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Gas-Phase Basicities of Amides and Imidates. Estimation of Protomeric Equilibrium Constants by the Basicity Method in the Gas Phase

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Abstract: The gas-phase basicities of 2-methoxypyridine (**3**), 1-methyl-2-pyridone (**4**), 1-methyl-2-pyrrolidone (**8**), 2-methoxy-1-pyrrolidene (**9**), 1-methyl-2-piperidone (**10**), 2-methoxy-1-piperidene (**11**), 6-chloro-2-methoxypyridine (**12**), and 6-chloro-1-methyl-2-pyridone (**13**) are reported. The importance of considering the relative energies of isomeric bases in assessing structural effects on gas-phase and solution basicities is illustrated by a comparison of **3**–**4**, **9**–**10**, and **12**–**13**. The relative basicities of **3**–**4** and **12**–**13** are used to provide estimates of the protomeric equilibrium between 2-hydroxypyridine (**1**)–2-pyridone (**2**) and 6-chloro-2-hydroxypyridine (**18**)–6-chloro-2-pyridone (**19**) which are in approximate agreement with the independently measured values. The gas-phase basicities of **8**–**9** and **10**–**11** are used to estimate the amide-imidic acid equilibrium of pyrrolidone and piperidone in the vapor. The compensations in energies which are required for successful application of the basicity method for estimation of protomeric equilibria in the vapor and solution are discussed.

It has been recently demonstrated that the position of protomeric equilibrium for the hydroxypyridines–pyridones and their derivatives can change in direction and by orders of magnitude on transfer from solution to the vapor.[2a] Analysis of these differences in terms of solvation and association effects requires reasonably accurate knowledge of the equilibrium constants in both the vapor and solution.[2-4] However, in many cases the minor isomer is undetectable and the equilibrium constant must be estimated indirectly.

The use of basicities of appropriate models to estimate protomeric equilibrium constants was devised by Ebert and has been widely extended, particularly in the field of heterocyclic chemistry.[5,6] The approach is illustrated by the formulas and equations in Scheme I for 2-hydroxypyridine (**1**)–2-pyridone (**2**). The central assumption of the method is that the relative basicities of the model compounds, 2-methoxypyridine (**3**) and 1-methyl-2-pyridone (**4**), can provide an accurate assessment of the relative basicities of **1** and **2**, respectively. The classic work of Albert and Phillips,[7] and of Mason,[8] provides an estimate of the equilibrium constant in water of 900 and a free energy difference of 4 kcal/mol in favor of **2** for the case in Scheme I. Extension of the Ebert approach to comparisons of enthalpies provides an enthalpy difference of 3.4 kcal/mol in favor of **2** under the same conditions.[9] The gas-phase free-energy difference for **1**–**2** is 0.8 kcal/mol in favor of **1**, while the enthalpy difference is 0.3 ± 0.3 kcal/mol in favor of **2**.[1] The larger difference in energy between the isomers in aqueous solution must be due entirely to the difference in solvation energies of the isomers.

More information about the gas-phase stabilities of isomeric

Scheme I

$$K_1 = \frac{[5]}{[1][H^+]} \qquad K_2 = \frac{[5]}{[2][H^+]} \qquad K_T = \frac{K_1}{K_2} = \frac{[2]}{[1]}$$

$$\text{if } \frac{K_3}{K_4} \cong \frac{K_1}{K_2} \qquad K_T \cong \frac{K_3}{K_4}$$

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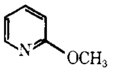
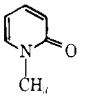
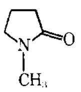
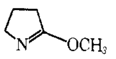
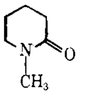
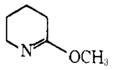
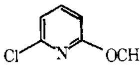
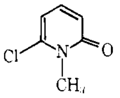
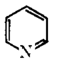
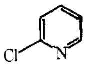
Table I. Free Energies and Heats of Protonation in the Gas Phase and in Water at 25 °C[a]

		gas phase		aqueous solution	
		$-G°_{\text{prot,g}}$, GB[b]	$-\Delta H°_{\text{prot,g}}$, PA[c]	$\Delta G°_{\text{prot,s}}$	$\Delta H°_{\text{prot,s}}$
3		210.5	218.3	−4.17[d]	−3.63[e]
4		209.2	217.0	−0.43[f]	−0.23[g]
8		206.0	213.8	0.5[h]	0[i]
9		215.1	222.9	−8[j]	−8[i]
10		208.5	216.3	0.5[h]	0[i]
11		217.3	225.1	−8[j]	−8[i]
12		205.1	212.9	0.2[k]	~1[k]
13		207.0	214.8	0.5[k]	~1[k]
		209.6[l]	217.4	−7.12[d]	−4.80[f]
		204.0[l]	211.8	−0.98[d]	−0.25[f]

[a] All values in kcal/mol. [b] GBs measured relative to GB(NH_3) = 193 kcal/mol, PA(NH_3) = 202.3 kcal/mol, and GB(CH_3NH_2) = 202.7 kcal/mol, PA(CH_3NH_2) = 211.1 kcal/mol, ref 14. See also ref 4 and J. F. Wolf, R. H. Staley, J. Koppel, M. Taagepera, R. T. McIver, J. L. Beauchamp, and R. W. Taft, *J. Am. Chem. Soc.*, **99**, 5417 (1977). [c] Calculated from GBs by correction for symmetry effects and the entropy of the free proton, ref 14. [d] Reference 13a. [e] References 9 and 11. [f] Reference 13c. [g] Reference 9. [h] Estimated from pK_as of dimethylacetamides and other amides in ref 13a. [i] Estimated from $\Delta G°_{\text{prot,s}}$ and entropy effects for **4** and **3**. [j] Estimated from a pK_a of 5.5 for 2-methyl-2-oxazoline from ref 13a. See also M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J. Chem. Soc., Perkin Trans. 2*, 1295 (1972), and references cited therein. [k] Reference 26. [l] References 11 and 14.

protomers would be desirable. In conjunction with liquid-phase data, such studies provide information needed to gain better understanding of the effect of environment on molecular energies. Moreover, the relative gas-phase stabilities of protomeric isomers can give the fundamental differences in chemical binding energies required to establish unambiguous structure-stability relationships.

