

A Theoretical Approach to Substituent Effects. Examination of Phenoxides and Anilides as Models for Benzyl Anions

Gary Kemister,^{1a} Addy Pross,^{*1a,b} Leo Radom,^{*1a} and Robert W. Taft^{*1c}

Research School of Chemistry, Australian National University, Canberra, ACT 2600, Australia, and Department of Chemistry, University of California, Irvine, California 92717

Received October 25, 1979

Ab initio molecular orbital calculations with the minimal STO-3G basis set have been carried out for a series of meta- and para-substituted benzyl and anilide anions with substituents CH₃, NH₂, OH, OCH₃, F, NO₂, CN, CHO, and CF₃. The results are analyzed in terms of substituent interactions and compared with previously reported data for toluenes, anilines, phenols, and phenoxide anions. The results suggest that (a) substituted phenoxide anions are useful models for substituent effects in corresponding benzyl anions in the gas phase, (b) effects of substituents on acidities of toluenes, anilines, and phenols are largely due to substituent interactions in the anions and only to a smaller extent to interactions in the neutrals, (c) the sensitivity of acidity to substituent change increases slightly in the order anilines < phenols < toluenes due in part to substituent effects in the neutrals, and (d) differences in the solution behavior of substituted phenoxide and benzyl anions stem from the large differences in solvent effects for these two systems.

Organic chemists have for many years considered the possibility that phenolates or anilides might be used to model substituent behavior in carbanions, e.g., benzyl anions. The most quantitative comparisons which were available up until the past few years did not indicate much success for the model.^{2,3} Recent progress in the quantitative measurement of gas-phase acidities,^{4,5} of acidities in aprotic solvents, e.g., dimethyl sulfoxide (Me₂SO),⁶ and in theoretical ab initio molecular orbital calculations of relative acidities⁷ now permits a tentative reassessment and the prospect of a definitive conclusion.

In this paper we report the results of an ab initio molecular orbital study carried out at the STO-3G level⁸ using modified versions of the GAUSSIAN 70 program.⁹ This study was prompted by our recent theoretical study of the interactions of substituents with the phenolic and phenoxide centers.^{10a} In the present work, the study has been extended to the corresponding interactions with the aniline and anilide centers,^{10b} as well as with the toluene and benzyl anion centers. In this manner, an analysis is provided for the effects of meta and para substituents upon the theoretically calculated relative acidities of a select series of phenols, anilines, and toluenes. The results of this work provide new insight into the interpretation of existing data for acidities both in the gas phase and in Me₂SO or aqueous solutions. Several predictions are made by the theoretical study which will be critically tested by

Table I. Calculated Total Energies (hartrees) for Substituted Benzyl Anions

substituents				
X	Y	isomer	conformation ^a	energy
CH ₂ ⁻	H			-265.67016
CH ₂ ⁻	CH ₃	meta	C _α C...CCH cis	-304.25389
		para	C _α C...CCH planar	-304.25167
CH ₂ ⁻	NH ₂	meta	θ = 110.1 ^b	-319.99029
		meta	C _α C...CNH planar	-319.98258
		para	θ = 108.5 ^b	-319.97832
		para	C _α C...CNH planar	-319.96583
CH ₂ ⁻	OH	meta	C _α C...COH cis	-339.51479
		meta	C _α C...COH trans	-339.51361
		meta	C _α C...COH orthogonal	-339.50495
		para	C _α C...COH orthogonal	-339.50145
		para	C _α C...COH planar	-339.50116
CH ₂ ⁻	OCH ₃	meta	C _α C...COC cis	-378.08914
		meta	C _α C...COC trans	-378.07466
		para	C _α C...COC planar	-378.07701
CH ₂ ⁻	F	meta		-363.13853
		para		-363.13020
CH ₂ ⁻	NO ₂	meta	C _α C...CNO planar	-466.39145
		meta	C _α C...CNO orthogonal	-466.38378
		para	C _α C...CNO planar	-466.41536
		para	C _α C...CNO orthogonal	-466.39145
CH ₂ ⁻	CN	meta		-356.24592
		para		-356.26082
CH ₂ ⁻	CHO	meta	C _α C...CCO trans	-376.90497
		meta	C _α C...CCO cis	-376.90406
		para	C _α C...CCO planar	-376.92075
CH ₂ ⁻	CF ₃	meta	C _α C...CCF cis	-596.64773
		meta	C _α C...CCF trans	-596.64744
		para	C _α C...CCF planar	-596.65442

^a The notation C_αC...CCH cis, for example, means that a C-H bond of the substituent is located cis to the C-C_α bond. ^b θ is the optimized value of the bond angles (assumed equal) about nitrogen.

experimental work actively in progress in several laboratories. In this manner, the predictive utility and limitations of the theoretical treatment will be definitively evaluated. First, unsolvated phenoxide ions are indicated by the theoretical calculations to be excellent models (in their inherent relative basicities) for the corresponding unsolvated benzyl or anilide anions. Second, the effects of meta and para substituents on the gas-phase acidities of anilines are indicated to be uniformly about 10% smaller than the corresponding effects on gas-phase acidities of phenols. Comparison of the theoretically calculated acidity results with the few currently available experimental gas-phase values^{4,5} appears to support these predictions. Finally, some comparisons with solution acidities are shown

(1) (a) Australian National University. (b) Permanent address: Department of Chemistry, Ben Gurion University, Beer Sheva, Israel. (c) University of California, Irvine, Calif.

