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Substituent and Solvation Effects on Gas-Phase Acidities[1]

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Abstract: The structure of a wide variety of Brønsted acids is related to their intrinsic gas-phase acidity. Polarizability is a major factor in the gas phase in the effect of all substituents on anionic centers, often reversing the "polar" effect assigned from solution phase reactivities of both electron-donating and electron-withdrawing groups. Methyl groups interact with anionic centers by a mixture of polar, polarizability, and hyperconjugative interactions. Solvation by dipolar aprotic solvents results in little compression of relative acidities, but water as solvent compresses many substituent effects to one-quarter of their intrinsic value.

Elucidation of the relationship between structure and reactivity has long been a chief goal of physical organic chemistry. The role of solvation in this endeavor has been an uncertain one, since modern structural concepts, though they provide a good framework for analysis of intramolecular interactions between substituent and reactive site, do not give very precise microscopic descriptions of the structure of the medium about the reactants. This is part of the reason that many structure–reactivity correlations deal only with intrinsic structure of the reagents, for which a good mental picture is available, and regard such poorly known factors as the substituent's influence on solvation of the reactive site, or variation of a substituent's intrinsic effect with changing nature of the solvation, as a second-order perturbation. This is certainly justifiable in a great many cases, as the success of linear free-energy relationships attests.[3] It is still surprising, however, when this assumption about the relative importance of intrinsic structure vs. solvation breaks down, as in the results of Brauman and Blair in 1968[4] where solvation was found to reverse the order of intrinsic acidity of the simple aliphatic alcohols.

Brønsted acidities are an excellent choice as a reaction type for investigation of intrinsic structure–reactivity relationships in the absence of solvation. Any molecule containing a hydrogen atom is potentially a Brønsted acid, so a given reaction can be observed with a tremendous variety of substituents. Proton transfer is one of the most conceptually simple reactions known. In the gas phase, there is no solvent leveling[5] to place bounds on the range of reactivities observable. There is also no compression[6] of substituent effects due to the solvent providing part of the stabilization for high-energy species, thus reducing the fraction and absolute magnitude of the intrinsic substituent effect. This allows for observation of substituent effects often too small to measure in solution. In this paper, the body of gas-phase acidity data,[1] measured by pulsed ion cyclotron resonance spectrometry, is analyzed in terms of intrinsic substituent effects. Solvation effects are inferred by differences with known solution acidities.

Results and Discussion

The gas-phase acidities analyzed in this paper are taken from Tables I and III of ref 1 unless otherwise stated. The relative values are believed to be accurate to ±0.2 kcal/mol, and the absolute values to ±2.0 kcal/mol.

Alkyl Effects. In all cases in Table I, increasing the size of the alkyl group is acid strengthening, due to polarizability interactions.[4,7] The effect falls off with distance, although the variety of structures, uncertainty of the exact charge distribution in the delocalized anions, and uncertainty of the mechanism of the interaction[8] prevent testing of the theoretical $1/r^4$ nature of the decrease.[9] The smaller effects in the thiols compared with the alcohols can either be due to this distance effect with the longer C–S bond ($\sim 1/r^{2.4}$ for Me vs. Et), or to a saturation effect[10] where the inherently more stable RS^- anion is less in need of the ion-induced dipole stabilization than the RO^- anion. A saturation effect is also observed for α-methyl substitution into methanol and methanethiol: each successive methyl has a smaller effect. This is not seen for β-methyl substitution into ethanol or 2,2-dimethyl-3-butanol where every new β-methyl increases acidity by a constant amount. Examination of molecular models reveals that a β-methyl in certain configurations can approach more closely to the oxyanion than an α-methyl can, and may as a result be more effective at stabilization due to polarizability, though farther away in bonding terms. The relative acidities of the aliphatic alcohols have been explained in terms of a large polarizability effect and a small, acid-weakening, polar effect.[11] The saturation effect observed for α-methyl, but not β-methyl, substitution may be due to the polar effect being more important in α substitution, or due to the highly variant nature of the polarizability interaction on the intramolecular distance scale.[8] Since polarizability is anisotropic and is important in

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Table I. Effect of Alkyl Group Size on Gas-Phase Acidity[a]

acid	R = Me	Et	*n*-Pr	*i*-Pr	*t*-Bu
ROH	(0)	3.1	4.5	5.1	5.9
RCH_2OH	(0)	1.4		2.7	4.3
RSH	(0)	1.6	2.6	3.4	4.3
RC≡CH	(0)		1.3		3.0
RCH=NOH	(0)				1.6
RCH_2NO_2	(0)				1.1
p-RC_6H_4OH[b]	(0)			1.0	1.8
RCO_2H[c]	(0)	1.2	2.0		

[a] $\delta\Delta G^\circ = \Delta G^\circ_{acid}(R = Me) - \Delta G^\circ_{acid}(R)$, kcal/mol, 298 K. [b] Ref 35a. [c] Ref 25.

polar interactions as well (see Methyl Effects, below), the present data require a more exact model of microscopic polarizability for further analysis. Different steric interactions in the acid and the anion between the two ends (β-methyl and acidic site) of the molecule can lead to variations in acidity for entropic reasons.[12] Variable temperature studies are needed to determine the extent of this last effect.

