6.9	10.3	11.7	13.8	10.3	12.4	13.8	20.8			
anthracene	76	$ND_3{}^b$	178	3.6	8.5	7.3	13.4	8.5	8.5	9.7	11.0	12.2	17.3	
phenanthrene	77	$ND_3{}^b$	178	3.0	7.5	10.4	10.5	10.4	8.9	9.0	10.5	13.4	16.4	
pyrene ($C_{16}H_{10}$)	78	$ND_3{}^b$	202	5.6	11.3	12.4	14.1	11.3	10.7	10.2	9.0	8.8	6.6	
chrysene ($C_{18}H_{12}$)	79	$ND_3{}^b$	228	6.7	11.2	9.9	13.4	10.3	8.9	8.1	7.2	6.8	6.7	$d_{10}M - 1^-$ (6.3), $d_{11}M -$ $d_{11}M - 1^-$ (4.5)
benzo[*a*]pyrene ($C_{20}H_{12}$)	80	$ND_3{}^b$	252	4.4	29.2	14.7	11.9	8.0	6.4	5.5	5.6	4.7	4.8	$d_{10}M - 1^-$ (3.2), $d_{11}M - 1^-$ (1.6)
ferrocene	81	$ND_3{}^b$	186	8.3	16.1	15.3	12.5	11.1	9.7	7.6	6.9	6.3	6.2	
ferrocene	82	$ND_3{}^{b}{}_{q}$	214	1.4	2.0	2.0	4.0	3.8	3.8	6.7	10.0	19.6	40.0	223 (6.7)
phenylferrocene	83	$ND_3{}^b$	262	0.5	2.4	2.4	3.1	2.1	2.7	3.7	4.4	5.9	8.4	$d_{10}M - 1^-$ (14.7), $d_{11}M - 1^-$ (16.5) $d_{12}M - 1^-$ (16.5), $d_{13}M - 1^-$ (16.7)
(toluene) chromium tricarbonyl	84	$ND_3{}^b$	228	30.8	27.9	19.7	12.0	6.2	2.4	0.5	0.5			
		D_2O^b		43.2	22.8	13.2	8.4	6.0	4.8	1.2	0.4			

[a] Ion abundances are not corrected for contributions due to ^{13}C isotopes. [b] Data recorded on an AEI MS-902 double-focusing magnetic mass spectrometer at the optimal ion-source temperature for exchange, 100 °C for D_2O and 175 °C for EtOD, CF_3CD_2OD, and ND_3, as read on a thermocouple gage. [c] Data recorded on a Finnigan Model 3200 quadrupole mass spectrometer at the optimal ion source temperature for exchange, 100 °C, as read on a thermocouple gage. [d] In this spectrum the $(M - 1)^-$ ion refers to the ion resulting from the loss of deuterium and subsequent $d_nM - 1^-$ ion refers to ions resulting from the sequential exchange of deuterium for hydrogen.

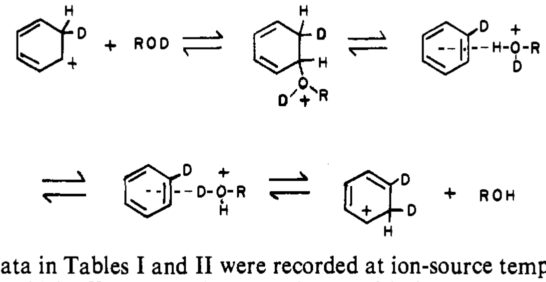
forward reaction increases the activation energy required for the exchange step increases and the internal energy of the cluster ion decreases. In the experiments performed in the present study very little exchange of deuterium was observed when the forward reaction was exothermic by more than 25 kcal.

Ion/molecule isotope exchange on aromatic systems under positive ion CI conditions can be explained by invoking a set of intermediates similar to those outlined above for negative ions (see eq 10). Alternately the exchange may be envisioned as proceeding

$$HRD^+ + ROD \rightleftarrows DR\overset{+}{-}H\cdots\underset{\displaystyle D}{\underset{|}{O}}R \rightleftarrows DR\cdots H-\underset{\displaystyle D}{\underset{|}{\overset{+}{O}}}R \rightleftarrows DR\cdots D-\underset{\displaystyle H}{\underset{|}{\overset{+}{O}}}R \rightleftarrows$$

$$DR\overset{+}{-}D\cdots\underset{\displaystyle H}{\underset{|}{O}}R \rightleftarrows DR-D^+ + ROH \quad (10)$$

through a deuterated cyclohexadiene intermediate as shown in eq 11.