(2) A. Streitwieser, Jr., and H. F. Koch, *J. Am. Chem. Soc.*, **86**, 404 (1964).

(3) L. D. McKeever and R. W. Taft, *J. Am. Chem. Soc.*, **88**, 4544 (1966).

(4) P. Kebarle, *Annu. Rev. Phys. Chem.*, **28**, 445 (1977).

(5) J. E. Bartmess, J. A. Scott, and R. T. McIver, Jr., *J. Am. Chem. Soc.*, **101**, 6046 (1979).

(6) (a) F. G. Bordwell, *Pure Appl. Chem.*, **49**, 963 (1977); (b) F. G. Bordwell, D. Algrim, and N. R. Vanier, *J. Org. Chem.*, **42**, 1819 (1977);

(c) D. Algrim, J. E. Bares, J. C. Branca, and F. G. Bordwell, *ibid.*, **43**, 5024 (1978).

(7) L. Radom, *J. Chem. Soc., Chem. Commun.*, 403 (1974).

(8) W. J. Hehre, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.*, **51**, 2657 (1969).

(9) (a) W. J. Hehre, W. A. Lathan, R. Ditchfield, M. D. Newton, and J. A. Pople, QCPE, Program No. 236; (b) D. J. DeFrees, B. A. Levi, S. K. Pollack, E. S. Blurock, and W. J. Hehre, to be submitted to QCPE; (c) D. Poppinger, M. A. Vincent, A. L. Hinde, and L. Radom, unpublished work.

(10) (a) A. Pross, L. Radom, and R. W. Taft, *J. Org. Chem.*, in press; (b) A. Pross and L. Radom, *Prog. Phys. Org. Chem.*, in press.

(11) (a) M. Fujio, R. T. McIver, Jr., and R. W. Taft, work in progress; (b) J. E. Bartmess, private communication; (c) F. G. Bordwell, private communication.

Table II. Mulliken Charges for Substituted Benzyl Anions

substituent	$q_{\sigma}(Y)^a$	$q_{\sigma}(X)^a$	$q_{\pi}(Y)^a$	$q_{\pi}(X)^a$	$\pi(\text{Ph-Y})^b$	$\pi(\text{Ph-X})^b$
H	-0.078		-0.519		0.257	
<i>m</i> -CH ₃	-0.077	+0.071	-0.521	-0.003	0.258	0.010
<i>m</i> -NH ₂	-0.077	+0.189	-0.521	-0.070	0.259	0.048
<i>m</i> -OH	-0.078	+0.232	-0.523	-0.086	0.260	0.044
<i>m</i> -OCH ₃	-0.077	+0.247	-0.524	-0.086	0.260	0.047
<i>m</i> -F	-0.079	+0.253	-0.529	-0.070	0.261	0.035
<i>m</i> -NO ₂	-0.083	+0.287	-0.554	+0.053	0.263	0.041
<i>m</i> -CN	-0.082	+0.167	-0.546	+0.040	0.263	0.047
<i>m</i> -CHO	-0.079	+0.060	-0.530	+0.057	0.258	0.054
<i>m</i> -CF ₃	-0.079	+0.093	-0.536	+0.017	0.261	0.020
<i>p</i> -CH ₃	-0.078	+0.067	-0.520	+0.008	0.256	0.011
<i>p</i> -NH ₂	-0.082	+0.194	-0.503	-0.042	0.245	0.004
<i>p</i> -OH ^c	-0.083	+0.198	-0.502	-0.059	0.250	0.008
<i>p</i> -OCH ₃	-0.083	+0.252	-0.506	-0.057	0.251	0.011
<i>p</i> -F	-0.082	+0.251	-0.514	-0.048	0.254	0.008
<i>p</i> -NO ₂	-0.062	+0.276	-0.630	+0.169	0.281	0.075
<i>p</i> -CN	-0.068	+0.168	-0.593	+0.103	0.275	0.072
<i>p</i> -CHO	-0.066	+0.054	-0.587	+0.153	0.271	0.089
<i>p</i> -CF ₃	-0.074	+0.112	-0.555	+0.036	0.267	0.034

^a $q_{\sigma}(Y)$, $q_{\sigma}(X)$, $q_{\pi}(Y)$, and $q_{\pi}(X)$ are the total σ and π charges, respectively, donated by the substituent, Y or X, to the ring. Y = CH₂⁻, X = substituent. A positive value indicates that the substituent is an electron acceptor from the ring. ^b $\pi(\text{Ph-Y})$ and $\pi(\text{Ph-X})$ are Mulliken overlap populations of the adjacent π -type p orbitals in the bond joining Y and X, respectively, to the ring. Y = CH₂⁻, X = substituent. ^c Results for a planar OH substituent (not lowest energy conformation).

