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(13) The generous support of the Research Corporation is gratefully acknowledged.

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Sequential Deuterium Exchange Reactions of Protonated Benzenes with D_2O in the Gas Phase by Ion Cyclotron Resonance Spectroscopy

Sir:

Deuterium exchange has been used in mass spectrometric studies to determine the number of acidic hydrogens in a molecule. Together with knowledge of the heteroatom content from high resolution mass spectrometry, the results afforded by this method aid considerably in functional group identification and hence the elucidation of complex molecular structures.[1,2] Hunt and co-workers have developed a simplified procedure utilizing chemical ionization mass spectrometry (CIMS) with D_2O as the reagent gas.[3] Their findings indicate that hydrogen bonded to heteroatoms in aliphatic alcohols, phenols, carboxylic acids, amines, amides, and mercaptans undergo essentially complete exchange in the ion source prior to protonation by the reagent ions. In addition they report that unsaturated compounds such as benzene, stilbene, and 3,3-dimethyl-1-butene fail to exchange, and that the extent of substitution with ketones, aldehydes, and esters is negligible.

We wish to report preliminary results on a novel deuterium exchange reaction, observed using ion cyclotron resonance (ICR) spectroscopy,[4] which have a bearing on the above findings and interesting implications for further study. In apparent contrast to the results of Hunt et al., sequential reactions of protonated aromatic compounds with D_2O in the gas phase occur which lead to various degrees of ring deuteration. For example, in a mixture of benzene and D_2O (Figure 1), reactions 1 and 2 lead to the formation of $C_6H_6D^+$ which in further reaction with D_2O undergoes rapid stepwise exchange of H for D (reaction 3).[5] From these data it is possible to determine the number of deuteriums exchanged in addition to kinetic parameters describing the exchange process.[6]

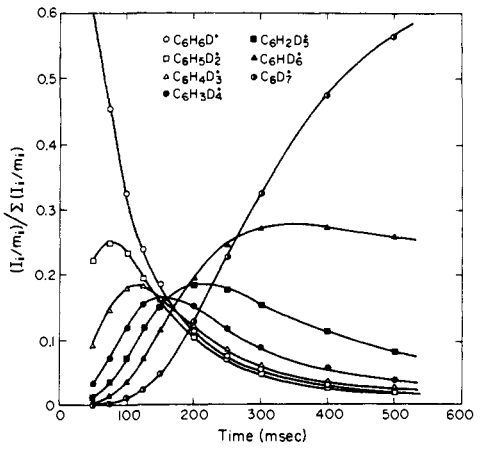


Figure 1. Temporal variation of the abundances of the variously deuterated benzene ions observed in a mixture of benzene (2×10^{-7} Torr) and D_2O (3.5×10^{-6} Torr) at an electron energy of 70 eV. Other species present, not included in the normalization, are D_2O^+ and D_3O^+, which are precursors to $C_6H_6D^+$, as well as $C_6H_6^+$ and fragment ions derived from benzene.

$$D_2O^+ + C_6H_6 \rightarrow C_6H_6D^+ + OD \quad (1)$$

$$D_3O^+ + C_6H_6 \rightarrow C_6H_6D^+ + D_2O \quad (2)$$

$$C_6H_{7-n}D_n^+ + D_2O \rightarrow C_6H_{6-n}D_{n+1}^+ + HDO \quad (n = 1\text{–}6) \quad (3)$$

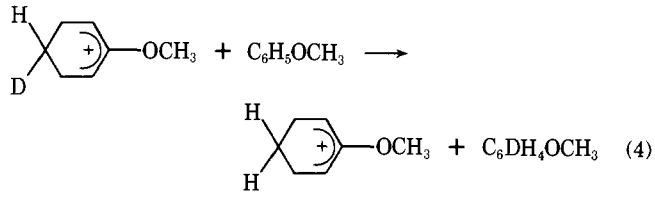
From the data summarized in Table I for the halo and alkyl substituted benzenes it is apparent that deuterium exchange varies significantly for different structural isomers. Thus while *o*- and *p*-difluorobenzene exchange all hydrogens rapidly, the meta isomer slowly exchanges only a single hydrogen. A similar comparison can be made for the xylenes and trisubstituted benzenes. *These results are especially important since the mass spectra of these isomeric compounds are in general indistinguishable.*[7,8]