(11)

Data in Tables I and II were recorded at ion-source temperatures which afforded maximum exchange with the various reagent gases. We assume that the temperature dependence of the exchange process is related to the internal energy requirements of the intermediate cluster ions A and B in Figure 1. If the temperature of the ion source is too low, the internal energy of the cluster ion will be insufficient and the exchange will proceed at less than the optimum rate. If the temperature of the ion source is too high, the cluster ion will have excess internal energy and a lifetime too short for optimal exchange to occur.

Note also that the entropy of the dissociation reaction for the cluster ion is considerably higher than that of the internal rearrangement step leading to isotope exchange. Since the importance of the entropy term increases with increasing internal energy, the rate of cluster ion dissociation eventually becomes significantly higher than that of the exchange reaction at high temperature.[20]

Isotope-Exchange Reactions on Positive Ions

Alkylbenzenes. Results of ion/molecule-exchange reactions run under positive ion CI conditions in D_2O are similar to those reported by Beauchamp and co-workers using ICR.[7] Deuteron transfer from D_2O to benzene (**1**), toluene (**2**), *o*-xylene (**3**), and *p*-xylene (**4**) is exothermic by 11, 17, 20, and 20 kcal, respectively.[17] All ring carbon atoms in these compounds have similar basicities[21] and deuterium incorporation occurs rapidly at all positions. Placement of methyl groups meta to each other on the ring enhances the basicity of the carbon atoms ortho and para to the substituents. *m*-Xylene (**5**) and mesitylene (**6**) are estimated to have PA's which exceed that of water (PA = 170 kcal)[17] by 24 and 28 kcal, respectively. In agreement with the proposed mechanism we observe only slow hydrogen–deuterium exchange for these compounds in D_2O. Replacement of the deuterium oxide by the stronger base EtOD (PA = 186 kcal)[17] should increase the strength of the interactions between the MD^+ ion and EtOD and lower the activation energy required for interconversion of the hydrogen-bonded intermediates in the exchange process (see eq 12). In agreement with this picture, incorporation of deuterium into *m*-xylene and mesitylene occurs to a much greater extent in EtOD than in D_2O.

Oxygenated Benzene Derivatives. The site of protonation of oxygenated benzenes is a topic of considerable interest. In solution

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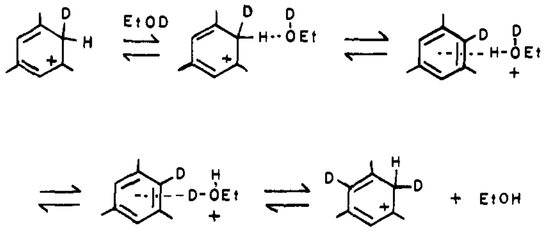
(21) D. L. Devlin, III, J. F. Wolf, R. W. Taft, and W. J. Hehre, *J. Am. Chem. Soc.*, **98**, 1990 (1976).



(12)

phenol and several of its derivatives protonate both on oxygen and on the aromatic ring.[22] The extent of protonation at the two sites is dependent on the pattern of substitution, the temperature, and the solvent system. Results obtained from experimental ICR studies and theoretical STO-3G calculations led McIver et al.[23] to suggest that in the gas phase, protonation of phenol on the aromatic ring is 15 kcal more exothermic than protonation on oxygen. Lau and Kebarle[24] reached the same conclusion by comparing the experimentally determined PA of phenol (195 kcal) with a previously published theoretical value.[25] Protonation on carbon is also indicated by the small PA difference observed between phenol and anisole (4.5 or 4.8 kcal).[23,24] In contrast the difference in PA between simple aliphatic alcohols and the corresponding methyl ethers, both of which protonate on oxygen, is 7.9 and 9.3 kcal for the methyl and ethyl compounds, respectively.[23]

In a recent study of cluster ions produced under CI conditions in water, Martinson and Butrill[8] observed that only aromatic compounds with strongly basic substituents formed stable ions of the type $MH^+(H_2O)$. Spectra recorded on alkylbenzenes and benzene itself did not contain these ions so it was concluded that substituent protonation was a necessary condition for production of the cluster ion. Since anisole formed a stable $MH^+(H_2O)$ ion, it was suggested that the preferred site of protonation was on oxygen rather than on carbon. Beauchamp and co-workers drew the opposite conclusion from ICR studies.[7] Catalan and Yanez[26] have recently calculated that the PA's of the oxygen atoms and the para ring position in anisole should be 196.7 and 196.5 kcal, respectively. Their results also predict that rotation of the methoxy group about the ring oxygen bond can increase the PA of the oxygen atom to a maximum value of 199.5 kcal and reduce the PA of the para position to a minimum value of 184.6 kcal. The experimentally determined PA of anisole is 199.4 kcal.[24] Lau and Kebarle have pointed out that the preferred site of protonation in many compounds may depend on the degree of solvation of the MH^+ ion.[24]