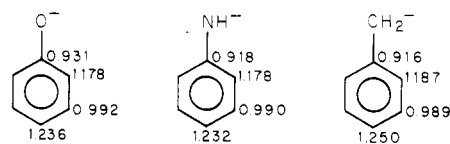
to be consistent with the expected large specific medium effects on acidity which destroy the use of phenoxides as effective models for carbanions.^{6,12}

Methods and Results

The STO-3G calculations were carried out with standard model geometries¹³ for all substrates except CH₃O and NH₂ substituents. For the amino group, the three bond angles about nitrogen were assumed equal and optimized for each system examined. For the methoxy group, COC = 118° was used, this being the optimized value for anisole.¹⁴ The C-O bond length (1.28 Å) of phenoxide anion and the C-N bond length (1.34 Å) of anilide anion were obtained by optimization of the unsubstituted parent ions and were used for all of the substituted anions. Geometric parameters defining the CH₂⁻ group in benzyl anion were fully optimized, and the calculated bond lengths (C_{ar}-C_α = 1.372 Å, C_α-H = 1.072 Å) and bond angles (C_{ar}C_αH = 121.7°) were used in subsequent calculations. Calculations for appropriate substrates were conducted for a number of possible conformations and the results for the energetically favored conformation (cf. Table I) were utilized in all subsequent analyses. Total energies for the substituted benzyl anions are shown in Table I, with Mulliken charges and overlap populations in Table II. Similar results for the other substituted benzene systems are given elsewhere.¹⁰

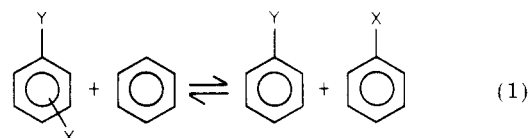
The present study is based upon nine meta and nine (corresponding) para substituents in toluene, aniline, and phenol. These substituents were selected because each is stable and capable of an experimental determination of its effect on gas-phase acidity. In addition, a wide variety of substituent types are represented: CF₃, CN, and NO₂ are both σ - and π -electron acceptors. Although CHO is often associated with this group, the calculations suggest that, while its π -electron-acceptor ability is comparable to that of NO₂,¹⁰ it possesses no significant σ effect. F, OH, and NH₂ are indicated to be increasingly stronger as π -

electron donors, but increasingly weaker as σ -electron acceptors.^{10,14} OCH₃ is similar (theoretically at least) in behavior to OH. The CH₃ substituent is indicated to be a very weak π -donor and essentially noninteracting in the σ framework.^{10,14} All three anionic substituents, CH₂⁻, NH₂⁻, and O⁻, are indicated to be powerful π -electron-donor substituents, whose π -donating ability increases in the order O⁻ ~ NH₂⁻ < CH₂⁻. This order is discernible from the π -electron populations, particularly at the para position, for phenoxide, anilide, and benzyl anions:



It receives further confirmation from the $q_{\pi}(X)$ values for para +R groups (e.g., *p*-NO₂) in the three systems which also increase in the order O⁻ ~ NH₂⁻ < CH₂⁻.¹⁵ However, due to the powerful influence of the negative charge associated with these groups, the differences between them appear to be slight in comparison to the magnitude of the overall effect. Interestingly, despite the negative charge, all three groups appear to have only relatively weak σ effects.

Interaction energies ($\delta_X E_Y$) are given by energy changes in reactions of the type 1, where X is a substituent and



Y is any one of the six functional groups (i.e., CH₃, NH₂, OH, CH₂⁻, NH₂⁻, O⁻). A positive value of the interaction energy $\delta_X E_Y$ denotes a favorable interaction between X and Y; i.e., X and Y prefer to be in the same ring. Conversely,

(12) (a) R. W. Taft, *Kinet. Ion-Molec. React.*, NATO Adv. Stud. Inst., 1970, 40, 271 (1979); (b) cf. Figure 2 of this reference.

(13) J. A. Pople and M. S. Gordon, *J. Am. Chem. Soc.*, 89, 4253 (1967).

(14) W. J. Hehre, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.*, 94, 1496 (1972); *J. Chem. Soc., Chem. Commun.*, 669 (1972).

(15) $q_{\pi}(Y)$ values for O⁻, NH₂⁻, and CH₂⁻ which might have been expected to provide the most direct measure of the π -donating ability of these groups are considered unreliable due to the limitations inherent in the Mulliken analysis when comparing charge distributions of different atomic groupings (i.e., CO⁻, CN⁻, CC⁻).