The present work details our measurement and use of the gas-phase basicities of methyl amides and methyl imidates to test and extend the basicity approach for estimation of equilibria between amide and imidic acid isomers. In the course of this work we have carried out an analysis of the effect of aromatic unsaturation on the basicities of the amide and imidate functions which shows the importance of considering the relative stabilities of the bases in interpreting substitutional effects on basicities. We also present an analysis of the compensations which are required for the basicity method to succeed both in the gas phase and in aqueous solution.[2a,3,4,9-14]

Results

The relative free energies of protonation in the gas phase, i.e., gas-phase basicities (GB), in Table I have been established by measuring free energies of proton transfer in the gas phase by techniques described in detail elsewhere.[14a,15] The enthalpies of protonation in the gas phase, proton affinities (PA), can be derived from the GBs by taking into account the entropy of the free proton and symmetry changes.[14] The equilibrium data leading to these GBs are summarized in Table II. The equilibrium constants and free energies of proton transfer were measured using both drift cell and trapped ion cell ion cyclotron resonance techniques as indicated (see Experimental Section). In several cases, the approach to proton transfer equilibrium met with some interference from competing condensation reactions of the reactant ions.[15] To establish the error limits in these equilibrium measurements, rates of proton transfer and chemical and physical ion loss were measured under trapped ion cell conditions.[16] The kinetic data indicate that proton-transfer reactions are much more rapid ($k_2 \simeq$ 5–10 × 10^{-10} cm^3 molecule^{-1} s^{-1}, pseudo-first-order $k \simeq$ 2–10 s^{-1}) than ion loss rates ($k \simeq$ 0–1 s^{-1}) for equilibria involving **3**, **9**, **11**, and **12**. The amides, **4**, **8**, **10**, and **13**, however, show slow enough proton transfer rates ($k_2 \simeq$ 2–5 × 10^{-10} cm^3 molecule^{-1} s^{-1}, pseudo-first-order $k \simeq$ 2–5 s^{-1}) and rapid enough ion loss rates ($k \simeq$ 3–6 s^{-1}) under the reaction conditions that equilibrium is not fully achieved for these compounds.[15,16] Kinetic simulations of these reaction schemes indicate that the resultant errors in the GBs may be as large as ±0.5 kcal/mol in such experiments.[16] The lack of close agreement of all the experiments with different reference bases for **8** and **10** constitutes further evidence that equilibria are not fully achieved. In these cases, special care was taken to confirm the equilibrium measurements with double resonance experiments, which are generally accurate to ca. ±2 kcal/mol.

Discussion

In order to appreciate why the basicity method provides

Table II. Experimental Free Energies for Proton Transfer in the Equilibria $AH^+ + B = BH^+ + A$[a]

A	B	$\Delta G°$ [b]	GB(B)[c]
3	Me_2NH	$+1.3^e$	209.3
3	pyridine	$+0.9^e$	209.6
3	2-thiomethylpyridine	-0.7 ± 0.1^e	211.2
4	*sec*-$BuNH_2$	$-0.0 \pm 0.2^{d,f}$	209.1
4[j]	Me_2NH	$+0.15^{f,i}$	209.3
8	3-bromopyridine	$+1.6 \pm 0.2^{d,f}$	205.5
8	$EtNH_2$	$+0.25 \pm 0.2^{d,f,i}$	205.7
8	*n*-$PrNH_2$	$-1.6 \pm 0.8^{d,f,g}$	207.1
9	piperidine	$+0.8 \pm 0.1^d$	214.2
9	3,5-dimethylpyridine	$+0.2 \pm 0.1^d$	214.7
9	Me_2NEt	$-0.6 \pm 0.1^{e,i}$	215.8
10	*i*-$PrNH_2$	$+0.4 \pm 0.1^{d,f}$	208.0
10	*i*-$BuNH_2$	$+0.4 \pm 0.1^{d,f,h}$	208.1
10	*n*-$amylNH_2$	$+0.7^{d,f,k}$	208.3
10	*sec*-$BuNH_2$	$-0.6 \pm 0.1^{d,f}$	209.1
11	*n*-Pr_2NH	$+1.4 \pm 0.1^d$	215.9
11	*i*-Pr_2NH	-0.5 ± 0.2^d	217.7
11	$MeNEt_2$	-0.5 ± 0.1^d	218.2
12	2-bromopyridine	$+0.21 \pm 0.03^e$	204.8
12	$CH_2{=}CHCH_2NH_2$	$+0.08 \pm 0.04^e$	205.1
12	$EtNH_2$	-0.3 ± 0.1^e	205.7
13	$EtNH_2$	$+1.15 \pm 0.1^{f,i}$	205.7
13	*n*-$PrNH_2$	$+0.1 \pm 0.1^f$	207.1

[a] All values in kcal/mol. [b] Error limits indicate reproducibility of multiple runs at different pressure ratios of A and B. Measured in a trapped ion cell unless otherwise indicated. Actual errors may be larger, up to ±0.5 kcal/mol, for **4, 8, 10**, and **12.** [c] Values derived from ref 14a and 11 but corrected for a newly assigned value for NH_3 (see footnote *b*, Table I). [d] Proton transfer rates measured by ion ejection techniques (ref 16). [e] Measured in a drift cell at high pressues ($>10^{-4}$ Torr). [f] Slow proton transfer and rapid loss rates could lead to errors as large as ±0.5 kcal/mol owing to nonequilibrium conditions. [g] Negative double resonance signal detected for $AH^+ \rightarrow BH^+$. [h] Positive double resonance signal detected for $AH^+ \rightarrow BH^+$; negative double resonance signal detected for $BH^+ \rightarrow AH^+$. [i] Negative double resonance signals for $AH^+ \rightarrow BH^+$ and $BH^+ \rightarrow AH^+$. [j] Additional double resonance experiments for compound **4** with *i*-$PrNH_2$, MeNHEt, and Me_3N determine that $208.0 < GB(\mathbf{4}) < 211.8$. [k] Negative double resonance signal detected for $BH^+ \rightarrow AH^+$.

useful estimates of both gas- and aqueous-phase protomeric equilibrium constants, a detailed analysis of the factors affecting the acid-base equilibria involved is necessary. The gas-phase basicity data also provide information about substituent effects on the stabilities of some of these heterocyclic ions.