Species such as the benzoyl cation, radical cations, and $C_7H_7^+$ derived from toluene and cycloheptatriene do not undergo exchange. It appears that ring protonation is a necessary condition for exchange to occur. Two experiments which ascertain the site of protonation of substituted aromatics (Table I) include the observation of thermoneutral

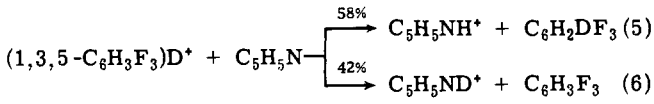
Table I. Summary of Deuterium Exchange Results

Compound	No. of exchanges starting with deuterated parent ion[a] 1	2	3	4	5	6	Relative rate of first exchange[b]	Site of protonation[c]
Benzene	+	+	+	+	+	+	f	R
Fluorobenzene	+	+	+	+	+	NA	f	R
o-Difluorobenzene	+	+	+	+	NA	NA	f	R
m-Difluorobenzene	+	–	–	–	NA	NA	m	R
p-Difluorobenzene	+	+	+	+	NA	NA	f	R
1,3,5-Trifluorobenzene	–	–	–	NA	NA	NA	–	R
1,2,4-Trifluorobenzene	+	+	+	NA	NA	NA	f	R
Toluene	+	+	+	+	+	NA	m	R
o-Xylene	+	+	+	+	NA	NA	m	R
m-Xylene	+	–	–	–	NA	NA	s	R
p-Xylene	+	+	+	+	NA	NA	m	R
Mesitylene	–	–	–	NA	NA	NA	–	R
Anisole	–	–	–	–	–	NA	–	R
Benzonitrile	–	–	–	–	–	NA	–	S
Benzaldehyde	–	–	–	–	–	NA	–	S
Acetophenone	–	–	–	–	–	NA	–	S

[a] NA indicates not applicable, + exchange observed, and – exchange not observed. [b] The symbols f, m, and s indicate, respectively, fast ($1\text{–}5 \times 10^{-10}$ cm^3 mol^{-1} sec^{-1}), medium ($10^{-11}\text{–}10^{-10}$ cm^3 mol^{-1} sec^{-1}), and slow ($\leq 10^{-11}$ cm^3 mol^{-1} sec^{-1}) reaction rates. [c] R and S indicate that evidence was obtained for the *favored* site of protonation being on the ring and substituent, respectively. With sufficiently acidic donors both sites may be protonated.



proton transfer processes (e.g., reaction 4 which proceeds to completion)[9] and a comparison of the relative extent of proton and deuteron transfer to stronger bases such as pyridine (e.g., reactions 5 and 6). With sufficiently acidic donors (e.g., D_3O^+ reacting with benzonitrile) protonation occurs on both the ring and the substituent. In this case reaction 4 is observed but does not proceed to completion. In the case of reactions 5 and 6 this situation is clarified by using an equilibrated population whereby several collisions with the aromatic species lead to deuterium transfer to the more basic site in the molecule.



While necessary, it is evident from the data in Table I that ring protonation is not a sufficient condition to observe exchange. The exchange mechanism most likely involves transfer of the labile proton to D_2O forming an activated complex of D_2OH^+ with the aromatic compound. This species dissociates to regenerate the isotopically exchanged reactants. We are currently investigating a range of aromatic compounds including naphthalene, anthracene, and biphenyl as well as a variety of other saturated and unsaturated carbonium ions where the extent of exchange may clarify additional features of the reaction mechanism and provide other interesting structural information.

Acknowledgments. This work was supported in part by the Energy Research and Development Administration under Grant No. AT(04-3)767-8 and by the National Science Foundation under Grant No. NSF-GP-18383.