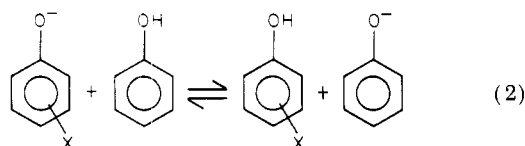
Table III. Interaction Energies ($\delta_X E_Y$, kcal mol⁻¹) for Substituted Phenoxide, Anilide, and Benzyl Anions

X	$\delta_X E_{O^-}$ ^a	$\delta_X E_{NH^-}$ ^b	$\delta_X E_{CH_2^-}$ ^c
<i>m</i> -CH ₃	-0.1	-0.1	0.0
<i>m</i> -NH ₂	+0.7	+0.7	+0.8
<i>m</i> -OH	+3.8	+3.6	+3.8
<i>m</i> -OCH ₃	+3.0	+2.9	+3.0
<i>m</i> -F	+5.8	+5.5	+5.7
<i>m</i> -NO ₂	+17.6	+16.9	+17.6
<i>m</i> -CN	+14.1	+13.5	+14.1
<i>m</i> -CHO	+5.9	+5.7	+5.7
<i>m</i> -CF ₃	+8.2	+7.7	+8.2
<i>p</i> -CH ₃	-1.4	-1.4	-1.4
<i>p</i> -NH ₂	-6.4	-6.4	-6.7
<i>p</i> -OH	-4.4	-4.4	-4.7
<i>p</i> -OCH ₃	-4.3	-4.4	-4.6
<i>p</i> -F	+0.7	+0.5	+0.4
<i>p</i> -NO ₂	+30.4	+29.9	+32.6
<i>p</i> -CN	+22.2	+21.7	+23.5
<i>p</i> -CHO	-14.5	-14.3	+15.6
<i>p</i> -CF ₃	+11.9	-11.5	+12.4

^a Values represent energy changes for the reactions $XC_6H_4O^- + C_6H_6 \rightarrow C_6H_5O^- + C_6H_5X$. ^b Values represent energy changes for the reactions $XC_6H_4NH^- + C_6H_6 \rightarrow C_6H_5NH^- + C_6H_5X$. ^c Values represent energy changes for the reactions $XC_6H_4CH_2^- + C_6H_6 \rightarrow C_6H_5CH_2^- + C_6H_5X$.

a negative interaction energy indicates that X and Y prefer separate rings.

The difference in the substituent interaction energies between the neutral acids (CH₃, NH₂, OH) and that for the conjugate base (CH₂⁻, NH⁻, O⁻, respectively) gives the calculated effect of substituent on acidity ($\delta_X \Delta E_a^\circ(Y)$). For example, the effect of substituents on acidity of phenols is given by the energy changes in reactions of the type 2: $\delta_X \Delta E_a^\circ(OH) = \delta_X E_{O^-} - \delta_X E_{OH}$. A positive sign denotes greater acidity for the substituted phenol.



Calculated interaction energies for substituted phenoxide, anilide, and benzyl anions are listed in Table III. Interaction energies involving the corresponding neutral groups are listed in Table IV. Both theoretical and available experimental effects of substituents on acidities are presented in Table V. The average deviation between calculated and experimental values is ± 1.3 kcal mol⁻¹, which is 4% of the total range of substituent effects (-6.3 to +31.9). While the agreement in several instances (in particular, for strongly interacting substituents) is only fair, the general accord may be regarded as satisfactory.

Discussion

Comparison of interaction energies for substituted phenoxide, anilide, and benzyl anions (Table III) indicates a remarkable similarity between the three series. For the meta-substituted anions and the para -R substituted anions the corresponding interaction energies are essentially the same. For the four para +R substituents, the substituent stabilization energies increase slightly (~8% overall) in the order anilide < phenoxide < benzyl anion. This reflects the small differences in π -donating ability demonstrated by the three groups. It appears that in the gas phase the negative charge associated with O⁻, NH⁻, and CH₂⁻ constitutes a sufficiently large perturbation to these groups so as to reduce significantly any intrinsic differences

Table IV. Interaction Energies ($\delta_X E_Y$, kcal mol⁻¹) for Substituted Phenols, Anilines, and Toluenes

X	$\delta_X E_{OH}$ ^a	$\delta_X E_{NH_2}$ ^b	$\delta_X E_{CH_3}$ ^c
<i>m</i> -CH ₃	+0.3	+0.2	0.0
<i>m</i> -NH ₂	+0.8	+0.8	+0.2
<i>m</i> -OH	+0.8	-0.8	+0.3
<i>m</i> -OCH ₃	+0.9	+0.7	+0.2
<i>m</i> -F	+0.4	+0.6	+0.3
<i>m</i> -NO ₂	-0.5	0.0	+0.3
<i>m</i> -CN	-0.4	+0.1	+0.2
<i>m</i> -CHO	0.0	0.0	+0.1
<i>m</i> -CF ₃	+0.1	+0.1	-0.2
<i>p</i> -CH ₃	-0.4	-0.5	-0.1
<i>p</i> -NH ₂	-1.5	-1.6	-0.5
<i>p</i> -OH	-1.4	-1.5	-0.4
<i>p</i> -OCH ₃	-1.3	-1.5	-0.4
<i>p</i> -F	-0.9	-0.8	-0.2
<i>p</i> -NO ₂	+1.3	+2.2	+0.8
<i>p</i> -CN	+0.8	+1.4	+0.5
<i>p</i> -CHO	+0.7	+1.0	+0.3
<i>p</i> -CF ₃	+0.4	+0.8	+0.3

^a Values represent energy changes for the reactions $XC_6H_4OH + C_6H_6 \rightarrow C_6H_5OH + C_6H_5X$. ^b Values represent energy changes for the reactions $XC_6H_4NH_2 + C_6H_6 \rightarrow C_6H_5NH_2 + C_6H_5X$. ^c Values represent energy changes for the reactions $XC_6H_4CH_3 + C_6H_6 \rightarrow C_6H_5CH_3 + C_6H_5X$.

between them. As a result, our calculations suggest that unsolvated phenoxide ions are quite acceptable models for the correspondingly substituted benzyl anions.