Gas-Phase Basicities. The GBs of *N*-methyl-2-pyridone (**4**) and *N*-methylpiperidone (**10**) of 209.2 and 208.5 kcal/mol, respectively, are about that expected for simple amides from the GBs of 201.6 kcal/mol for dimethylformamide and of 205.3 kcal/mol for dimethylacetamide.[17,18,19] The imidates **11** and **3** are also reasonably close to those of models. Thus, **11** has a GB of 217.3 kcal/mol, 5 kcal/mol higher than that of the imine $CH_3CH{=}NCH_2CH_3$,[20] while 2-methoxypyridine (**3**) is at 210.5 kcal/mol, 1 kcal/mol higher than that of pyridine.

A simple comparison of the PAs of **11** and **3** could be taken to suggest that the additional two ring double bonds in **3** lower its PA relative to that of **11** by a 7 kcal/mol inductive effect of the sp^2 centers in the ring. However, if **10** and **4** are compared directly, this inductive effect seems to be absent. Like most analyses of relative basicities, such a comparison does not take into account structural effects on the relative stabilities of the neutral bases, and can be misleading.

For the isomer pairs **3-4** and **10-11**, the relative gas-phase stabilities are known and therefore a more complete analysis than usual is possible. The enthalpic relationships between the isomeric neutral amides **10** and ethers **3** and **4** are derived from experimental gas-phase enthalpy data for reactions 1 and 2, respectively.[3,10]

$$\mathbf{11} \rightleftarrows \mathbf{10} \quad \Delta H°_g = -14.6 \pm 1.7 \text{ kcal/mol} \qquad (1)$$

$$\mathbf{3} \rightleftarrows \mathbf{4} \quad \Delta H°_g = -8.0 \pm 2.3 \text{ kcal/mol} \qquad (2)$$

$$\mathbf{12} \rightleftarrows \mathbf{13} \quad \Delta H°_g = +0.3 \pm 3.7 \text{ kcal/mol} \qquad (3)$$

From these values and the relative PAs, Scheme II can be constructed. The N-methylated cation **14** is found to be 6 kcal/mol more stable than the isomeric O-methylated ion **15** from the thermodynamic cycles summarized in Scheme II. The relative neutral stability data are useful in avoiding the pitfall of attributing the 9 kcal/mol higher PA for **11** vs. **10** to a greater stability of the cation **15** relative to **14.** In fact, the energy difference between **14** and **15** is seen to be 8 kcal/mol less than the difference between **10** and **11** with **14** the more stable by 6 kcal/mol. The opposite order might have been assigned from a simple comparative approach. Similarly, the cations **6** and **7** differ in stability by 7 kcal/mol, with **7** favored, but in this case **4** is known to be only 8 kcal/mol more stable than **3**. Since **14-15** and **6-7** differ by the same bond interchanges, the correspondence in these energy differences is quite reasonable.

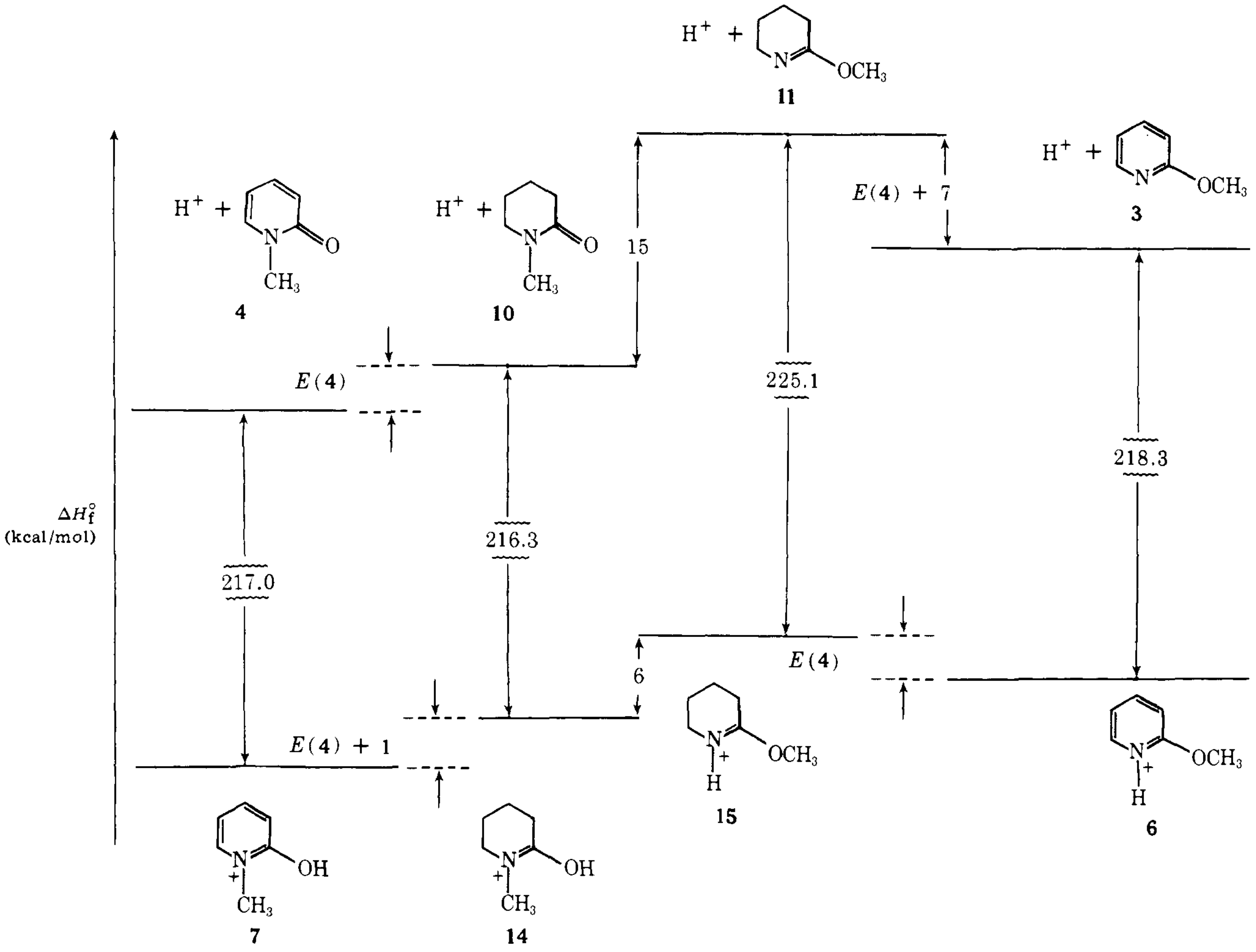
The source of the apparent differential effect of the double bond on the basicities of **3** vs. **11** and **4** vs. **10** is clarified by the energy relationships in Scheme II. The dotted-line energy relationships in Scheme II show an arbitrary assignment of a lower energy for **4** relative to **10** by an energy attributable to the energy of two double bonds and an aromatic resonance stabilization energy for **4**, $E(\mathbf{4})$.[21] The methoxypyridine **3** then is stabilized relative to **11** by 7 kcal/mol more resonance energy than is **4** relative to **10.** Since the pyridinium ions **6** and **7** have electronic structures comparable to **3**, they could also reasonably be assumed to have resonance energies of $E(4) + 7$ kcal/mol, relative to **15** and **14,** respectively. The differences in energies between **6** and **15** and **7** and **14** are only $E(4)$ and $E(4) + 1$ kcal/mol, however, apparently because of a 7 kcal/mol inductive destabilization effect in both **6** and **7** relative to **14** and **15** resulting from the added ring double bonds.[22] In the absence of information about the energies of the neutral species, the apparent difference in the effect of the formal double bonds on the basicities of **3** and **4** relative to **11** and **10** is inexplicable.