Phenyl Effects. Replacing a methyl group directly on an acidic site with a phenyl group capable of stabilizing the anion by delocalization greatly increases acidity, as is seen in the data in Table II. The phenyl effects are considerably larger than those seen in solution.[13] The value for ethane is assumed to be 408 kcal/mol, equal to that of methane.[1] This is in good accord with theoretical calculations[14] which place ethane and methane as approximately equal in acidity, and 42 kcal/mol less acidic than HF. This results in a phenyl effect for toluene of 35.7 kcal/mol. For the first row elements, the effect is in the order C ≅ N > O, or inverse with respect to electronegativity. Delocalization of negative charge increases with decreasing ability of the acidic atom to support the charge. The change in acidity is also affected by resonance forms in the neutral aniline and phenol which should decrease the phenyl effect for those cases relative to toluene. The phenyl effect for sulfur is slightly smaller than that for oxygen, due to either poorer p-π overlap of the ring with the larger 3p orbitals on sulfur or to the saturation effect mentioned above for the thiols. The much smaller second phenyl effect for methane ($PhCH_2CH_3$ vs. Ph_2CH_2) is attributable to steric hindrance to coplanarity of the second phenyl group with the first π system, as indicated by molecular models. The smaller changes in acidity with phenyl substitution seen for the nitrile, ketone, and oxime functionalities reflect the progressively smaller amount of delocalizable charge on the carbon attached to the ring in these series (see Methyl Effects, below). While the negative charge in the acetylide and carboxylate anions is not capable of formal delocalization into the phenyl group, the size of the effect here does not represent the polar and polarizability effects of phenyl alone, since I_π effects[15] can stabilize the localized anion by decreasing electron density on the p orbital on carbon orthogonal to the anionic sp orbital. Benzyl alcohol, with the phenyl ring isolated from the anionic atom by a methylene group, is a better model for the case involving no resonance.

Electron-Withdrawing Group (EWG) Effects on Carbon Acidity. The relative acidities for a variety of carbon acids, CH_3EWG, are given in Table III. The values are presented relative to methane at 408.6 kcal/mol.[1] The compounds from toluene to nitromethane have been measured relative to each other in this study.[1] Propene is equal to H_2O in acidity.[16] Deuteration experiments[1,18] indicate that $CD_3C{\equiv}CH$ is between H_2O and MeOH in acidity for deuteron loss; the site of reprotonation of the delocalized anion is uncertain (propyne vs. allene) and thus only a very rough estimate is given. Trifluoromethyl methyl sulfone is completely deprotonated by HS^- with no back reaction observed by double resonance, making it at least 4 kcal/mol more acidic than H_2S.

Table II. Phenyl Effects on Acidity

acid	$\delta\Delta G^\circ_{acid}$[a]
RCH_3	35.7[b]
RNH_2	35.9[c]
ROH	28.1
RSH	~25[d]
RCH_2CN	19.4
RCH_2COCH_3	~14
RCH_2Ph	12.8
RCH=NOH	11.6
RC≡CH	9.3
RCO_2H	9.8[e]
RCH_2OH	4.3

[a] $\delta\Delta G^\circ_{acid} = \Delta G^\circ_{acid}(R = Me) - \Delta G^\circ_{acid}(R = Ph)$; kcal/mol, 298 K. [b] Assuming $\Delta G^\circ_{acid}(CH_3CH_3)$ = 408 kcal/mol, ref 1. [c] $\Delta G^\circ_{acid}(MeNH_2)$ = 395.7 kcal/mol, ref 52. [d] $\Delta G^\circ_{acid}(PhSH)$ = 328 kcal/mol, ref 53. [e] Ref 25.

Table III. Electron-Withdrawing Group (EWG) Effects on Acidity of Carbon Acids, CH_3EWG

-EWG	$\delta\Delta G^\circ_{acid}$[a,b]	σ_I[c]	σ_R^-[c]	α[d]
-CH=CH_2	24.4	0.05		6.1
-C≡CH	31[e]	0.35[f]		5.3
-Ph	36.3	0.10	0.04	12.3
$-CONMe_2$	41.8	0.21[g]	0.31[h]	9.7
-SOMe	43.0	0.50		8.0
-CN	44.2	0.56	0.33	4.4
$-CO_2Me$	44.3	0.30	0.34	6.7
-COMe	47.0	0.28	0.47	6.4
-CHO	49.0	0.31	0.55[h]	4.6
$-SO_2Me$	49.6	0.59	0.38	8.1
-COPh	52.2			14.4
$-NO_2$	56.6	0.65	0.46	5.0
$-SO_2CF_3$	>64	0.78[i]	0.57	8.1

[a] $\Delta G^\circ_{acid}(CH_4)$ = 408.6 kcal/mol, ref 1. [b] $\delta\Delta G^\circ_{acid} = \Delta G^\circ_{acid}(CH_4) - \Delta G^\circ_{acid}(CH_3EWG)$, kcal/mol. [c] Ref 19, unless otherwise indicated. [d] Polarizability of CH_3EWG, Å^3, ref 54. [e] ±5 kcal/mol, see text. [f] M. C. Charton, *J. Org. Chem.*, **29**, 1222 (1964). [g] For $-CONH_2$. [h] R. W. Taft, personal communication. [i] W. A. Sheppard and R. W. Taft, *J. Am. Chem. Soc.*, **94**, 1919 (1972).

From the results in Table III, it is evident that varying the nature of a single electron-withdrawing group can increase the acidity of methane by more than 65 kcal/mol. The rough trend of acidities with σ_I(EWG) indicates that polar effects are important for these compounds. A plot of these relative acidities against σ_I in Figure 1 shows considerable scatter (r = 0.694), due to resonance and polarizability contributions also being important. The substituent parameter σ_R^- can be taken as another measure of resonance stabilization of the anions.[19] This substituent constant is strictly defined only for solution cases where the EWG is bonded to sp^2 carbon in both cationic anilinium and neutral aniline forms,[19] so may be expected to be only a qualitative measure of delocalization in the present case. Those EWG's with $\sigma_R^- > \sigma_I$, such as $-CO_2Me$, -COMe, and -CHO, lie in the upper part of the trend in Figure 1, as expected if extra stabilization of the anion by resonance increases acidity. Those compounds with $\sigma_R^- < \sigma_I$, like $-SO_2Me$ and -CN, fall below the general trend, consistent with less resonance stabilization. The true "no resonance" line should lie below all the compounds shown in Figure 1. A dual substituent parameter analysis[19] yields a correlation with ρ_I = 11.4 and ρ_R^- = 16.1 (f = 0.17, r = 0.93). Some of the scatter may be attributable to polarizability effects as well, but the most polarizable of the carbonyl groups, $-CONMe_2$, is the least acidic of them. Likewise, the most polarizable low-resonance groups, $-SO_2Me$ and -SOMe, are low in acidity compared with the general trend.