Interaction energies for the neutral acids (Table IV) show relatively small but expected effects of π -electron delocalization.^{14,16} Since the acid groups are increasingly π donor in the sequence CH₃ < OH < NH₂, stabilizing conjugation effects of +R para electron substituents are found in this order, as well as destabilizing π -saturation effects of -R para substituents.^{10,17}

The large interaction energies associated with the anions coupled with the small interaction energies associated with the corresponding neutral acids indicate that the predominant effect of substituent on acidity stems from the anions. The effects of substituents on acidity are given by the difference between interaction energies for the anions and corresponding neutral acids and are listed in Table V along with the available gas-phase experimental data. Strong acid-weakening effects are exhibited by π -electron donors, which from the para position destabilize each of the strong π -donor anion groups by repulsive π -saturation effects.¹⁸ Strong acid enhancements arise with σ and π acceptors which have a strong stabilizing influence on the anions.

However, substituent effects in the neutrals do have some effect on the acidities. Whereas the range of interaction energies for substituted toluenes (from *p*-NH₂ to *p*-NO₂ substituents) spans only 1.3 kcal mol⁻¹, the corresponding range for the aniline series is 3.8 kcal mol⁻¹. Thus, these substituent effects in the un-ionized acids will tend to make corresponding effects of substituents on acidity increase slightly in the sequence anilines < phenols

(16) These are the predominant effects, but others also contribute. For example, it will be noted in Table IV that *m*-CN and *m*-NO₂ slightly stabilize toluene, have little effect on aniline, and destabilize phenol by small amounts. These trends are accounted for by increasing σ -electron-acceptor abilities: CH₃ < NH₂ < OH. More detailed considerations are given in ref 10.

(17) (a) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry", Prentice-Hall, New York, 1941, pp 250-2; (b) A. J. Hoefnagel, M. A. Hoefnagel, and B. M. Wepster, *J. Am. Chem. Soc.*, **98**, 6194 (1976).

(18) An intriguing manifestation of this effect is a preferred orthogonal orientation of the OH substituent in *p*-hydroxybenzyl anion.

Table V. Effect of Substituent on Acidities ($\delta_X E_a^\ominus(Y)$, kcal mol⁻¹) of Phenols, Anilines, and Toluenes

X	$\delta_X \Delta E_a^\ominus(\text{OH})$		$\delta_X \Delta E_a^\ominus(\text{NH}_2)$		$\delta_X \Delta E_a^\ominus(\text{CH}_3)$	
	theor	exptl	theor	exptl	theor	exptl
<i>m</i> -CH ₃	-0.4	-0.4, ^a -0.5 ^b	-0.3	-0.5 ^c	-0.1	
<i>m</i> -NH ₂	-0.1	-0.9 ^a	-0.1		+0.6	
<i>m</i> -OH	+3.0	+4.3 ^a	+2.8		+3.5	
<i>m</i> -OCH ₃	+2.1	+1.1, ^c +1.5 ^a	+2.2		+2.8	
<i>m</i> -F	+5.4	+5.8, ^a +5.3 ^c	+5.0	+4.0 ^e	+5.4	
<i>m</i> -NO ₂	+18.1	+15.7 ^a	+16.9		-17.3	
<i>m</i> -CN	+14.5	+14.3 ^a	+13.4		+13.9	
<i>m</i> -CHO	-5.9	+8.6 ^c	+5.7		+5.6	
<i>m</i> -CF ₃	-8.4	+9.7 ^c	+7.6	+8.0 ^e	-8.1	
<i>p</i> -CH ₃	-1.0	-1.2, ^b -1.3 ^a	-1.0	-1.2	-1.3	-1.4 ^e
<i>p</i> -NH ₂	-4.9	-4.2 ^a	-4.8		-6.3	
<i>p</i> -OH	-2.9	-1.7 ^c	-2.9		-4.2	
<i>p</i> -OCH ₃	-3.0	-1.2, ^c -0.8 ^a	-2.9	-0.9	-4.2	
<i>p</i> -F	+1.6	+2.1, ^b +2.6 ^a	+1.3	+1.6 ^e	+0.6	
<i>p</i> -NO ₂	+29.2	(+25.8) ^{a,d}	+27.7		+31.9	+26.3 ^f
<i>p</i> -CN	+21.4	+17.7 ^a	+20.2		+23.0	
<i>p</i> -CHO	+13.8		+13.3		+15.3	
<i>p</i> -CF ₃	-11.5	+12.0 ^c	+10.7	+11.5 ^e	-12.1	

^a Reference 18. ^b R. T. McIver, Jr., and J. H. Silvers, *J. Am. Chem. Soc.*, **95**, 8462 (1973). ^c M. Fujio, R. T. McIver, Jr., and R. W. Taft, unpublished results. ^d Estimated value. ^e Reference 5. ^f J. B. Cumming and P. Kebarle, cf. ref 5.