Here we report that MD^+ ions from both phenol (**7**) and anisole (**8**) incorporate three deuterium atoms slowly in D_2O and more rapidly in EtOD. Since the PA's of the meta carbons are ca. 15 kcal less than the PA's of the other ring positions, it is reasonable that exchange should only occur on the ortho and para carbon atoms. These results clearly indicate that deuteron transfer from D_3O^+ and $EtOD_2^+$ to the aromatic ring can occur. Further since the distribution of deuterium-labeled product ions in phenol (**7**), anisole (**8**), and mesitylene (**6**) do not differ greatly, we conclude that the rates of deuterium incorporation for the three compounds must be similar. The data are then consistent with the PA of the ring being either comparable to or greater than that of the oxygen substituent. The results are incompatible with proton transfer to oxygen being greatly favored over protonation on the aromatic ring.

Exchange studies on the isomeric hydroxy- and methylphenols show that the ortho and para isomers incorporate deuterium slowly at all four available ring positions. The process appears to be somewhat more efficient for the para isomers **10** and **12** than for the ortho-substituted isomers **9** and **13**. Both of the meta isomers **11** and **14** incorporate three deuteriums into the aromatic ring. The fourth site is essentially unactivated by either of the substituents and is therefore much less basic than the other three ring positions. In the case of the two trisubstituted benzene derivatives **15** and **16** each of the remaining unsubstituted carbon atoms are activated equally by all three substituents and the PA of the ring undoubtedly exceeds that of ammonia (PA = 202.3 kcal).[17] Incorporation of three deuteriums with ND_3 occurs rapidly into **15** and slowly into **16**. The trimethoxybenzene **16** is apparently too basic to undergo exchange with the weaker base, EtOD.

Amino-Substituted Benzenes. Isotope-exchange reactions on amino-substituted benzenes are of interest in light of recent evidence that protonation of aniline (PA = 208.8 kcal) at the para position of the aromatic ring is only 1–3 kcal less favorable than protonation at nitrogen.[24,27,28] Taft and Hehre et al.[28] have calculated the effect of ring substituents on the PA of aniline and conclude that ring protonation is favored over N-protonation in the gas phase when electron-donating groups like Me–, MeO–, and NH_2– are introduced meta to the amino group. Placement of a methyl group in the meta position has little effect on the basicity of the nitrogen but does increase the PA of the para ring position by ~6 kcal. The aromatic ring in *m*-toluidine is, therefore, estimated to be more basic than the amino group by 2.8 kcal. In the case of *m*-phenylenediamine the PA of the ring was shown to exceed that of the amino substituent by 17 kcal. Kebarle and co-workers have recently determined the PA of *m*-phenylenediamine to be 19.7 kcal higher than that of ammonia.[29]

Results of ion/molecule-exchange reaction reported in Table I are in agreement with all of the above data. Aniline (**17**), *o*-toluidine (**18**), *p*-toluidine (**19**), *o*-phenylenediamine (**21**), and *p*-phenylenediamine (**22**) fail to incorporate deuterium on the aromatic ring when D_2O, EtOD, or ND_3 is employed as the CI reagent gas. We interpret this to mean that the amino group has a higher PA than that of the ring and is, therefore, the preferred site of protonation. Benzonitrile (**24**) and acetophenone (**25**) are known to protonate on the substituent also,[7,11] and they too fail to undergo isotope exchange under our experimental conditions. In contrast to the above data, both *m*-toluidine (**20**) and *m*-phenylenediamine (**23**) suffer partial exchange of aromatic hydrogen in ND_3. These results provide support for the thesis that the preferred site of protonation in **20** and **23** is the ring rather than the amino substituent.

Naphthalene (**26**), 2,3-dimethylnaphthalene (**27**), and phenanthrene (**28**) suffer exchange of all aromatic protons in EtOD but are not sufficiently basic to accept a deuteron from ND_4^+. Anthracene (**29**) does have a PA greater than that of ammonia and undergoes exchange of two hydrogens in ND_3.[30] Since 9,10-dimethylanthracene (**30**) fails to incorporate deuterium in this medium, it is reasonable that protonation of anthracene occurs selectively at the 9- and 10-carbon atoms. Pyrene (**31**) and chrysene (**32**) suffer partial exchange in ND_3 and EtOD, respectively. Deuteron transfer from ND_4^+ to chrysene (PA = 203 kcal) is endothermic.[30]

Studies of acid-catalyzed hydrogen–deuterium exchange in solution on thiophenes indicates that incorporation of deuterium into the 2 and 5 positions is about 10^3 times faster than replacement of the hydrogens on the C-3 and C-4 carbons.[31] We observe a similar result in the gas phase with MeOD as the CI reagent. 2,5-Dimethylthiophene (**34**) and thiophene (**33**) exchange

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(22) For reviews see: (a) D. M. Brouwer, E. L. Mackor, and C. McLean in "Carbonium Ions", Vol. II, G. L. Olah and P. v. R. Schleyer, Eds., Wiley, New York, 1970; (b) M. Liler, *Adv. Phys. Org. Chem.*, **11**, 267 (1975).