The desirability of complete analyses of relative perturbational effects on basicity is again revealed by comparison with the usual and simpler analysis of substituent effects from basicity data alone for the cases of **3-4** and **12-13.**

The chlorine substituent effects on the PAs of **12** vs. **3** and chloropyridine vs. pyridine show satisfyingly similar values of 5.4 and 5.6 kcal/mol, respectively.[11,14] This seems to be a simple inductive effect in the ions, while comparison of the PAs of **13** and **4** appears to show only a small 2.2 kcal/mol inductive effect in ion **16.**

The effect of a chloro substituent on the neutral and cationic gas-phase enthalpies in the pyridine system may be derived from the gas-phase enthalpies of reactions 2 and 3[10b] and from the PA data in Table I. Scheme III shows these relationships. The chloro substituent shifts the energy for **12-13** by 8.3 kcal/mol in favor of **12** relative to **3-4**. If this 8 kcal/mol effect is attributed to an *X* kcal/mol stabilization of the polar resonance contributor for **12** and a *Y* kcal/mol destabilization of the polar amide contributor to **13,**[10] as shown in Scheme III, then the cation **16** appears to be destabilized inductively by $Y + 2$ kcal/mol relative to **7**, but **17** appears to be destabilized by $5 - X$ kcal/mol. While the absolute magnitudes of these effects are unknown, the inductive destabilization effect in the N-methylated ion **16** is 5 kcal/mol larger than in the O-

Scheme II. Relative Ionic and Neutral Enthalpies in the Gas Phase Showing the Relative Perturbational Effects of Unsaturation



Scheme III. Relative Ionic and Neutral Enthalpies in the Gas Phase Showing the Perturbational Effect of Chloro Substituents

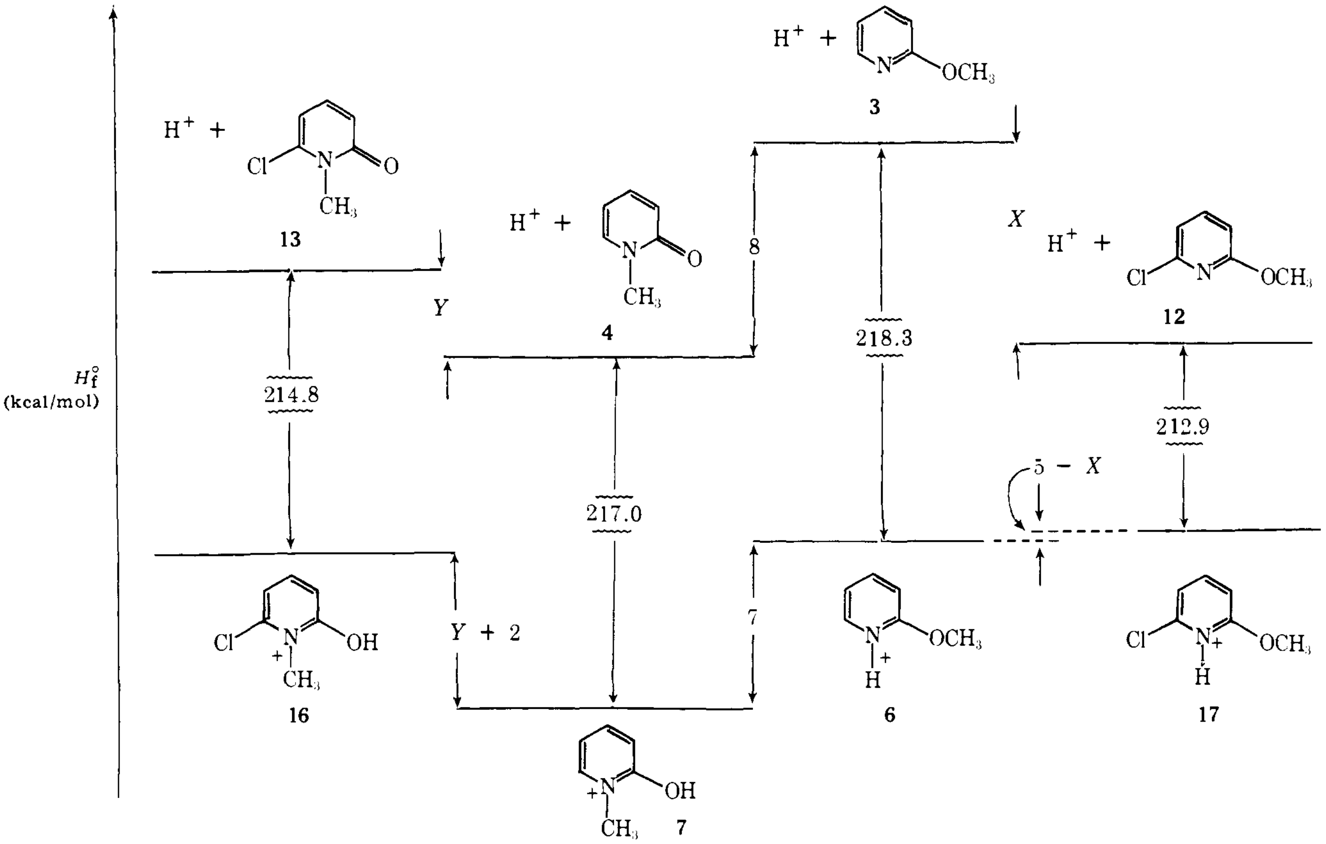


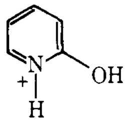
Table III. Heats of Solvation of Ions and Neutral Bases in Water at 25 °C[a]