< toluenes. Indeed, the theoretical calculations of relative acidities (Table V) predict that rather precise linear free-energy relationships will be observed in the gas-phase acidities with slopes of ~ 1.2 (the slope of $\delta_X \Delta E_a^\ominus(\text{CH}_3)$ vs. $\delta_X \Delta E_a^\ominus(\text{NH}_2)$ values) for toluenes vs. anilines and ~ 1.1 (the slope of $\delta_X \Delta E_a^\ominus(\text{OH})$ vs. $\delta_X \Delta E_a^\ominus(\text{NH}_2)$ values) for phenols vs. anilines.

The recent results of Bartmess, Scott, and McIver⁵ and of Fujio^{11a} (Table V) do support this prediction for phenols vs. anilines. The 26.3 kcal mol⁻¹ greater gas-phase acidity of *p*-nitrotoluene than toluene is also consistent with Kebarle's estimate of 25.8 kcal mol⁻¹ for the acidity difference between *p*-nitrophenol and phenol,¹⁹ but a much more stringent test is obviously required.

In view of the presently available experimental gas-phase acidity results and the STO-3G theoretical calculations which we have reported herein, it is clear that the earlier failures of the phenoxide ion model for carbanions are due largely to solvation effects (including effects of counterions) and are not inherent. Indeed, there are dramatic specific variations in the effects of solvent on the acidifying effects of the *p*-NO₂ substituent, which may now be estimated to quantitative approximation. Converting the medium effects on acidity obtained as $\delta_X \Delta G_a^\ominus(\text{g}) - \delta_X \Delta G_a^\ominus(\text{soln})$ to more familiar $\text{p}K_a$ units, the following results are obtained: (a) aqueous medium reduces the inherent acidifying effect of the *p*-NO₂ substituent for phenol by 16 $\text{p}K_a$ units;²⁰ (b) dimethyl sulfoxide solution reduces this acidity effect by 11 $\text{p}K_a$ units for phenol²¹ and by 7 $\text{p}K_a$ units for aniline,²² but increases the *p*-NO₂ effect by 2 $\text{p}K_a$ units for toluene.²³

These medium effects are readily understood in terms of Bordwell's work^{6a} and the classification given recently by Taft.¹² Phenoxide ion is specifically solvated by Me₂SO and (particularly) by water.^{12b} The *p*-nitro substituent

reduces these specific solvations very substantially, resulting in large reductions (in this order) in the acidifying effects of the *p*-NO₂ substituent compared to its inherent gas-phase effect. The anilide ion is also specifically solvated (again Me₂SO < H₂O), but to an appreciably smaller degree than phenoxide ion. This gives rise to smaller medium effects for aniline than phenol acidity. The benzyl anion appears to be essentially nonspecifically solvated by either water or Me₂SO. The charge distribution in *p*-nitrobenzyl anion, however, places the negative charge primarily on the two nitro oxygen atoms, making this anion weakly to moderately specifically solvated. The result is a greater apparent acidifying effect of *p*-NO₂ in Me₂SO solution²⁴ than in the gas phase. It is implied that the development of a solvent and counterion system, both of which are designed to avoid specific solvation effects, will enable the use of phenoxides as models for carbanion behavior.

Conclusions

The following points emerge from this work.

(1) The effect of substituents on the acidities of toluenes, anilines, and phenols is dominated by the effect in the anions (benzyl, anilide, and phenoxide, respectively) rather than in the neutral acids.

(2) Interaction energies in substituted benzyl, anilide, and phenoxide anions are predicted to be very similar.

(3) The sensitivity of acidity to the effect of substituent increases slightly in the order anilines < phenols < toluenes due to a small but systematic effect in the neutrals, in addition to the contribution of the anions.

(4) Substituted phenoxide anions are satisfactory models for the corresponding benzyl anions in the gas phase but not in solution, owing to specific solvation effects.

Acknowledgment. This research was supported in part by a grant (RWT-UCI) from the U.S. Public Health Service. The award of an ANU vacation scholarship (to G.K.) is gratefully acknowledged. We are pleased to acknowledge helpful comments from Professor F. G. Bordwell.

(24) A similar but larger solvent effect occurs with nitromethane, which, in the gas phase, is 21 kcal mol⁻¹ more acidic than toluene,⁵ but in Me₂SO, is 34 kcal mol⁻¹, and, in water, is 42 kcal mol⁻¹ more acidic than toluene.¹²

(19) T. B. McMahon and P. Kebarle, *J. Am. Chem. Soc.*, **99**, 2222 (1977).

(20) Based upon gas-phase data of Table V and $\Delta \text{p}K_a(\text{aq}) = 2.85$: A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961).

(21) Based upon gas-phase data of Table V and $\Delta \text{p}K(\text{Me}_2\text{SO}) = 3.6$: private communication from F. G. Bordwell and W. N. Olmstead. Also, for *p*-nitrophenol, cf. I. M. Kolthoff, M. K. Chantooni, and S. Bhowmik, *J. Am. Chem. Soc.*, **90**, 23 (1968).