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(25) J. M. McKelvey, S. Alexandratos, A. Streitweiser, Jr., J. L. M. Abbound, and W. J. Hehre, *J. Am. Chem. Soc.*, **98**, 244 (1976).

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(28) K. D. Summerhays, S. K. Pollack, R. W. Taft, and W. J. Hehre, *J. Am. Chem. Soc.*, **99**, 4585 (1977).

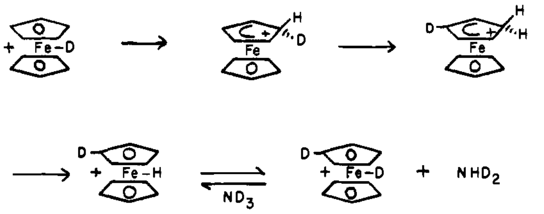
(29) Y. K. Lau, P. P. S. Saluja, P. Kebarle, and R. W. Alder, *J. Am. Chem. Soc.*, **100**, 7238 (1978).

(30) M. Moet-Ner (Mautner), E. P. Hunter, and F. H. Field, 27th Annual Conference on Mass Spectrometry and Allied Topics, Seattle, WA, June 3–8, 1979, Paper No. RAM0B6.

(31) A. F. Thomas, "Deuterium Labeling in Organic Chemistry", Appleton-Century-Crofts Education Division, New York, 1971, p 149.

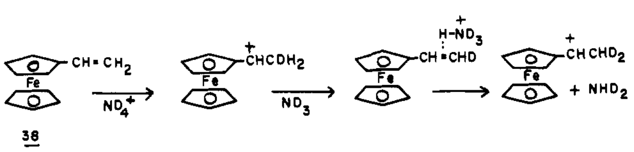
zero and two deuteriums, respectively. We conclude that protonation of thiophene in the gas phase occurs preferentially at the positions adjacent to sulfur.

Metallocene Compounds. In solution ferrocene (**35**) forms stable metal-protonated cations[32] and also undergoes facile acid-catalyzed exchange of all ring hydrogens.[31] Direct metal participation in the exchange mechanism may or may not occur.[33] One possible sequence of steps involves metal deuteration, migration of the deuteron to the endo side of the five-membered ring, isomerization of the methylene proton on the exo side of the ring, and removal of the newly exposed endo methylene hydrogen by solvent (see eq 13). Beauchamp has recently determined a PA of 213 kcal for ferrocene[34] but failed to observe isotope-exchange reactions of the MD^+ ion in D_2O under ICR conditions.[35]



(13)

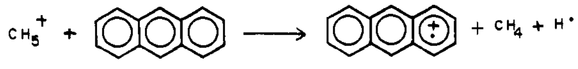
Here we report that ferrocene (**35**) suffers slow exchange of 1 and 5 hydrogens in C_3H_7OD and ND_3, respectively. Since the PA's of ND_3 and ferrocene are within 11 kcal of each other, more extensive exchange is expected. Slow incorporation of deuterium into ferrocene can be explained if the energy released on solvation of the highly delocalized charge in the MD^+ ion is low or if there is an unusually high activation energy required for the interconversion of the solvated intermediates required in the exchange process. Both possibilities seem reasonable in the absence of additional data. We note without comment that the MD^+ ion from ruthenocene (**39**) fails to exchange ring hydrogen in ND_3. All of the ferrocene derivatives, **36**, **37**, and **38**, accept a deuteron from ND_4^+ at the substituent, but only vinylferrocene (**38**) undergoes the isotope-exchange reaction, presumably via the series of steps shown in eq 14.



(14)

Molecular Ion Formation. Many of the spectra reported in Table I contain abundant molecular ions, $M^{+\cdot}$. We note that the percent total sample-ion current carried by $M^{+\cdot}$ increases as the PA difference between sample and reagent gas decreases and also as the temperature of the ion source decreases. In contrast the rate of proton transfer from reagent to sample decreases as the PA of the reagent gas and sample approach each other. At low ion-source temperatures the reagent ion population is dominated by cluster ions which have a higher proton affinity than the simple monomeric reagent ion.[36] Accordingly slow proton transfer is expected at low ion source temperatures when the PA of the sample is greater than the monomer reagent ion but less than or equal to the PA of the dimeric cluster ions. In general the abundance of molecular ions is high when the rate of proton transfer is slow.