	$-\Delta H°_g(BH^+)$[b]	$-\Delta H°_g(B)$[c]
3	65.5	10.4
4	70.3	17.3
10	72[d]	18.6
11	66[d]	13.7

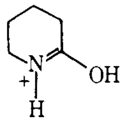
[a] All values in kcal/mol. [b] Calculated from $\Delta H°_g(BH^+) = PA + \Delta H°_{prot,s} + \Delta H°_g(B) + \Delta H°_g(H^+)$, using $\Delta H°_g(H^+) = 269.8$ kcal/mol. See ref 14b. [c] Reference 9. [d] Derived from estimated values of $\Delta H°_{prot,s}$ (Table I).

methylated ion **17**. This difference could be attributed to the expected shift of positive charge in these ions toward the site of methyl substitution, since the methyl groups serve as a source of charge stabilization via polarization.[14] The positive charge in **16** would then be closer to the chloro substituent than in **17**, and the inductive effect in **16** should be correspondingly larger.

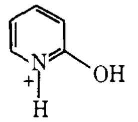
From consideration of Scheme II ions **5** and **18** can be seen



5



18



19

to be more stabilized by N-methylation than by O-methylation by 7 and 6 kcal/mol, respectively. The gas-phase stability data for the chlorinated pyridinium ions in Scheme III, however, indicate that N-methylation of **19** is preferred by only 2 kcal/mol. These effects will be seen to be important in the subsequent analysis of the basicity method.

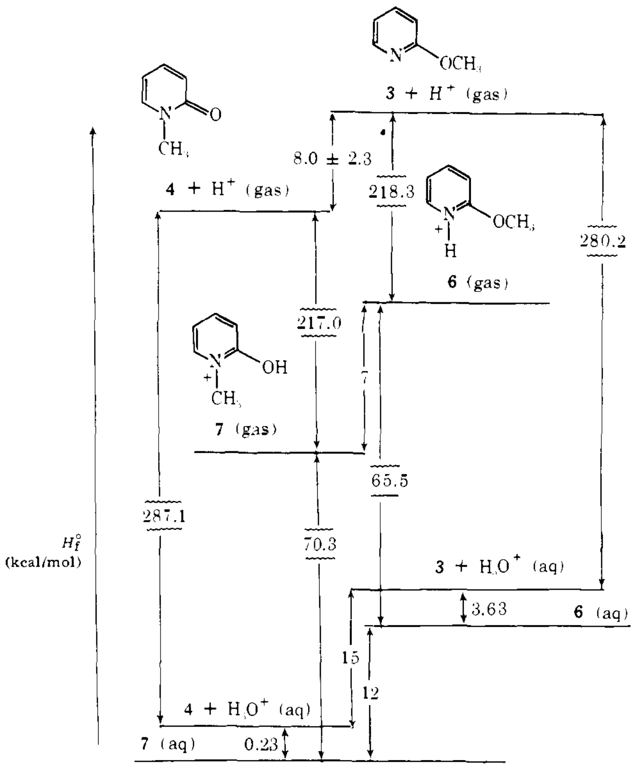
Solution-Phase Basicities. Applications of the Ebert approach to estimates of protomeric equilibria have been almost totally based on solution basicities.[4,6] Since we will relate the gas-phase results to aqueous solutions, consideration needs to be given to the thermodynamics of such a transfer.

From the aqueous heats of solution of the liquid bases[9] **3**, **4**, **10**, and **11** and their heats of vaporization,[10] the heats of solvation, $\Delta H°_S(B)$, from the gas phase to water can be derived. From these values, shown in Table III, the aqueous heats of protonation, $\Delta H°_{prot,s}$,[9,13] and the gas-phase proton affinities in Table I, a complete thermodynamic cycle can be constructed.[14b] The aqueous heats of solvation for the free ions, $\Delta H°_s(BH^+)$, then can be derived. These data are shown in Table III and represented graphically in Schemes IV and V for the isomer pairs **3**-**4** and **10**-**11**. The enthalpies of reactions 1 and 2 in the gas phase[3,10] permit a complete comparison of the enthalpies of all of the ionic and neutral species in these systems.

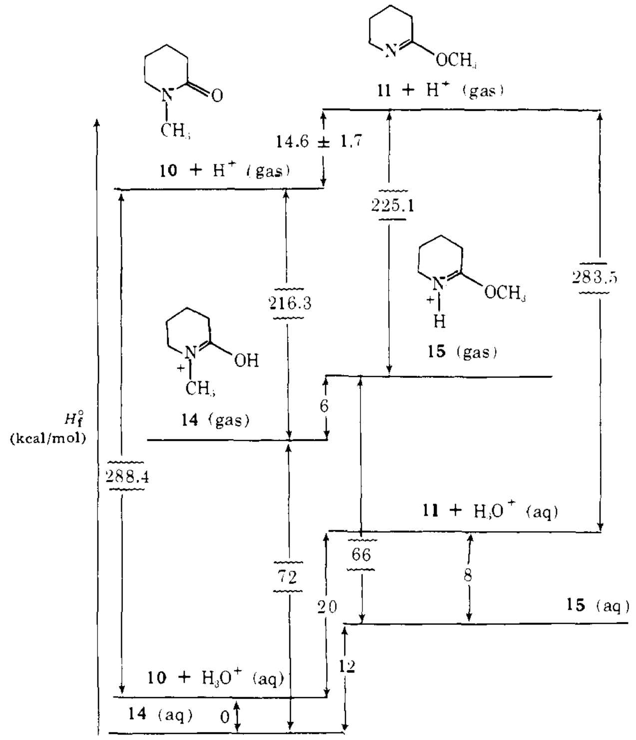
As expected from solvation theory, $\Delta H°_S(B)$ is 7 kcal/mol more exothermic for the pyridine **4** than for the pyridine **3**, because of the higher dipole moment of **4**.[2a,3,23,24] Similarly, the $\Delta H°_s(B)$'s for **10** and **11** differ by 5 kcal/mol for the same reason (Table III).