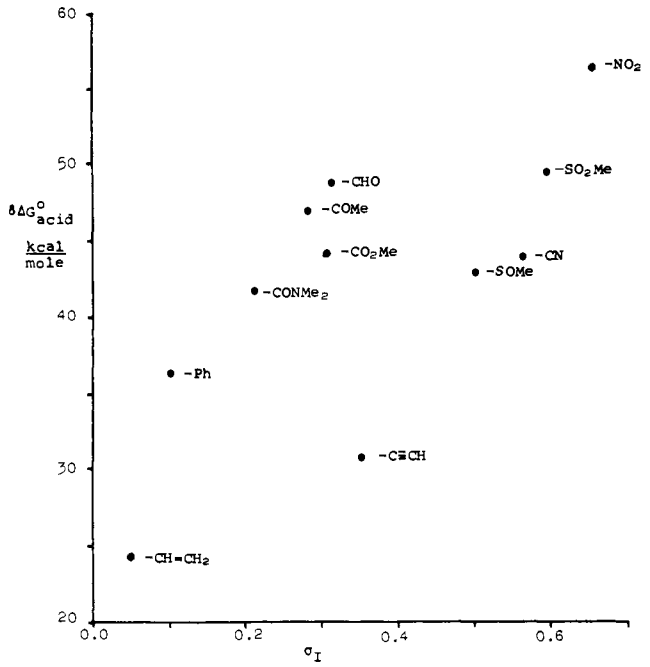

Figure 1. Gas-phase acidities of CH_3EWG vs. σ_I(EWG). Data are from Table III.

Methyl Effects. Substitution of a methyl group for hydrogen in a compound results in small and variable effects on acidity, as Table IV reveals. The effect is dependent on the nature of the anion-stabilizing group and the site of substitution. Considering the variety of effects by which methyl can interact with the rest of the molecule differently from hydrogen (polar and polarizability effects, hyperconjugation, steric hindrance to resonance, etc.), it is not surprising that no single trend is observed. Methyl has generally been regarded as electron-donating relative to hydrogen,[3,19,20] though there are situations where the opposite polarity appears to be the case.[21] Electron donation should result in methyl being acid weakening relative to hydrogen, due to destabilization of the anion by the polar effect. In contrast, it is possible for methyl to be acid strengthening due to its greater polarizability.[4] When methyl is attached to an sp^2 carbon, it should stabilize that form due to hyperconjugation, but whether this is acid strengthening or weakening depends on whether that form is the acid or its conjugate base. The net effect of steric hindrance by methyl likewise depends on the relative sensitivities of acid vs. anion to this interaction. By dividing the available data into the groups shown in Table IV based on the nature of the site of substitution, the methyl effects can be analyzed in terms of the above interactions.

For the group a acids, where the substitution is on an sp^2 carbon in both acid and anion, methyl is consistently acid weakening. Hyperconjugation should be of minor importance on net acidity since it approximately cancels in acid and anion. In the *p*-phenyl-substituted acids, the group is distant enough from the reactive site that steric hindrance and polarizability (a $1/r^4$ effect) are negligible, and as a result the polar effect should be the major determinant of acidities. The observed effect is consistent with a destabilization of the anion due to the increased electron donation of methyl relative to hydrogen. This polar effect should increase with proximity to the charge.[22] Of the three *p*-phenyl type acids, the largest effect is seen for toluene, where the primary acidic site is least able to support the negative charge by its electronegativity. The large effects seen for acetaldehyde and acetylene are probably a combination of increased polar effects, due to proximity to the negative charge, and nonperfect cancellation of hyperconjugative effects.

Table IV. Methyl Effects on Acidity

	acid	$\delta\Delta G^\circ_{acid}$,[a] kcal/mol
a.	*p*-$RC_6H_4CH_3$	−1.5
	p-$RC_6H_4NH_2$	−1.1
	p-RC_6H_4OH	−1.2
	$RCOCH_3$	−2.4
	RC(Me)=NOH	−0.5
	RC≡CH	−4.2
b.	RCH_2Ph	0.7, 0.8
	RCH_2CHO	0.5
	RCH_2COPh	0.8
	RCH_2NO_2	0.6, −0.1
c.	RCH_2CN	−1.5, 0.1
d.	ROH	12.0[b]
	RSH	−5.2
	RNH_2	0.6[c]

[a] $\delta\Delta G^\circ_{acid} = \Delta G^\circ_{acid}(R = H) - \Delta G^\circ_{acid}(R = Me)$, 298 K, statistically corrected; second number is dimethyl compound compared with monomethyl. [b] $\Delta G^\circ_{acid}(H_2O) = 384.2$ kcal/mol, ref 1, 51. [c] Ref 52.

By similar arguments, methyl substitution into an oxime should result in a considerable decrease in acidity, due to the appreciable amount of charge on the methyl-bearing carbon in the anion. Instead, a relatively small decrease is observed. The hydrogen substituted compound, E-acetaldoxime, has the hydrogen cis to the negative oxygen atom in the anion. The *cis*-methyl group in acetoxime may destabilize the partial carbanion by polar effects, but will stabilize the oxyanion by a through-space (ca. 3.3 Å) polarizability interaction, resulting in a smaller decrease than expected in acidity.