To explain formation of $M^{+\cdot}$, we first considered a mechanism, eq 15 and 16, involving charge exchange between sample and CI reactant ion. This process is feasible in methane but highly endothermic for all of the CI reagents employed in the present study.[37] It, therefore, seems improbable that a charge-exchange mechanism can be responsible for the formation of sample molecular ions.



(15)

ΔH = -15.4 kcal

$$R\overset{+}{D}_2 + M \longrightarrow RD + M^{+\cdot} + D^{\cdot} \quad \text{WHERE } R = -OD,\ -OEt,\ -ND_2 \qquad (16)$$

We next considered the possibility that $M^{+\cdot}$ ions are produced by EI under CI conditions. Recently it has been estimated that 65% of the electrons in a CI source have less than 0.45 eV of energy. Electrons having energies near 6.5, 8.6, and 11.4 eV total about 3% of the population.[38] From the above data we speculate that as many as 10% of the electron population might have energies greater than 6 eV and, therefore, might be capable of producing $M^{+\cdot}$ ions from most of the compounds in Table I. If we take the cross section for ionization of sample by a 10-eV electron as 1×10^{-18} cm^2 and the velocity of the 10-eV electron as 2×10^8 cm/s,[39] we calculate a rate constant for EI on the order of 2×10^{-10} cm^3/(molecule s). Ion molecule reactions that occur on every collision exhibit a rate constant of $(1-3) \times 10^{-9}$ cm^3/(molecule s).[40] Thus, if the populations of positive ions and electrons in a CI source are equal but only 10% of the electrons are capable of ionizing sample, we expect under most conditions that the ratio of the rates of ionization by CI and EI will be $\sim 10^2$. Sample ions produced by EI should make little or no contribution to the spectrum. On the other hand, if the rate constant for CI decreases and sample concentration in the source is high, then EI can become a significant and even dominant ionization mechanism under CI conditions. We believe that the formation of $M^{+\cdot}$ ions in the present study is due to EI of sample.

Isotope-Exchange Reactions on Negative Ions

The data in Table II indicate that ion/molecule isotope-exchange reactions on negatively charged $M - 1$ ions can be employed to selectively incorporate deuterium into several different chemical environments. The resulting increase in the m/z ratio of the $M - 1^-$ ion provides a count of the protons in the specific chemical location. Since this information can be obtained on nanogram samples, the gas-phase ion/molecule isotope-exchange technique should become quite useful to those involved in structural studies.

Alkylbenzene and Carbonyl Compounds. Proton abstraction from alkylbenzenes (PA of A^- from toluene = 378 kcal)[41] by OH^- is exothermic by 10–14 kcal. Accordingly, $M - 1^-$ ions from compounds **40**–**42** undergo efficient exchange of benzylic hydrogens when D_2O is employed as the CI reagent. Aromatic, alkyl, and allylic hydrogens are not sufficiently acidic to react with OH^- and, therefore, do not suffer exchange under our experimental conditions. Note that D_2O is also the reagent of choice for exchanging aromatic hydrogens in alkylbenzenes under positive ion CI conditions. Thus both aromatic and benzylic protons can be counted simultaneously when the PPINICI technique is used to record CI spectra.

Abstraction of hydrogen in the α-carbon of simple aldehydes, ketones, and esters is also observed with OH^-, but the exothermicity of the process approaches 20–30 kcal (PA of A^- from

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[32] (a) M. Rosenblum and J. O. Santer, *J. Am. Chem. Soc.*, **81**, 5517 (1959); (b) T. C. Curphey, J. O. Santer, M. Rosenblum, and J. H. Richards, *ibid.*, **82**, 5249 (1960); (c) M. Rosenblum, J. O. Santer, and W. G. Howells, *ibid.*, **85**, 1450 (1963).

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[37] Heat of formation data were taken from: H. M. Rosenstock, K. Draxl, B. W. Steiner, and J. T. Herron, *J. Phys. Chem. Ref. Data*, **6**, Suppl. No. 1 (1977).