From Schemes IV and V, the N-methylated cations **7** and **14** are both seen to be 6-7 kcal/mol more stable than their corresponding O-methylated cations **6** and **15** in the gas phase. In aqueous solution, however, this difference increases to 12 kcal/mol in both cases. Thus, the neutral solvation terms and the ionic solvation terms run closely parallel in the saturated and unsaturated systems. In both cases, the neutral *N*-methyl form is more strongly solvated by 5-7 kcal/mol, and the N-methylated cations are more exothermically solvated by 5-6 kcal/mol.[25] The saturated ions **14** and **15** are both 1-2 kcal/mol more exothermically solvated than their unsaturated analogues. This difference, though small, is explicable as the result of somewhat lower charge density and correspondingly weaker solvation in the more delocalized unsaturated cations **6** and **7**.

Scheme IV. Gas-Phase and Aqueous Thermodynamic Data for 2-Methoxypyridine and *N*-Methyl-2-pyridone at 25 °C



Scheme V. Gas-Phase and Aqueous Thermodynamic Data for *N*-Methyl-2-piperidone and 2-Methoxy-1-piperidene at 25 °C



Since $\Delta H°_g(B)$ and $\Delta H°_g(BH^+)$ *both* decrease by about 5-7 kcal/mol in going from **10** to **11** or **4** to **3**, there is very little change in the relative basicities of **10** and **11** or **4** and **3** on transfer from the gas phase to aqueous solution. The imidate **11** is 8-9 kcal/mol more basic than the amide **10** in both gas

Table IV. Free Energies and Enthalpies for Gas-Phase and Aqueous Tautomeric Equilibria[a]

tautomers	$\Delta G°_g$	$\Delta G°_{g,est}$[b]	$\Delta G°_{aq}$	$\Delta G°_{aq,est}$[b]
1⇄**2**	0.8[c]	−1.3	<−2[c]	−3.7
18⇄**19**	1.1[c]	1.9	−1.8[c]	−0.3
20⇄**21**		−8.8		
22⇄**23**		−9.1		

[a] All values in kcal/mol. [b] Estimated by the basicity method. [c] Reference 3.

phase and in solution. The methoxypyridine **3** is only 1.3 kcal/mol more basic than the pyridone **4** in the gas phase and 3.4 kcal/mol more basic in aqueous solution. In contrast to **3** and **4**, the chlorinated methoxypyridine 13 is 2 kcal/mol less basic than the pyridone **12** in the gas phase. Solvation effects enhance the basicity of **13** slightly, as with **3**, such that the solution basicities of **12** and **13** are nearly equal (Table I).

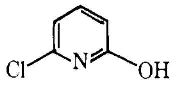
Estimation of Protomeric Equilibria by the Basicity Method. The central assumption of the Ebert method, that the relative basicities of the *N*-methyl and *O*-methyl model compounds approximate those of the NH and OH tautomers, is expressed in terms of free energies for the case of **1**–**2** in eq 4. Rearrangement of eq 4 to expression 5 shows the assumption of the approach to be that compensation of substitution arises from the cancellation of the similar NCH_3 and OCH_3 substitutions in the sets **3**–**4** and **6**–**7**. Expression 6 makes the comparison in terms of the methylation energy differences for **6**–**7** being compensated by similar bond changes for **1**–**3** and **2**–**4**. Similar enthalpy expressions can be constructed.[9] For the gas-phase data, only relative energies need to be considered, whereas, for comparison in the liquid phase, energies of solvation would be included.

$$(G°_1 - G°_5) - (G°_2 - G°_5) = (G°_3 - G°_6) - (G°_4 - G°_7) \quad (4)$$

$$(G°_1 - G°_2) = (G°_3 - G°_4) - (G°_6 - G°_7) \quad (5)$$

$$(G°_1 - G°_3) - (G°_2 - G°_4) = (G°_7 - G°_6) \quad (6)$$

From the data of Table I and gas-phase tautomeric equilibria measurements extension of the basicity approach to the gas phase may be tested.[2a,3,4] Comparisons of gas-phase thermodynamic data for 2-hydroxypyridine (**1**) and 2-pyridone (**2**) are summarized in Table IV. From the difference in GBs for **3** and **4**, a $\Delta G°_{g,est}$ of −1.3 kcal/mol is estimated for **1**–**2**. This compares with the observed $\Delta G°_g$ of 0.8 kcal/mol, a discrepancy of 2 kcal/mol. It should be noted that $\Delta H°_g$ for **1**–**2** is −0.3 kcal/mol, so the possibility of a significant entropy effect which would upset the correlation can be discounted.[26] The gas-phase basicities of **12** and **13** may similarly be used to test the approach. As shown in Table IV, a $\Delta G°_{g,est}$ of 1.9 kcal/mol is obtained for **20**–**21** and this value compares well with the 1.1 kcal/mol experimentally observed free energy for this reaction.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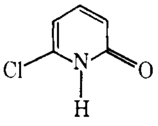
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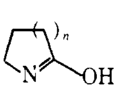
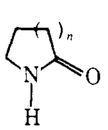
The agreement of these estimated and observed equilibrium constants to within 2 kcal/mol suggests that the basicity method can be applied to the estimate of similar gas-phase equilibria. In that case the data in Table I may be used to estimate the protomeric equilibria for **22**–**23** and **24**–**25** as 9 kcal/mol in favor of the amides in the gas phase.[4] This result compares favorably with the estimate of 7 kcal/mol for **22**–**23**[2a,3] but seems in disagreement with the values of 15 and 25 kcal/mol for **24**–**25** recently estimated by a modified basicity method and by MINDO calculation.[27]


22, *n* = 1
24, *n* = 0


23, *n* = 1
25, *n* = 0

For the Ebert method to be applicable in solution as well as in the gas phase, appropriate solvation energies must cancel so that eq 4–6 continue to hold. For the 2-hydroxypyridine-2-pyridine system, this requires that the enthalpies of solvation[9] be related as indicated in eq 7. Substitution of the known solvation energies of **3**, **4**, **6**, and **7** from Scheme IV and Table III into the equation

$$[\Delta H°_s(1) - \Delta H°_s(2)] \simeq [\Delta H°_s(3) - \Delta H°_s(4)] - [\Delta H°_s(6) - \Delta H°_s(7)] \quad (7)$$

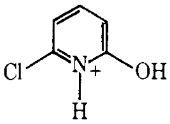
$$[\Delta H°_s(1) - \Delta H°_s(2)] \simeq 2 \text{ kcal/mol}$$

gives a predicted value of 2 kcal/mol for the effect of water solvent on the enthalpy for **1**–**2** in favor of **2**. This solvation effect may be low and can be tested only qualitatively but is in the proper direction to explain the observation that **2** is the favored protomer in water. The solvation effects for the amide-imidate pair **10** and **11** have been less accurately determined from Scheme V. They likewise show that the amide tautomer **10** and its conjugate acid **14** have larger heats of solution than **11** and **15** by 5 and 6 kcal/mol, respectively, suggesting that the effect of solvation on the protomeric equilibrium **22**–**23** is likely to be small.