For the group b acids, where substitution is directly on the acidic carbon, methyl is acid strengthening. Neither hyperconjugative nor polar effects operate in the acid forms here, since both those effects require that methyl be attached to sp^2 carbon for π overlap or for the electronegativity difference needed to create a dipole. Substituent constants such as σ, σ^*, or σ_I, which imply methyl is electron donating relative to hydrogen, are defined in systems with substitution at sp^2 carbon.[20,23] In the original σ_I system, the 4-X-bicyclo[2.2.2]-octanecarboxylic acids, methyl substitution at sp^3 carbon had an effect on acidity within experimental error of that for hydrogen.[24] Thus for group b structural effects in the anion are the primary determinants of relative acidity. The polar effect should be acid weakening for methyl, the hyperconjugative effect, acid strengthening. The net effects observed imply that the hyperconjugative effect is more important for the group b acids and the polar effect more important for the structurally similar group c acid. The difference between these two sets of acids is in the relative amount of negative charge on carbon due to polar and resonance effects by the EWG. As mentioned in the Electron Withdrawing Group section, there is a larger ratio of resonance to polar effects for the group b acids than for group c. The proximity of charge to the substituent thus controls the balance of the two effects here. The sulfones, where delocalization of charge by resonance is small compared with the group b acids, show a similar decrease in acidity with α-methyl substitution.[25]

Polarizability does not appear to be an important factor in the relative acidities for these two groups, since it should be largest (acid strengthing) for the nitriles where the least delocalization of charge occurs. Instead, methyl is the most acid weakening in that case. It appears that polarizability and hyperconjugation[26] are nearly balanced by polar effects in groups

Table V. Dual Substituent Parameter Analysis of Substituted Aniline Acidities

	NH_3[a]		Me_2SO[b]		gas phase	
solvent	*m*	*p*	*m*	*p*	*m*	*p*
ρ_I	4.8	5.7	5.1	5.6	10.4	12.3
ρ_R^-	1.4	6.6	1.5	6.8	5.1	11.1
λ[c]	0.3	1.2	0.3	1.2	0.5	0.9
n[d]	4	5	7	7	6	6
r	0.999	0.998	0.984	0.995	0.991	0.991
ρ[e]		5.3		5.7		10.4

[a] Ref 36a. [b] Ref 44. [c] $\lambda = \rho_R^-/\rho_I$. [d] Number of compounds. [e] Hammett ρ.

b and c and it is the later interaction which determines relative acidities.

The effect of a second methyl group is variable. An increase comparable to the first is seen in toluene but negligible effects are observed in nitromethane and acetonitrile. This may be a saturation effect[10] on polar interactions[27] or a "cross-hyperconjugation" problem where the second group interferes with π interactions[26] of the first group.

Methyl effects have been previously analyzed in terms of homolytic bond energies DH° (A-H) and electron affinities EA(A·),[28] in a somewhat analogous pattern to the hyperconjugative and polar effects described here. A problem in that analysis is that, while α-methyl substitution decreases the bond strength by stabilization of the radical through hyperconjugative delocalization,[29] it also decreases the electron affinity by stabilizing the radical to which the electron is being attached. Any change in DH° due to radical stability thus is canceled by an necessarily equal change in EA. It is the interactions which are responsible for variation in DH° and EA which are important in determining methyl effects, not DH° and EA themselves.

The methyl effects on the acidities of the hydrides H_2O, H_2S, and NH_3 are shown in part d of Table IV. These effects may be analyzed, as before, in terms of polar effects, hyperconjugation, and polarizability. The size of methyl effects on acidity correlates with the secondary deuterium isotope effects[26] in these systems ($r = 0.999$). While the excellence of the correlation is probably fortuitous considering the uncertainties of up to 27% in the isotope effects,[26] a qualitative trend is certainly evident and makes sense on the conceptual basis of anionic hyperconjugation. This interaction should stabilize the methyl-substituted anion relative to the hydrogen substituted one and increase acidity. The smallest effect is seen for sulfur, where the anionic atom and methyl group are most disparate in size, reducing π-π^* overlap. Polarizability may also contribute to this ordering of acidities. In CH_3S^-, the bond between the methyl and the anionic atom is considerably longer than for the first row elements, reducing the $1/r^4$ polarizability effect. This still does not explain the order MeSH < H_2S. A polar interaction, acid weakening for methyl in all three cases, must be invoked. Since the electronegativity of carbon is less than that of oxygen or nitrogen, it is reasonable that it could be electron donating to them. The electronegativity of an anionic group should logically be less than that of the corresponding neutral; however, examination of group electronegativities[30] reveals rather small changes. For example, $\chi(-CH_3) < \chi(-S^-) < \chi(-SH)$. Thus, methyl could conceivably be electron donating by polar interactions in all three CH_3X^- anions under consideration. The electronegativity of hydrogen is even less than that of carbon, so electronegativity alone cannot explain these data. Polar effects, however, are a combination of electronegativity differences and a group's ability to respond to them, which is its polarizability. Methyl is more electron donating than hydrogen since it can be polarized to a greater extent in response to whatever electronegativity difference exists. This combination of electronegativity and polarizability has been remarked on for electron-withdrawing groups;[31] there is no reason to suppose it does not exist for the donating counterparts. Thus, in general, methyl (and other alkyl groups) should reduce acidity by polar effects, relative to hydrogen as substituent, but may increase it, depending on the structure of the anion and site of attachment, due to hyperconjugative and polarizability interactions.

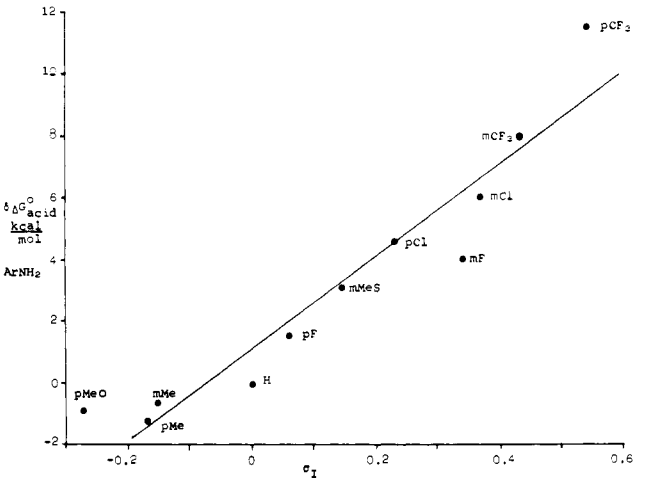

Figure 2. Hammett correlation of gas-phase acidities of anilines vs. σ_I.