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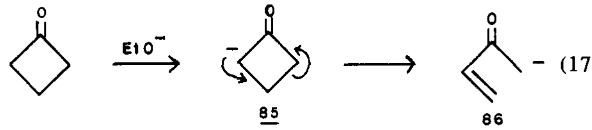
[41] J. E. Bartmess and R. T. McIver, Jr., "Gas Phase Ion Chemistry", M. T. Bowers, Ed., Academic Press, New York, 1979.

acetone = 368 kcal).[41] The exchange reaction between the resulting M − 1⁻ ion and D_2O is, therefore, highly inefficient. Selective incorporation of deuterium into the M − 1⁻ ion of simple unconjugated carbonyl compounds can be accomplished in EtOD. EtO^- (PA = 378 kcal)[41] is not sufficiently basic to abstract a hydrogen from alkylbenzenes but does react readily with carbonyl compounds (PA = 360–370 kcal). Isotope exchange of the resulting M − 1⁻ ions in EtOD is much more extensive than in the weaker acid D_2O. Even the deuterium-labeled diketosteroid (**52**) which contains two widely separated carbonyl groups suffers partial exchange of all seven remaining deuterium atoms in the M − 1⁻ ion when EtOH is employed as the reagent. Use of the stronger acid CF_3CD_2OD (Pa of A^- = 363.5 kcal)[41] as the reagent gas is required for efficient exchange of the remaining doubly-activated α-hydrogen in the M − 1⁻ ion from the highly acidic β-dicarbonyl compounds acetylacetone (**64**) (PA of A^- = 343.7 kcal)[41] and diethyl malonate (**65**). The $CF_3CD_2O^-$ anion does not generate M − 1⁻ ions from simple carbonyl compounds under our experimental conditions. Note that the hydrogens on the methyl groups in acetylacetone do not incorporate deuterium in either EtOD or CF_3CD_2OD. Both the hydrogen abstraction and the subsequent isotope-exchange reaction occur preferentially at the methylene carbon between the two carbonyl groups. Thus the ion/molecule isotope-exchange technique under negative ion CI conditions is only capable of counting the number of hydrogens located in the most acidic site in a multifunctional molecule.

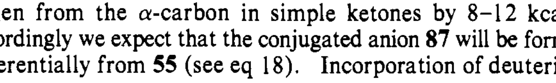
In addition to determining the number and location of certain hydrogens in a sample, we can also employ the exchange reaction as a probe of ion structure. Proton abstraction from cyclobutanone (**53**) might afford either of the two anions **85** or **86**. In EtOD **86** should undergo rapid exchange of the two methylene hydrogens adjacent to the carbonyl group and possibly slow exchange of the methine hydrogen on the other α-carbon atom. In structure **85** we expect rapid exchange of all three methylene hydrogens remaining in the M − 1⁻ ion. The latter situation is observed experimentally so we conclude that the M − 1⁻ ion has structure **85**. Rearrangement of **85** to **86** should in fact have a fairly high activation energy since the orbitals involved in forming the carbon–carbon π bond in **86** are nearly at right angles to each other in the highly strained starting material (**53**). Delocalization of the negative charge into the carbonyl group is also impossible in the transition state leading from **85** to **86** (see eq 17).



85 86

(17)

Conjugated Carbonyl Compounds. The exothermicity of hydrogen abstraction from the α-carbon in an α,β-unsaturated carbonyl system should be greater than that for removal of hydrogen from the α-carbon in simple ketones by 8–12 kcal.[42] Accordingly we expect that the conjugated anion **87** will be formed preferentially from **55** (see eq 18). Incorporation of deuterium



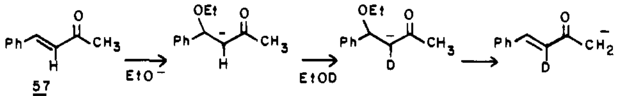
55 87

(18)

into the conjugated anion **87** by the exchange mechanism can occur at either the γ- or α-carbon atoms. Proton transfer to C-2, the site of highest electron density, and to C-4, the site that affords the most stable product, is favored under conditions of kinetic and thermodynamic control, respectively.[43] The M − 1⁻ ions from compounds **55**, **56**, and **59** contain 2, 5, and 2 exchangeable hydrogens on the conjugated anion system, respectively. Experimentally we find that all three compounds incorporate a single deuterium atom into the M − 1⁻ ion with moderate efficiency in EtOD. This result is consistent with either preferential exchange of the α-methine hydrogen or with slow but indescriminate exchange of all α and γ hydrogens in the conjugated anion. The latter possibility is not unreasonable since the PA difference between the reagent ion EtO^- and the sample approaches 20 kcal. Additional labeling experiments are required to resolve the two possibilities.

6-Methoxy-1-tetralone (**58**) is an interesting example because the intervening conjugated system between the γ-hydrogens and the carbonyl group is an aromatic ring rather than a simple double bond. Since delocalization of the negative charge at C-4 destroys the aromatic character of the phenyl ring, we expect that the γ-hydrogens will be less acidic than in the previous examples. Exchange data obtained in EtOD are consistent with this view and show incorporation of three deuterium atoms, presumably at C-2 and C-4 in the M − 1⁻ ion from (**58**).