(22) Based upon the gas-phase estimate of $\delta_{p\text{-NO}_2} \Delta E_a^\ominus(\text{NH}_2) = 26/1.1 = 23.6$ kcal mol⁻¹ (cf. Discussion) and $\Delta \text{p}K_a(\text{Me}_2\text{SO}) = 9.8$.^{6b}

(23) Based upon gas-phase data of Table V and $\Delta \text{p}K_a(\text{Me}_2\text{SO}) = 20.4$.^{6b}

Registry No. *m*-Methylphenoxide, 20227-79-6; *m*-aminophenoxide, 68743-37-3; *m*-hydroxyphenoxide, 20217-24-7; *m*-methoxyphenoxide, 40529-20-2; *m*-fluorophenoxide, 32376-33-3; *m*-nitrophenoxide, 16554-54-4; *m*-cyanophenoxide, 18938-12-0; *m*-formylphenoxide, 38144-52-4; *m*-(trifluoromethyl)phenoxide, 72332-16-2; *p*-methylphenoxide, 22113-51-5; *p*-aminophenoxide, 19052-59-6; *p*-hydroxyphenoxide, 20217-26-9; *p*-methoxyphenoxide, 29368-59-0; *p*-fluorophenoxide, 32376-34-4; *p*-nitrophenoxide, 14609-74-6; *p*-cyanophenoxide, 14609-76-8; *p*-formylphenoxide, 18938-17-5; *p*-(trifluoromethyl)phenoxide, 72332-17-3; *m*-methylanilide, 37062-12-7; *m*-aminoanilide, 72611-39-3; *m*-hydroxyanilide, 72611-40-6; *m*-methoxyanilide, 72611-41-7; *m*-fluoroanilide, 72611-42-8; *m*-nitroanilide, 72611-43-9; *m*-cyanoanilide, 72611-44-0; *m*-formylanilide, 72611-45-1; *m*-(trifluoromethyl)anilide, 72611-46-2; *p*-methylanilide, 37062-13-8; *p*-aminoanilide, 72611-47-3; *p*-hydroxyanilide, 72611-48-4; *p*-methoxyanilide, 72611-49-5; *p*-fluoroanilide, 72611-50-8; *p*-nitroanilide, 934-70-3; *p*-cyanoanilide, 66365-37-5; *p*-formylanilide, 72611-51-9; *p*-(trifluoromethyl)anilide, 72611-52-0; *m*-methylbenzyl anion, 59305-38-3; *m*-aminobenzyl anion, 72611-53-1; *m*-hydroxybenzyl anion, 72611-54-2; *m*-methoxybenzyl anion, 72611-55-8; *m*-fluorobenzyl anion, 72611-56-4; *m*-nitrobenzyl anion, 72611-57-5; *m*-cyanobenzyl anion, 72611-58-6; *m*-formylbenzyl anion, 72611-59-7; *m*-(trifluoromethyl)benzyl anion, 72611-60-0; *p*-methylbenzyl anion, 59305-42-9; *p*-aminobenzyl anion, 72638-42-7; *p*-hydroxybenzyl an-

ion, 72611-61-1; *p*-methoxybenzyl anion, 72611-62-2; *p*-fluorobenzyl anion, 72611-63-3; *p*-nitrobenzyl anion, 72409-67-7; *p*-cyanobenzyl anion, 18802-90-9; *p*-formylbenzyl anion, 72611-64-4; *p*-(trifluoromethyl)benzyl anion, 72611-65-5; *m*-methylphenol, 108-39-4; *m*-aminophenol, 591-27-5; *m*-hydroxyphenol, 108-46-3; *m*-methoxyphenol, 150-19-6; *m*-fluorophenol, 372-20-3; *m*-nitrophenol, 554-84-7; *m*-cyanophenol, 873-62-1; *m*-formylphenol, 100-83-4; *m*-(trifluoromethyl)phenol, 98-17-9; *p*-methylphenol, 106-44-5; *p*-aminophenol, 123-30-8; *p*-hydroxyphenol, 123-31-9; *p*-methoxyphenol, 150-76-5; *p*-fluorophenol, 371-41-5; *p*-nitrophenol, 100-02-7; *p*-cyanophenol, 767-00-0; *p*-formylphenol, 123-08-0; *p*-(trifluoromethyl)phenol, 402-45-9; *m*-methylaniline, 108-44-1; *m*-aminoaniline, 108-45-2; *m*-methoxyaniline, 536-90-3; *m*-fluoroaniline, 372-19-0; *m*-nitroaniline, 99-09-2; *m*-cyanoaniline, 2237-30-1; *m*-formylaniline, 1709-44-0; *m*-(trifluoromethyl)aniline, 98-16-8; *p*-methylaniline, 106-49-0; *p*-aminoaniline, 106-50-3; *p*-methoxyaniline, 104-94-9; *p*-fluoroaniline, 371-40-4; *p*-nitroaniline, 100-01-6; *p*-cyanoaniline, 873-74-5; *p*-formylaniline, 556-18-3; *p*-(trifluoromethyl)aniline, 455-14-1; *m*-methyltoluene, 108-38-3; *m*-methoxytoluene, 100-84-5; *m*-fluorotoluene, 352-70-5; *m*-nitrotoluene, 99-08-1; *m*-cyanotoluene, 620-22-4; *m*-formyltoluene, 620-23-5; *m*-(trifluoromethyl)toluene, 401-79-6; *p*-methyltoluene, 106-42-3; *p*-methoxytoluene, 104-93-8; *p*-fluorotoluene, 352-32-9; *p*-nitrotoluene, 99-99-0; *p*-cyanotoluene, 104-85-8; *p*-formyltoluene, 104-87-0; *p*-(trifluoromethyl)toluene, 6140-17-6.