Only for the 6-chloro-2-pyridone can the effect of solvent on a protomeric equilibrium be accurately evaluated experimentally. In this case, the solvent effect is 2.9 kcal/mol in favor of the amide forms. The basicity method has been applied to this equilibrium in aqueous solution and in the gas phase, and it leads to a predicted solvent effect of 1.6 kcal/mol in favor of the amide protomer.[28] Useful agreement is found in this case.

The success of the Ebert method in predicting gas-phase protomeric equilibria can be conveniently discussed in terms of the bond-energy changes required to fit eq 6. Thus, the difference in methylation enthalpies of the neutral protomers **1** and **2** in Scheme I is 8 kcal/mol (see Scheme II and Table IV),[29] which is nearly equal to the enthalpy difference of 7 kcal/mol between the O- and N-methylated ions **6** and **7** in Scheme II. These methylation energy differences are not significantly altered by the presence of the positive charge in **5**.[30] This maintenance of N- and O-methylation energy differences in the neutral and cationic species means that the *N*-methyl and *O*-methyl bond energy differences are canceled by the comparisons used in the basicity method of estimating protomeric equilibria. It is this cancellation that fundamentally accounts for the success of the approach. This compensation is likely to remain true for pyrrolidone and piperidone as well, so the predicted gas-phase energies for **22**–**23** and **24**–**25** in Table IV should be reasonably accurate.

Interestingly, the data in Table IV and Scheme III show that the methylation enthalpies of **20** and **21** show a difference of only 1 kcal/mol in favor of N-methylation. However, the Ebert method still is valid because this small difference in methylation energies is similar to the 2 kcal/mol difference in methylation energies for the chlorinated ion **25**, as required by eq


25

7.[31] Whether this compensatory energy effect is fortuitous or general can only be determined as further data become available. For the present, the cancellation of the substituent effect seems encouraging for further investigation of the method.[4-9]

Conclusions

The basicity method devised by Ebert for the estimation of protomeric equilibria has been widely used but not extensively tested quantitatively.[4-8,32] The present results may be taken to suggest that the gas-phase basicities of appropriate *N*-methyl amides and *O*-methyl imides models provide estimates of protomeric equilibria for corresponding amides–imidic acids which are reliable within a few kilocalories per mole. Moreover, this analysis shows that the compensations of solvation energies required for application of this method to solution are also as required for the two cases considered. This approach will probably continue to be most useful for highly biased cases where errors of a few kilocalories per mole are tolerable because the basicity approach is the only method presently available for the estimation of protomeric equilibria.

Experimental Section

Apparatus. Experiments were performed on two ion cyclotron resonance spectrometers: a drift-cell spectrometer[33] and a trapped-ion spectrometer.[34] In the drift-cell ICR, ions are formed by electron impact and are modulated with a square wave on a grid located between the filament and the cell.[15] This facilitates phase-sensitive signal detection, greatly enhancing the signal to noise ratio. Electron trap currents are regulated during the course of an experiment and usually (especially at high neutral concentrations) kept below 1×10^{-9} A to prevent space-charge phenomena which could lead to differential ion loss in the cell. The absolute pressures are measured on a Baratron capacitance manometer connected to the vacuum chamber housing the cell.

In the trapped-ion cell, ions are formed by a pulsed electron beam. The width of the initial gate pulse is usually kept at about 5 ms, but may be shortened at high neutral concentrations to prevent an overabundance of ions, which leads to differential ion loss through space-charge effects. After this initial pulse, ions are trapped in the cell by a combination of magnetic and electric field components. After a delay time, a detection plate (connected to a marginal oscillator) is pulsed to bring ions of the desired mass into resonance. This delay time is varied and the ion intensity is monitored with respect to time. After some 500–1500 ms, a quench pulse is applied to the cell, driving all the ions from the reaction chamber. The neutral pressures are measured on an ionization gauge, which is calibrated at high pressures using a Baratron capacitance manometer.

Double Resonance Experiments. Double resonance experiments can be performed on either spectrometer. In such experiments on the drift cell, the neutral bases, A and B, are admitted into the cell at pressures of about 2×10^{-5} Torr of each. (Higher pressures cause peak broadening and lower the mass resolution.) The bases are protonated by their parent and fragment ions. The single resonance intensity of the protonated base is monitored while an irradiating field sweeps over the cyclotron frequency of the other protonated base. The change in intensity of BH^+ with amplitude of the irradiating voltage thus measures the rate of change in k_1 with energy for reaction 8. The intensity of BH^+ when irradiating AH^+ may (1) decrease, indicating that the reaction is taking place at thermal energies and is therefore exothermic or thermoneutral; (2) increase, indicating that the enthalpy of the reaction is either exothermic or endothermic; or (3) remain unchanged in intensity, indicating that the rate is energy independent, or that the reaction does not occur at all.[35] The positive double resonance signal may be examined further by increasing the amplitude of the irradiating voltage to a point where AH^+ is ejected from the cell. If the intensity of BH^+ then falls below its intensity with no irradiation of AH^+, the reaction can be considered exothermic or approximately thermoneutral.[33] If, when AH^+ is being ejected, the intensity of BH^+ falls only to its value when no irradiating field is applied, it can be inferred that the reaction only occurs when energy is added to the system, and the reaction is endothermic. Double resonance experiments with molecules of known GB indicate that the change from negative to positive double resonance signals occurs over about a 2 kcal/mol range of base strengths.

$$AH^+ + B \overset{k_1}{\rightleftarrows} BH^+ + A \qquad (8)$$

Drift Cell Equilibrium Measurements. The technique used to measure equilibrium constants on the drift-cell ICR mass spectrometer has been discussed in detail elsewhere.[14a,15] To study the equilibrium reaction 8, the neutral bases, A and B, are admitted into the cell at total pressures of 3-8 $\times 10^{-4}$ Torr. The pressure ratio A/B is varied over as wide a range as possible (the ratios being limited by kinetic and instrumental restrictions). The ion intensities, AH^+ and BH^+, are measured at constant field (typically 14 kG), the marginal oscillator detection frequency being set at the respective cyclotron frequencies of AH^+ and BH^+. The equilibrium constant and free energy for reaction 8 can then be calculated from the ion intensities and neutral pressure ratio.[15]