Compounds **57** and **60** contain an α,β-unsaturated carbonyl system but are devoid of γ-hydrogens. The M − 1⁻ ion from *trans*-4-phenyl-3-buten-2-one (**57**) suffers exchange of two hydrogens with moderate efficiency and slow partial exchange of a third hydrogen. Back-exchange of the deuterium-labeled steroid **60** in EtOH suggests that it is the α-methine hydrogen in the conjugated system that undergoes slow exchange in both **57** and **60** (see eq 19). We conclude that the rates for Michael addition

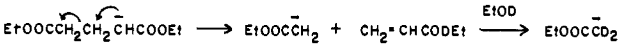


57

(19)

of ethoxide to the conjugated system and for proton abstraction from the saturated γ-carbon atom are not too dissimilar. Slow incorporation of deuterium into C-2 of α,β-unsaturated carbonyl compounds has also been observed in solution.[44]

Diesters. Reaction of EtO^- with diesters affords M − 1⁻ ions which undergo the expected exchange of hydrogens on the carbon atoms adjacent to both carbonyl moieties. Ester interchange, retro Michael addition, and Dieckmann cyclization reactions are also observed for several of the compounds. Diethyl succinate (**66**) follows the expected reaction pathway with EtO^- in EtOD and incorporates three deuterium atoms into the M − 1⁻ ion. In contrast, the M − 1⁻ ion from diethyl glutarate (**67**) undergoes a retro Michael addition to form the M − 1⁻ ion of ethyl acetate which in turn suffers exchange of two hydrogens on collision with EtOD. Note that the relative abundance and deuterium content of the ethyl acetate M − 1⁻ ion is higher than that of the parent M − 1⁻ ion. We interpret this to mean that the rate of isotope exchange in the parent M − 1⁻ ion is slower than both the intramolecular retro Michael addition step and the isotope-exchange reaction involving the resulting anion from ethyl acetate (see eq 20).



$$\mathrm{EtOOCCH_2CH_2\bar{C}HCOOEt} \longrightarrow \mathrm{EtOOC\bar{C}H_2} + \mathrm{CH_2{=}CHCODEt} \xrightarrow{\mathrm{EtOD}} \mathrm{EtOOC\bar{C}D_2} \tag{20}$$

Dimethyl esters of the C-6, C-7, and C-8 dicarboxylic acids (**68–70**) afford negative ion CI spectra which are devoid of M − 1⁻ ions but contain abundant M − 33⁻ ions (M − 1 − CH_3OH). The spectrum of the C-9 compound **71** exhibits both M − 1⁻ and M − 33⁻ ions in moderate abundance. We suggest that the M − 33⁻ ions correspond to enolate anions of cyclic β-ketoesters formed by the Dieckmann reaction as shown below. The first step in the reaction involves intramolecular displacement of methoxide which in turn must abstract a hydrogen from the neutral product during the lifetime of the ion molecule complex (see eq 21). Cyclization of the M − 1⁻ ions from the esters of the C-5 (**67**)

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[42] Estimated by the group equivalent method: S. W. Benson, "Thermochemical Kinetics", 2nd ed. Wiley-Interscience, New York, 1978.

[43] F. A. Carey and R. J. Sundberg, "Advanced Organic Chemistry", Part B, Plenum Press, New York, 1977, p 19.

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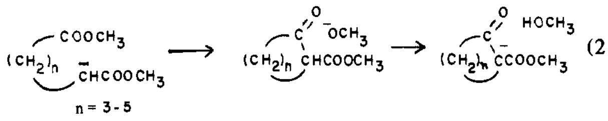
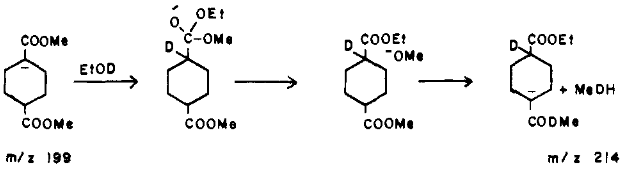


(21)

and C-10 (**72**) dicarboxylic acids is not observed under our experimental conditions.

When EtOD is employed as the CI reagent gas, ions corresponding to d_0-, d_1-, and $d_2M - 1 - CH_3OH^-$ are observed in the spectra of compounds **68–71**. Previously we noted that the M − 1^- ion from the β-dicarbonyl compound acetylacetone (**64**) fails to incorporate deuterium into the methyl groups adjacent to the carbonyl moieties. We conclude, therefore, that incorporation of deuterium into the β-ketoester enolate anions (M − 33^-) must occur in the M − 1^- ion prior to the cyclization step. Since the level of deuterium incorporation into the M − 33^- ion increases in the order **68** < **69** < **70** < **71**, we suggest that the order of preferred ring size in the transition state leading to the β-ketoester enolate anions is C-5 > C-6 > C-7 > C-8 ≫ C-4 or C_9.