Linear Free-Energy Relationships. Linear free-energy relationships have proven to be one of the most powerful tools of physical organic chemistry for analyzing the effect of structure on reactivity.[3,19] Although the various substituent constants have been shown to be slightly solvent dependent,[32] the primary effects of most substituents have been assumed to be due to their intrinsic structure. This is supported by the reasonably linear Hammett plots for gas-phase basicities of anilines[33] and pyridines,[34] and the acidities of phenols[35] and benzoic acids.[35] From the present work, the acidities of the anilines give a reasonably linear ($r = 0.948$) plot vs. σ, as shown in Figure 2. The *m*-F compound is considerably less acidic than expected, the *p*-MeO compound, more so. These same deviations are seen in other gas-phase acidity series, such as benzoic acids and phenols,[35] but not in their solution acidities.[20a,36] If a dual substituent parameter (DSP) analysis[19] is performed on the aniline acidities, utilizing σ_I and σ_R^-, the data in Table V are obtained. The basis sets are admittedly small.[19] In general, the gas-phase substituent effects are larger than in solution, due to lack of solvent compression. The effect of solvation on λ varies with position, with λ_{para} increasing and λ_{meta} decreasing upon going to the condensed phase. This may be due to a basis set lacking groups with large σ_R^- values or to the inappropriateness of σ_R^- for this correlation.[19]

For the alcohols GCH_2OH, with G = $-CF_3$, $-CHF_2$, CH_2OCH_3, -Ph, and $-CH_2CH_3$, $\rho_I = 17.0 \pm 0.7$ ($r = 0.998$). The larger alkyl groups lie on the more acidic side of the line; the smaller groups H and Me are on the less acidic side. Solvent compression is again evident, with $\rho_I = 7.5 \pm 0.3$ for the same alcohol acidities in H_2O solvent,[5] a reduction of 56%. In comparison, ρ_I for the acidity of the substituted carboxylic acids decreases by 76% upon going to aqueous solution[37] from the gas phase.[25] This increased compression effect is consistent with the greater number of anionic sites available for solvation in carboxylates compared with alkoxides.

Though there are only three points over a limited σ range, the Hammett ρ for $ArCOCH_3$ is ~8 ($r = 0.979$), comparable to that of the structurally similar benzoic acids in the gas phase.[35b] Upon going to Me_2SO as solvent,[38] ρ for the aceto-

Table VI. Gas-Phase vs. Solution Acidities

acid	gas phase[a]	H_2O[b]	Me_2SO[c]
H_2O	384.2	21.4	
MeOH	372.6	20.7	
EtOH	369.5	21.8	
n-PrOH	368.1	22.1	
i-PrOH	367.5	23.4	
i-BuOH	366.8	22.1	
t-BuOH	366.7	26.3	
$MeO(CH_2)_2OH$	365.6	20.3	
F_2CHCH_2OH	359.8	18.2	
F_3CCH_2OH	356.8	16.9	31.2[d]
$PhCH_2OH$	365.2	21.1	
PhOH	344.5	13.7	25.3[e]
HF	365.7	4.7	
HCN	345.8	12.75	
H_2S	347.1	9.4	
MeSH	352.7	19.4	
EtSH	351.1	19.9	
n-PrSH	350.1	20.0	
i-PrSH	349.3		
t-BuSH	348.4	20.7	
$ArNH_2$			
H	359.8		42.1
m-Me	360.3		42.5
m-Cl	353.8		39.1
m-CF_3	351.8		38.6
p-CF_3	348.3		37.0[d]
$PhC{\equiv}CH$	362.6		39.5
Ph_2CH_2	359.1		44.3
cyclopentadiene	349.9	21.4[g]	24.7[d]
MeCN	364.4		42.9
$PhCH_2CN$	346.7		30.0
CH_3COCH_3	361.6		36.3
$ArCOCH_3$			
H	356.4		33.8
m-MeO	356.0		33.6[d]
p-Cl	352.5		32.6[d]
$PhCOCH_2CH_3$	355.8		33.4
$PhCH_2COCH_3$	365.6		27.1
MeSOMe	359.0		48.1
$MeSO_2Me$	352.0		43.7
$MeNO_2$	351.7	14.0[f]	24.3
$EtNO_2$	352.2	11.6[f]	23.3
i-$PrNO_2$	350.6	10.5[f]	23.2
t-$BuCH_2NO_2$	350.6		25.2
$Me_2C{=}NOH$	359.8	17.0	

[a] $\Delta G°_{acid}$, kcal/mol. [b] 1.37 pK_a, kcal/mol; alcohols from ref 37, thiols from ref 55, others from ref 56, unless otherwise noted. [c] 1.37 pK, kcal/mol; ref 6a, 13, 41, 42, 44, 48. [d] Ref 38. [e] Ref 45. [f] T. Matsu and L. G. Hepler, *Can. J. Chem.*, **51**, 1941, 3789 (1973). [g] Ref. 47d.

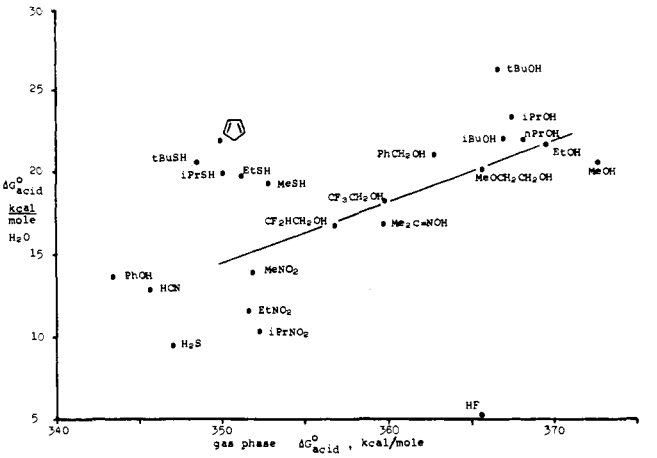

Figure 3. Plot of gas-phase acidities vs. aqueous acidities. Data are from Table VI. The line is for F_3CCH_2OH, F_2CHCH_2OH, $MeOCH_2CH_2OH$, and EtOH.