Kinetic Studies in Peptide Chemistry. Coupling, Racemization, and Evaluation of Methods Useful for Shortening Coupling Time¹

J. Kovacs,* E. M. Holleran, and K. Y. Hui

Department of Chemistry, St. John's University, Jamaica, New York 11439

Received July 10, 1979

Kinetic studies were carried out on *N*-protected methionine and glycylmethionine active esters to determine the racemization rate constants with triethylamine and the coupling rate constants with valine methyl ester. In contrast to cysteine dipeptide active esters, which racemize through an enolization mechanism, the methionine dipeptide active esters racemize through the usual 5(4*H*)-oxazolone route. The role of sulfur in the side chain is discussed. The time required for coupling a given percentage (e.g., 99%) of the amine component can be significantly reduced by using an excess of the active ester. This method is evaluated quantitatively for second-order kinetics.

It has been reported that *N*-carbobenzyloxy-*S*-benzyl-*L*-cysteine active esters racemize unusually fast² by the isomerization mechanism.³ It has also been established that the *N*-carbobenzyloxyglycyl-*S*-benzyl-*L*-cysteine *p*-nitrophenyl ester racemizes through enolization rather than the expected 5(4*H*)-oxazolone mechanism.^{4,5} The deviation from the 5(4*H*)-oxazolone mechanism is amino acid side chain dependent, and therefore it is of interest to compare the effect of the side chain of the other sulfur-containing amino acid, namely methionine, on the rate and mechanism of racemization.

For practical synthetic purposes the coupling time is another important aspect which must be considered, since coupling reactions must be completed within a reasonable period of time. There are several ways of decreasing the

coupling time. One is to choose a faster coupling active ester, avoiding such slow couplers as trichlorophenyl or *p*-nitrophenyl esters, which require days or even weeks to achieve 99% completion.⁶ Another way is to increase the concentrations of the coupling species, and a third way is to change the ratio of their initial concentrations. Practical aspects of these methods will be illustrated in this paper. A quantitative evaluation of the last method will also be included.

In this work, four frequently used active esters were selected for the study. These were pentachlorophenyl, *p*-nitrophenyl, pentafluorophenyl, and *N*-succinimidoyl active esters of *N*-carbobenzyloxy- and *N*-*tert*-butyloxycarbonylmethionine, as well as the corresponding glycyl dipeptide active esters. Racemization was studied in anhydrous tetrahydrofuran solution in the presence of triethylamine. Coupling with an equimolar amount of *L*-valine methyl ester was followed by IR analysis in the same solvent. The results are given in Table I which contains the experimental as well as the calculated second-order rate constants for both racemization and coupling. The calculated values are obtained using the additivity principle published previously.⁷

(1) Part of the paper was presented at the Fifth American Peptide Symposium, San Diego, CA, 1977, and the Fifteenth European Peptide Symposium, Gdansk, Poland, 1978.

(2) (a) J. Kovacs, G. L. Mayers, R. H. Johnson, R. E. Cover, and U. R. Ghatak, *J. Org. Chem.*, **35**, 1810 (1970); (b) J. Kovacs, G. L. Mayers, R. H. Johnson, and U. R. Ghatak, *J. Chem. Soc., Chem. Commun.*, 1066 (1968); (c) J. Kovacs, G. L. Mayers, R. H. Johnson, R. E. Cover, and U. R. Ghatak, *ibid.*, 53 (1970).

(3) (a) G. L. Mayers and J. Kovacs, *J. Chem. Soc. D*, 1145 (1970); (b) J. Kovacs, H. Cortegiano, R. E. Cover, and G. L. Mayers, *J. Am. Chem. Soc.*, **93**, 1541 (1971).

(4) J. Kovacs and Y. Hsieh, submitted for publication.

(5) J. Kovacs, Y. Hsieh, K. Y. Hui, and S. E. Kim, "Peptides, Proceedings of the Fifth American Peptide Symposium", M. Goodman and J. Meienhofer, Eds., Wiley, New York, 1977, p 461.

(6) J. Kovacs, Y. Hsieh, E. M. Holleran, and S. Ting, "Peptides 1978, Proceedings of the Fifteenth European Peptide Symposium", Gdansk, Poland, I. Z. Siemion and G. Kupryszewski, Eds., Wroclaw University Press, Poland, 1979, p 159.