Trapped Ion Cell Equilibrium Measurements. The technique used to measure equilibrium on the trapped ion cell has been described in detail elsewhere.[35] The total pressure of the neutral bases in a typical equilibrium experiment was in the low 10^{-6} Torr pressure region. The variation in the ion intensities AH^+ and BH^+ with time gives a good indication as to whether or not equilibrium has been achieved. At long reaction times the ratio of the two ionic species remains constant if equilibrium has been reached. All experiments were carried out at constant magnetic field (typically 15–17 kG) to eliminate the possibility of differential ion loss due to inadequate trapping at low magnetic fields. Rate constants for the forward and reverse proton transfer reactions have been obtained by pulsed ion ejection techniques[16,35] using a double-resonance rf pulse of 3-V peak to peak amplitude at the frequency of one of the reactant ions. The kinetic data are treated using a kinetic simulation technique[16] in cases where there is rapid ion loss.

Acknowledgment. We are very grateful to the National Science Foundation for support of this work.

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(19) Interestingly, decreasing the ring size of **10** by one methylene group to *N*-methylpyrrolidone (**8**) causes a 2.4 kcal/mol decrease in GB; that increase is significantly larger than the change of 1.1 kcal/mol between the PAs of pyrrolidine and piperidine.[14a] Both imidates **9** and **11** show GBs 9

kcal/mol higher than those of their corresponding amide isomers **8** and **10**, and the increase in PA for increasing the ring size from five to six members is 2.3 kcal/mol. The unusually large stabilizing effect of the extra methylene group in **10** and **11** could be attributed to a hyperconjugative delocalization of the positive charge into the ring unavailable to the piperidinium ion. These PA effects have been interpreted in the usual way in terms of changes in ionic stabilities rather than changes in neutral stabilities. This is usually the only approach available in the absence of information about structural effects on the stabilities of the neutral species. For an alternative approach which is useful if the relative stabilities of the bases are available, see the text.

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(25) The N-methylated and O-methylated cations should have similar ionic sizes, so this difference in solvation energy appears to be the result of preferential specific solvation for the proton bonded to positive oxygen over that for a proton bonded to a positive nitrogen. It is known, for example, that the hydronium ion is better solvated in water than the ammonium ion by some 14 kcal/mol as a result of stronger H bonding due to increased charge density at O vs. N.[14b]

(26) Entropy terms in gas-phase proton-transfer reactions are generally very small and can be neglected for systems considered here.[14] Therefore $\Delta H^\circ_{g,est}$ and $\Delta G^\circ_{g,est}$ from the Ebert equation are the same in the present cases.

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(30) Apparently the charge in **5** is distributed sufficiently equally between N and O that the polarization stabilization by the methyl group is the same at either site.

(31) Thus, the effect of chlorination is to produce an inductive effect making N-methylation relative to the pyridone **1** 7 kcal/mol less favorable than O-methylation relative to **2** and to produce a compensating 5 kcal/mol inductive effect in the ion **25** making N-methylation less favorable than in **5** relative to O-methylation. This small methylation energy difference may result because the inductive stabilization of the polar resonance contributor to **12** and destabilization of the polar contributor to **13** is much less significant for the unmethylated species **18** and **19**. In fact, the close correspondence between ΔG°_g for **1–2** and **20–21** in Table IV could be taken to indicate little or no such inductive effect in the latter pair. The methyl groups in **12** and **13** seem to be sufficiently capable of stabilizing positive charge in the dipolar resonance contributors in the gas phase to produce this net 8 kcal/mol inductive effect. Such an effect is found in other systems: ref 14.

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Rearrangements among Gas-Phase Ions of C_8H_8 Isomers. A Photodissociation-Spectroscopic Investigation

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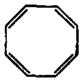
Abstract: Photodissociation spectroscopy is used to explore the structures of the $C_8H_8^{+\cdot}$ and $C_8H_9^+$ ions obtained in gas phase from styrene, cyclooctatetraene, and barrelene. The $C_8H_8^{+\cdot}$ ions do not interconvert on a time scale of seconds, and the parent ions of styrene and barrelene appear to retain the neutral structure, while the structure of the COT parent ion is uncertain. The $C_8H_9^+$ ions obtained by H_3O^+ protonation all have the same spectrum, and are assigned as having the styryl ion structure.

Introduction

The technique of photodissociation spectroscopy is ideally suited to investigating rearrangement processes in many gas-phase ions.[2a] It was recently shown[2b] that the $C_8H_8^{+\cdot}$ parent ions obtained from styrene (I) and from cyclooctatetraene (COT, II) do not interconvert, and that the styrene ions, at least, probably retain the structure of the neutral. The preparation of a sample of bicyclo[2.2.2]octa-2,5,7-triene (barrelene, III)[3] has provided a chance to extend our knowledge of rearrangements on the $C_8H_8^{+\cdot}$ potential surface. In addition, the recent demonstration[4] of rearrangement of protonated hexamethyl(Dewar benzene) to the hexamethylbenzene structure suggests the possibility that rearrangements are facile among protonated hydrocarbon isomers, and it was of interest to elucidate rearrangement processes on the $C_8H_9^+$ surface. Accordingly, photodissociation spectra were obtained for both the parent ions and the protonated parent ions of all three of these C_8H_8 isomers, in order to compare and identify the ion structures.


I


II


III

Experimental Section

The photodissociation spectra were taken with ICR detection, using a pulsed mode of ICR operation, which has been described.[4] Normally the ions were trapped and irradiated for 5 s before the detection pulse, although some checks were made to be sure that the measured rates were independent of trapping time. In looking at the parent ions, neutral gas pressures of $1-2 \times 10^{-8}$ Torr (indicated at the ion pump) were used, at an ionizing electron energy near 15 eV. The protonated molecules were observed by introducing 3×10^{-7} Torr of water at electron energies in the 11–15 eV range. H_3O^+ is formed rapidly at this pressure, and protonation of the hydrocarbon is presumably

0002-7863/79/1501-1368$01.00/0