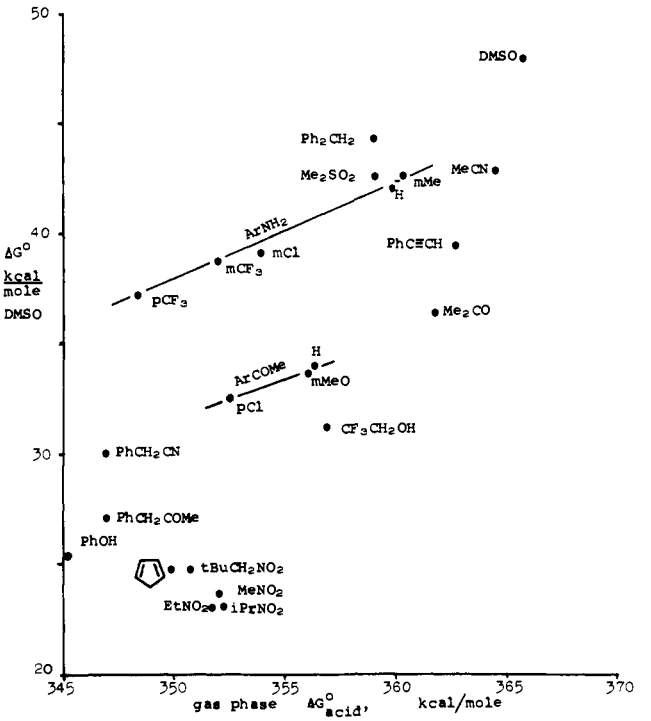

Figure 4. Plot of gas-phase acidities vs. acidities in Me_2SO (DMSO). Data are from Table VI.

phenones is attenuated by a factor of 2.0, similar to the anilines where $\rho(GP)/\rho(Me_2SO) = 2.3$.

Solvation Effects. The solution phase acidities of many of the compounds investigated in this work are available for comparison. The gas-phase acidities are compared with the acidities (in kcal/mol) in H_2O and dimethyl sulfoxide (Me_2SO) solvents in Table VI and Figures 3 and 4. For aqueous solution, there is a rough correlation between solution and gas-phase data, though with a great deal of scatter and an attenuation in relative acidity of about 75% upon solvation. The attenuation is due to solvent compression[5] of substituent effects: part of the net stabilization of the anion is now due to the solvent, so the intrinsic substituent effects are smaller. The most interesting aspect of this is not the fourfold compression, but the fact that the size of substituent effects changes so slightly when solvation stabilizes the ionic products relative to the acid by 350 kcal/mol! Clearly, intrinsic structural effects remain important upon solvation.

If the series RCH_2OH with R = -Me, $-CH_2OMe$, $-CHF_2$, and $-CF_3$ is chosen as an arbitrary series with approximately constant steric bulk and polarizability, and with large polar effects, then the line these four acids define in Figure 3 (r = 0.990) separates the larger alcohols above the line (less acidic in H_2O) and the smaller, below it. This scatter is most probably due to steric hindrance to solvation of the alkoxide by the bulky substituent.[4] Phenol is slightly less acidic than expected from this "polar" line. This is consistent both with the phenyl group's steric bulk and the poorer solvation of the delocalized charge[6] in the phenoxide. The thiols are less acidic in H_2O than in the gas phase by several measures: they lie above the general trend of compounds in Figure 3, and MeSH is 20.2 kcal/mol more acidic than MeOH in the gas phase, but only 1.3 kcal/mol more acidic in H_2O. Methoxide is much better solvated than MeS^- in H_2O, consistent with oxygen's better ability as a hydrogen bond acceptor.[39] Solvation of the alcohols is seen to be more sensitive to steric bulk than for the thiols. Both groups

Table VII. Ion-Pairing Solvent Effects on Acidity

acid	CH_3CN[a]	CHA[b]	gas phase[c]
$(CH_3)_3CH$	97		
$HC{\equiv}CCH_3$	86		384 ± 5[d]
$PhCH_3$	74	56	372.3
$CH_2{=}CHCH_3$	73		384.2
cycloheptatriene	51		367.9
C_6H_6		59	390 ± 5[e]
$PhC{\equiv}CH$		32	362.6
t-$BuC{\equiv}CH$		35	368.9
Ph_2CH_2		48	359.1
cyclopentadiene		16	349.9

[a] Acetonitrile solvent, ref 46, 1.37 pK, kcal/mol. [b] Cyclohexylamine solvent, ref 47, 1.37 pK, kcal/mol. [c] ΔG°_{acid}, kcal/mol. [d] Estimated, see text. [e] Ref 51.

show the inversion effect, due to solvation, of t-Bu more acidic than Me in the gas phase but less so in solution; however, the negative slope for the alcohols is much steeper than for the thiols. This can be rationalized in terms of the differing solvation forces involved. The alkoxides are strongly hydrogen bonded; such specific solvation, which implies certain configurations of solvent and anion, should be more sensitive to disruption by nearby steric bulk than that of less specifically solvated anions, like the thiolates.

Methyl substitution in the nitroalkanes results in much greater increases in acidity in solution than in the gas phase. This is consistent with the reasoning presented in the Methyl Effects section, where polar effects appear to be the controlling factors for methyl substitution directly on the acidic carbon. Hydrogen bonding by water to the oxygens in the nitronate should increase charge density there and reduce it on the carbanion. As a result, the acid-weakening polar effect should be smaller due to the decreased proximity to the negative charge. The balance between hyperconjugation and polar interactions is thus tipped in favor of the former by solvation.

Small acids, like HF, H_2O, H_2S, and HCN, are consistently in the lower part of Figure 3, more acidic in H_2O than expected from their gas-phase acidities. This is explicable in terms of their small steric hindrance to solvation and their good hydrogen-bonding properties. The largest deviation from the general trend is seen for HF, whose anion is the best hydrogen bond acceptor known.[39] The deviation for H_2S, where HS^- is a relatively poor hydrogen bond acceptor, is much smaller. The acidity of PH_3 in H_2O has been estimated at a pK of 29 (40 kcal/mol) by kinetic methods.[40] While caution is necessary in extrapolating equilibrium acidities from kinetic data,[41] PH_3 is clearly less acidic than the solvent in that experiment.[40] This places it on or above the RCH_2OH line in Figure 3, on the opposite side from the other simple hydrides. Either solvation of PH_3 is remarkably good (unlikely from electronegativity considerations), that of PH_2^- very poor, or the Brønsted correlation of rates and equilibria fails for this case.

