interpreting NMR spectral data and to the National Science Foundation for providing funds for the purchase of the NMR instrument.

Supplementary Material Available: Characterization data and general experimental procedures (10 pages). Ordering information is given on any current masthead page.

Enhanced Substituent Solvation Assisted Resonance Effects in Dipolar Non-Hydrogen-Bond-Donor Solvents

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A recent analysis of gas- vs. aqueous-phase data has revealed that phenol acidities in water have significant and specific dependencies on hydrogen bonding to substituents.[1] Strong hydrogen-bond-acceptor (HBA) substituents give relatively increased acidities due to the hydrogen-bond-donor (HBD) properties of water, whereas strong HBD substituents give relatively decreased acidities due to the HBA properties of water. These hydrogen-bond interactions act to modify both the substituent field/inductive (F) and resonance (R) effects.[1,2] Thus for those +R substituents that are *both* π electron and strong hydrogen-bond acceptors, the F effect is increased by hydrogen bonding in water about equally at the meta and para ring positions (we refer to these as specific substituent solvation assisted field (SSSAF) effects). The acidifying +R resonance effect is also significantly increased by substituent HBA hydrogen bonding (SSSAR), but *only* at the para position.[1,2]

We communicate here a preliminary report on the results of a complementary investigation of the effects of substituent solvation by Me_2SO based upon comparisons of phenol acidities in the gas phase vs. Me_2SO solution.[3,4] The inability of the Me_2SO solvent to act as an HBD toward either the phenoxide ion center or substituents with strong HBA properties[5] was expected to cause at least three significant changes, relative to those observed for the aqueous solvent. (1) The absence of hydrogen-bond solvation of phenoxide ions by Me_2SO,[5] together with the relative ineffectiveness of electrostatic or Lewis acid solvation,[2] should cause a much smaller solvent attenuation of gas-phase acidities, i.e., a smaller slope for the plot of gas phase vs. Me_2SO phenol acidities. (2) The absence of hydrogen-bond substituent solvation should cause SSSAF effects to be absent for all +R substituents at both meta and para positions in Me_2SO. (3) Enhanced acidity effects will be observed only for those +R para substituents that become sufficiently charge localized by their R effect as to cause electrostatic or nonprotonic Lewis acid solvation (SSAR[6] effect).

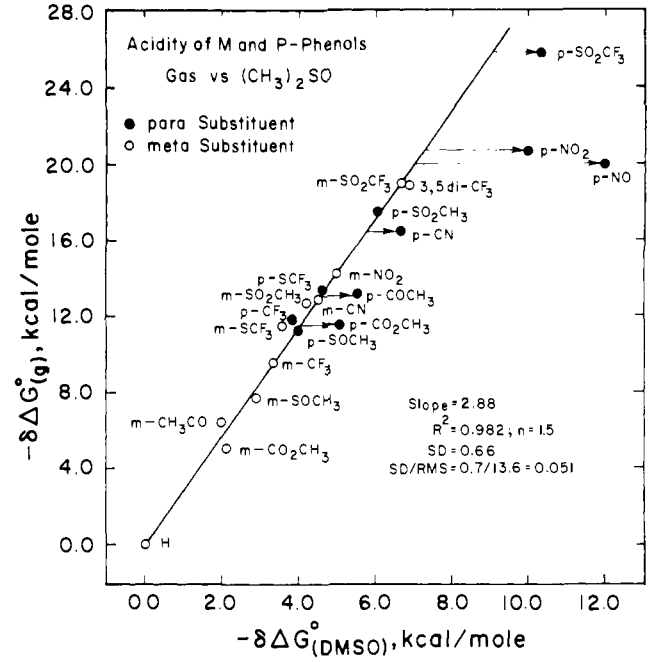

Figure 1. Relative acidities of meta- and para-substituted phenols: gas vs. $(CH_3)_2SO$ solution. Correlation statistics are as given. Ordinant: $-\delta\Delta G^\circ$(g), kcal/mol. Abscissa: $-\delta\Delta G^\circ((CH_3)_2SO)$, kcal/mol.