References and Notes

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(5) Only a single deuterium is exchanged per reaction as evidenced by the total disappearance of a product ion upon ejection of the ion having one less mass unit. Thus in reaction 3, H_2O is never a product.
(6) The decay of $C_6H_6D^+$ in Figure 1 is complicated, with the ion being more abundant at long times than expected for exponential decay. This behavior is attributed to the symmetrical proton transfer process analogous to reaction 4.
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(9) Protonation of anisole on the ring is in accord with the proton affinity of phenol and anisole differing by only ~0.3 kcal/mol (R. T. McIver, private communication). Protonation on oxygen accompanied by a slow intramolecular hydrogen rearrangement might also lead to the observation of reaction 4. The rate of such a process would be very dependent on the internal energy of the ion and thus lead to a distribution of rearranged (reactive) and nonrearranged (nonreactive) species. The kinetics of reaction 4 were not consistent with a distribution of reactive and nonreactive species.

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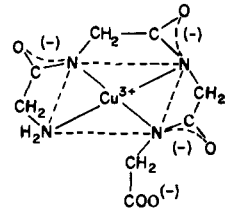
Characterization of a Readily Accessible Copper(III)–Peptide Complex

Sir:

The tripositive oxidation state of copper occurs in a number of compounds, many of which are not stable in aqueous solution. Thus, crystalline $NaCuO_2$ can be prepared[1] but it decomposes in solution in a few seconds.[2] Pulse radiolytic studies[3] have generated Cu(III)-aquo and Cu(III)-amine complexes, which are transient species with rapid rates of decay. Electrochemical preparation of Cu^{III} complexes of macrocyclic amines has been possible in acetonitrile solution but the complexes are unstable, undergoing spontaneous reduction to Cu^{II}.[4] Copper(III) intermediates have been proposed in the chloroiridate oxidation of copper(II)-oligopeptide complexes which leads to peptide oxidation and fragmentation.[5,6] Crystalline, highly insoluble Cu(III)-bis(biuret) and Cu(III)-bis(oxamide) compounds have been characterized.[7,8] Alkyl-substituted bis(biuretato) complexes of Cu^{III} were sufficiently soluble and stable in DMSO to permit measurements of their electronic spectra, NMR spectra, and polarographic properties,[8] but aqueous solutions were not prepared. Recent studies in this laboratory[9,10] of the autoxidation of copper(II)-peptide complexes suggested that relatively long-lived Cu(III)-peptide complexes could be formed in aqueous solution. In the present work we confirm that this is the case and show that with peptide complexes Cu^{III} is a much more accessible oxidation state than had been realized.

Cu(II)-tetraglycine can be oxidized quantitatively to $[Cu^{III}(H_{-3}G_4)]^-$ (I) by $IrCl_6^{2-}$. This oxidation is reversible with pH variations. If the iridium species are removed by anion exchange separation, the resulting solutions of $[Cu^{III}(H_{-3}G_4)]^-$ are slow to decompose in weakly acidic



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media. There are several types of evidence which show that the complex does indeed contain Cu^{III}. (1) The Cu^{II} electronic absorption spectrum is lost and an intense absorption band at 365 nm, characteristic of Cu^{III},[8] is formed as a result of the oxidation. (2) The EPR spectrum characteristic of the d^9 Cu^{II} disappears upon oxidation as expected for a diamagnetic d^8 Cu^{III} complex. The EPR signal slowly reappears as the Cu^{III} complex decomposes. (3) The oxidized complex is sluggish in its substitution reactions. This is characteristic of d^8 square-planar complexes such as the proposed $[Cu^{III}(H_{-3}G_4)]^-$ species. In solution the oxidized complex passes through a Chelex 100[11] ion exchange column which, under the same conditions, will quantitatively remove Cu^{II} from its tetraglycine complex. Similarly, the rate of reaction of acid with the oxidized complex is much slower than with $[Cu^{II}(H_{-3}G_4)]^{2-}$. (4) The proposed Cu^{III} complex is capable of oxidizing ferrocyanide ion, iodide ion, and sulfite ion. (5) The acid decomposition of the oxidized complex regenerates 50–65% of the tetraglycine that was initially present and releases small amounts of O_2. The above experimental observations strongly support the proposal that the metal center rather than the peptide is initially oxidized by $IrCl_6^{2-}$. In the decomposition reactions, however, some of the peptide is oxidized.

The molar absorptivity of the $[Cu^{III}(H_{-3}G_4)]^-$ complex