For Me_2SO as solvent,[6a,42] a much wider range of acidities is accessible compared with water. Figure 4 reveals little change in relative acidity upon solvation, though different anion-stabilizing groups fall on different lines.[6a] The slopes of these lines approach 1.0, indicating little solvent compression of relative acidities, unlike aqueous solution. For the various carbanion-stabilizing groups, the order of solvation effects (bottom to top of the overall trend) appears to be cyclopentadienyl ≈ nitro > carbonyl > cyano > sulfoxy > phenyl. This is approximately the order of the anion delocalizing ability of these groups,[19] and is consistent with Me_2SO's ability to solvate delocalized negative charge better than other, less polarizable solvents are able to.[43] If the estimate acidity of toluene in Me_2SO of pK = 44 ± 1 (ΔG° = 60 kcal/mol)[44] is valid, then phenol, aniline and toluene fall on a nearly straight line

Table VIII. Gas-Phase Hydrocarbon Acidities and Calculated Delocalization Parameters

acid	ΔM[a]	ΔG°_{acid}	α, Å^3 [b]
$CH_2{=}CHCH_3$	0.83	384.2	6.1
$PhCH_3$	0.721	372.3	12.3
cycloheptatriene	1.110	367.9	12.8
Ph_2CH_2	1.301	359.1	22.0
cyclopentadiene	2.000	349.9	8.7

[a] Ref 50. [b] Ref 54.

(r = 0.996) with toluene above the general trend of acids in Figure 4 and phenol below it. From this it appears that Me_2SO solvation of anions increases with increasing electronegativity and decreasing ionic radii, in support of solution calorimetric data.[45] The corrected heat of ionization of HF in Me_2SO,[45] ca. 20 kcal/mol, places it far below the other acids in Figure 4.

Aliphatic alkoxides are known to be extensively ion-paired in Me_2SO[45] and it has been stated that alkoxide and dimsylate anions are of comparable basicity in Me_2SO.[45] The gas-phase data support this: Me_2SO is similar in acidity to *tert*-butyl and neopentyl alcohols. Due to increased solvation by hydrogen bonding of ROH to Me_2SO, the alcohols should be relatively less acidic in Me_2SO solution than non-hydrogen-bonding acids are. This is in contrast to the aqueous acidities, where alcohols are strengthened relative to such acids, compared with the gas phase, due to the excellent hydrogen-bond acceptor properties of oxyanions.

The acidities of several hydrocarbons have been determined electrochemically in acetonitrile solvent,[46] as shown in Table VII. There is a general parallel trend with the gas phase, save that toluene and propene are inverted in acidity in the two phases. The greater polarizability of toluene controls the relative acidities of the two in the gas phase, while its concommitant bulk may hinder solvation of the anion in acetonitrile solvent. In cyclohexylamine (CHA) solvent for the localized carbon acids $PhC{\equiv}CH$, t-$BuC{\equiv}CH$, and C_6H_6, a roughly linear correlation, with a slope of about 1, is observed for the acidities vs. the gas phase. The delocalized acids Ph_2CH_2 and $PhCH_3$ lie above this line, less acidic in CHA compared with localized carbanions than expected from the gas phase. This provides further support for the concept of localized ion pairs being more stable than delocalized ones.[47a,48] Steric effects appear to be very important in ion-pair acidities: methyl substitution on the acidic site of toluene increases gas-phase acidity (0.7 kcal/mol per Me) but decreases the ion-pair acidity in hydrocarbon solvents by ~2 kcal/mol per methyl.[49] Ion-pair acidities, important though they be to synthetic chemists who need to know the reactivities of such systems, cannot be taken as measures of intrinsic anion stability, since it appears that the extent of ion pairing is highly sensitive to small structural modifications.

Hückel Molecular Orbital Calculations. The delocalization parameter ΔM, a measure of resonance energy from Hückel molecular orbital theory, has been shown to correlate with various hydrocarbon acidities in solution.[50] The correlation in the gas phase for some nonpolar hydrocarbons in Table VIII reveals a general trend with considerable scatter as seen in Figure 5. The smallest and least polarizable acid, propene, is above the general trend indicating that polarizability should also be taken into account. In addition, probably neither diphenylmethide[47] nor cycloheptatrienide[46b] are planar, so ΔM is not a good measure of π delocalization for them. For the three planar anions, the data are found to fit the DSP equation

$$\Delta H^\circ_{acid} = -24.4\,\Delta M - 2.4\alpha + 426.2 \text{ kcal/mol}$$

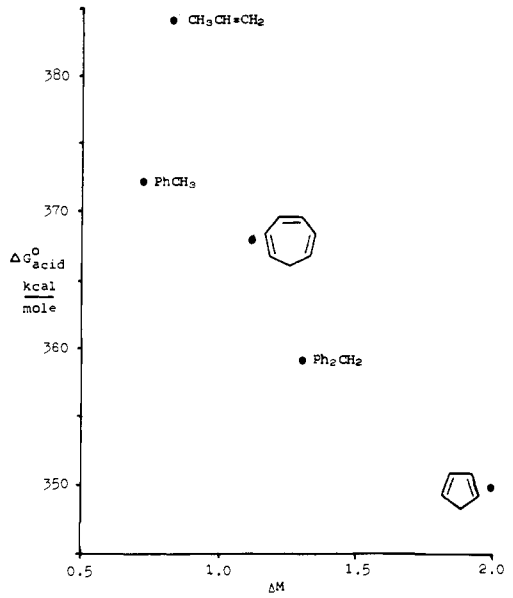

Figure 5. Gas-phase acidities of hydrocarbons vs. ΔM for delocalization.

where α is the bulk polarizability of the hydrocarbons in Å^3. The slope of 24.4 kcal/mol is a reasonable value for the β parameter. Methane with $\Delta M = 0$ and $\alpha = 2.66$ Å^3 fits the equation to 3 kcal/mol. Cycloheptatriene is 5 kcal/mol less acidic than predicted, in the direction expected but probably within the uncertainty of the equation considering the sparse basis set. Diphenylmethane is 23 kcal/mol lower in acidity than expected for a planar system, indicating considerable twisting of the anion.