Dimethyl 1,4-cyclohexanedicarboxylate (**73**) is an interesting example because it undergoes both the expected isotope-exchange reaction as well as ester interchange as diagrammed in eq 22.[45]



(22)

Aromatic Compounds. Aromatic hydrogens are not sufficiently acidic (PA of $C_6H_5^-$ = 398 kcal)[41] to react with either EtO^- or OD^- but can be removed with ND_2^- (PA = 402 kcal).[41] Shapiro et al. have generated $C_6H_5^-$ from benzene with ND_2^- and reacted it with D_2O under flowing afterglow conditions to produce OD^-.[9] Incorporation of deuterium into the $C_6H_5^-$ anion was not observed. As shown in Table II, partial exchange of all aromatic hydrogens in compounds **74–80** occurs under CI conditions when the weaker acid ND_3 is employed as the reagent gas. Incorporation of deuterium into aromatic anions is also observed in liquid ammonia solution.

Organometallic Compounds. Hydrogens attached to the cyclopentadienyl rings in ferrocene must be nearly as acidic as those on simple aromatic systems. All nine and thirteen hydrogens in the M − 1^- ions from ferrocene (**81**) and phenylferrocene (**82**), respectively, suffer exchange in ND_3. Ferrocenecarboxaldehyde (**82**) also incorporates nine hydrogens into the M − 1^- ion. We estimate the PA of CHO^- to be 401 ± 4 kcal.[47] Thus exchange of the aldehyde proton in ND_3 is not unexpected.

Previously we noted that the benzyl protons in toluene (**40**) are considerably more acidic than those on the aromatic ring (PA of Ph^7 = 398 vs. 378 kcal for $PhCH_2^-$). Only two deuterium atoms are incorporated into the M − 1^- ion of **40** in either D_2O or ND_3. In contrast, all seven of the protons in the (toluene)tricarbonylchromium (**84**) M − 1^- ion suffer exchange in ND_3. We assume that it is the positions meta to the benzylic carbon that incorporate deuterium at the slowest rate. The data indicate that charge delocalization in the benzylic anion increases significantly when it is coordinated to a chromium tricarbonyl moiety. Neither toluene nor its complex (**84**) undergo proton abstraction with EtO^- in EtOD. Thus the acidity of the chromium tricarbonyl complex is not appreciably different from that of toluene itself in the gas phase.

Conclusion

Results obtained in the present study indicate that hydrogens attached to aromatic rings, to carbons adjacent to aromatic rings, and to carbons α to carbonyl groups are readily exchanged for deuterium under CI conditions when deuterium-labeled reagent gases are employed. The extent of deuterium incorporation decreases as the proton affinity between sample and reagent gas molecules increases and is temperature dependent as well. A mechanism for the exchange process that is consistent with these observations is presented in both eq 7 and in Figure 1.

Data concerning the preferred site of protonation in substituted aromatic compounds were obtained from ion molecule isotope exchange reactions. We conclude that protonation occurs on the aromatic ring of oxygenated benzene derivatives and of anilines substituted in the meta position with groups such as Me–, MeO, and NH_2–. Aniline and its ortho- and para-substituted derivatives are protonated on the substituent. Protonation of thiophene occurs preferentially at the 2 and 4 positions.

Under negative ion CI conditions exchange of hydrogen for deuterium occurs at carbon adjacent to an aromatic ring in D_2O, at carbon adjacent to a simple carbonyl group in EtOD, and at the central carbon of a β-dicarbonyl group in CF_3CD_2OD. We suggest that these ion/molecule isotope-exchange reactions will be of considerable utility for counting protons in particular chemical environments within a sample molecule.

Molecular ion formation under Brønsted acid conditions increases as the PA between sample and reagent gas decreases and is temperature dependent as well. We conclude that formation of M^+ ions results from EI competing with CI under these conditions.

Examples of gas-phase Michael addition and Dieckmann cyclization reactions are reported. We conclude that the preferred ring size in the transition state for the latter reaction in the gas phase is C-5 > C-6 > C-7 > C-8 ≫ C-4 or C-9.

Acknowledgment. We are grateful to the U.S. Army Research Office, Grant DAAG 29-76-G-0326, and the U.S. Environmental Protection Agency, Grant R 805790-01, for their support of this research.

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