Conclusion

Gas-phase acidities are a powerful tool for analysis of substituent effects on anion stability and, by difference, of solvation effects on anions. Now that a linked scale of relative acidities has been achieved over a 65 kcal/mol range, we anticipate that many more such acidities will be forthcoming. We are continuing our investigations in this field.

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Alkylation Reactions of Mitomycin C at Acid pH

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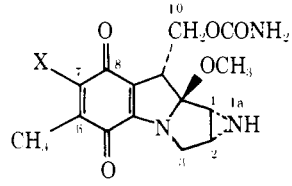
Abstract: Mitomycin C readily alkylates inorganic phosphate and the phosphate group of various nucleotides in aqueous solution at acid pH. The products of this type of reaction are 2,7-diaminomitosenes containing a phosphate group in the 1-position. The reaction is appreciable only below pH 5, requiring protonation of the aziridine ring of mitomycin C ($pK_a' = 4$). The specific reactions studied were the following: alkylation of inorganic phosphate yields 1,2-*cis*- and -*trans*-2,7-diaminomitosene 1-phosphate, in greater than 9/1 ratio. Alkylation of 5′-uridylic acid results in *cis*- and *trans*-2,7-diaminomitosene 1-(5′-uridylate), in approximately 4/1 ratio. 5′-Uridine triphosphate is alkylated at its terminal phosphate group, to give the corresponding 1-substituted 2,7-diaminomitosene, also with predominant cis composition. The structure of these products was proven by quantitative phosphate analysis, ultraviolet spectra, and enzymatic degradation into known products. UpU yields a small amount of a mitosene adduct which was not characterized. Uridine itself is not alkylated by mitomycin C. Hydrolytic ring opening of the protonated aziridine ring of mitomycin C competes with the phosphate alkylation reactions, yielding *cis*- and *trans*-2,7-diamino-1-hydroxymitosenes. The phosphate compounds described represent the first characterized examples of alkylation of nucleotides by mitomycin C, supporting the previous hypothesis that the mitomycins are biological alkylating agents.

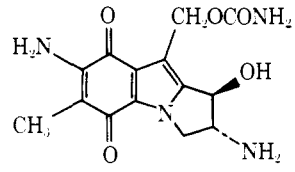
Mitomycin C (**1a**; MC), the potent antibiotic and clinically useful antitumor agent,[1-3] presents an interesting challenge to correlate chemical behavior and biological activity. It contains an aziridine ring, rare in natural products, and the well-known antitumor activity of various synthetic aziridines[4a] led early to the suggestion that the aziridine ring of MC is involved in its mechanism of action.[5] Since aziridines, including the class of N-mustards, where the aziridine form is the reactive tautomer,[6a] are powerful alkylating agents, MC was predicted to alkylate its biological target, most likely DNA, analogously.[5,7] Consistent with this hypothesis, DNA isolated from MC-treated bacteria contained covalently bound MC[8] and, in addition, its two complementary strands were cross-linked,[9,10] indicating two binding functions of MC to DNA rather than one. The cross-linking action was considered to be the direct cause of the cytotoxicity of the drug,[9] although more recently the monofunctional attachment which predominates 10- to 20-fold over the number of cross-links[8,11] has also been implicated as biologically significant damage to DNA.[12-14]

In the absence of cells, the DNA-binding and cross-linking effects of MC could only be demonstrated if a reducing agent (chemical or enzymatic) was also added, indicating that the active form of the drug is generated in the cell by reduction.[5,7] More recently, it was shown that low pH (pH 4) alone also activates MC to bind and cross-link DNA in vitro.[15]

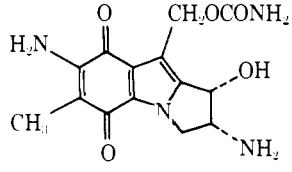
A detailed chemical hypothesis was advanced by Iyer and Szybalski[7] for the functioning of MC as a reductively activated bifunctional alkylating agent and this mechanism was further refined recently by Moore.[16] Despite this apparent interest in the molecular mode of action of MC, experimental verification of the proposed chemistry is lacking. Alkylation reactions of the mitomycins have not been characterized, the redox chemistry of MC itself is complex and not well understood,[17,18] and efforts to isolate and characterize MC-nucleotide adducts from model reactions or from MC-nucleic acid complexes have been unsuccessful so far.[19] The only product ever characterized from any reaction of reduced MC is the bisulfite adduct **5**;[18]



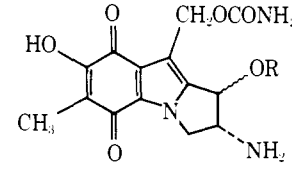
1a, X = NH_2
b, X = OCH_3



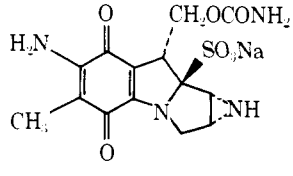
2



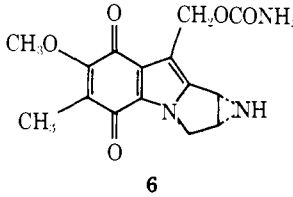
3



4a, R = H
b, R = PO_3H_2



5



6

Its mechanism of formation and relevance to the DNA-binding and cross-linking action of reduced MC is unknown. We undertook the task to seek basic evidence for the postulated alkylating properties of MC. As our first approach, we succeeded in observing the alkylation of a series of phosphate compounds by MC under the simple low pH activation conditions.

Experimental Section

Materials. The materials used and their sources are as follows: mitomycin C, Bristol Laboratories, Syracuse, N.Y.; bacterial alkaline phosphatase, snake venom phosphodiesterase, Worthington Biochem. Corp., Freehold, N.J.; nucleotide pyrophosphatase (type III, from

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