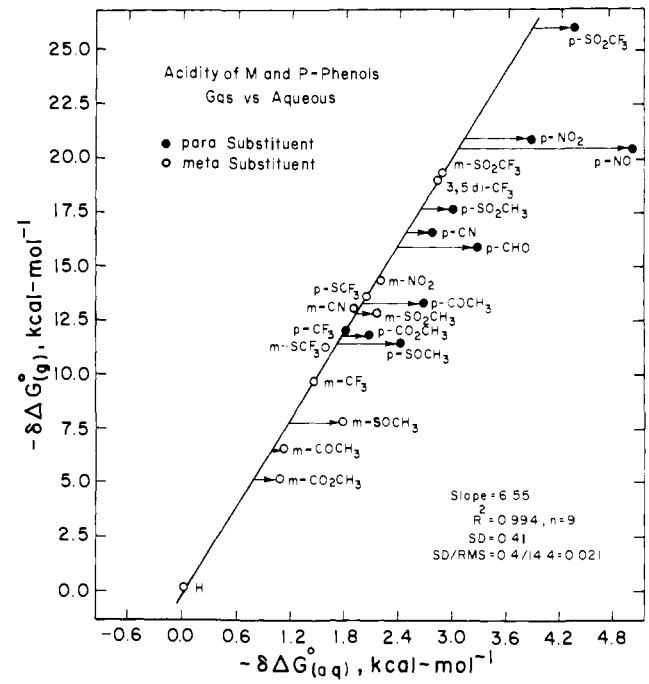

Figure 2. Relative acidities of meta- and para-substituted phenols: gas vs. aqueous solution. Correlation statistics are as given. Ordinant: $-\delta\Delta G^\circ$(g), kcal/mol. Abscissa: $-\delta\Delta G^\circ$(aq), kcal/mol.

The gas-phase acidities of an extended series of +R meta- and para-substituted phenols[1,7,8] are plotted in Figure 1 against the corresponding acidities of these phenols in dilute Me_2SO solution (each relative to that for the unsubstituted phenol). Examination of Figure 1 confirms the changes anticipated: (1) the slope of the line in Figure 1 is 2.9 compared to 6.6 observed in water (Figure 2); (2) there is no significant deviation from a linear

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(2) Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 305–346.
(3) The acidities of phenols in Me_2SO were measured and corrected for homo-hydrogen bonding between the phenol and its conjugate base as previously described.[4]
(4) Bordwell, F. G.; McCallum, R. J.; Olmstead, W. N. *J. Org. Chem.* **1984**, *49* (in press).
(5) Cf.: Kamlet, M. J.; Abboud, J. L. M.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877 and references therein.
(6) We omit the adjective "specific" for SSAR effects in Me_2SO since at present there is no compelling evidence as to which type is involved. Specific solvation is defined as involving discrete solvent–solute (or Lewis acid–base) complexes as contrasted to nondiscrete many molecule electrostatic solvation.
(7) Our new $-\delta\Delta G_p^\circ$ values in kcal/mol for the following para substituents: *p*-SCF_3, 13.5; *p*-SO_2CF_3, 25.9; *p*-NO, 20.2. $-\delta\Delta G_m^\circ$ values: *m*-SCF_3, 11.7; *m*-SO_2CF_3, 19.1; 3,5-$(CF_3)_2$, 19.0.
(8) The meta and para π electron-donor (–R) substituent points have been omitted from Figures 1 and 2. Substituent solvation effects for these functions will be discussed in a full paper now in preparation.

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correlation for the substituents *m*- and *p*-CF_3, 3,5-$(CF_3)_2$, *m*- and *p*-$SOCH_3$, *m*- and *p*-SO_2CH_3, *m*- and *p*-SCF_3, *m*-CO_2CH_3, *m*-CH_3CO, *m*-CN, *m*-NO_2, and *m*-SO_2CF_3; (3) there are even larger acidifying SSAR effects in Me_2SO than aqueous solution for the substituents *p*-CO_2CH_3 (0.8), *p*-CN (0.9), *p*-$COCH_3$ (1.1), *p*-SO_2CF_3 (1.3), *p*-NO_2 (2.7), and *p*-NO (4.9). (The figures in parentheses are these obtained from the horizontal deviation lines in Figure 1, in kcal/mol). A comparison plot for phenol acidities, gas vs. aqueous phase, is given in Figure 2, which includes recently obtained results for *m*- and *p*-SO_2CF_3, m- and p-SCF_3, *p*-NO, and 3,5-$(CF_3)_2$ phenols.[7]

The SSAR effects in Me_2SO solution appear to be determined by substituent charge localization, which depends upon a combination of a substituent's ability to attract π electrons (given by its $\sigma_{R^-(g)}$ value[1]) and the degree of localization of negative charge on an oxygen or nitrogen atom at the perimeter of the substituent. The size of the latter effect depends upon the extent of conjugation through the first atom of the substituent (for example, less for S and sp^3 C than for sp^2 C or sp^2 N) as well as the number of N or O atoms that share the charge (for example, less for NO_2 than NO).

The SSAR effects in Me_2SO are roughly 2.5 times *greater* than the corresponding SSSAR effects in H_2O. (The latter were obtained by taking the difference in horizontal deviations in Figure 2 for para substituents minus those for the corresponding meta substituents in order to eliminate SSSAF effects.) This SSAR/SSSAR ratio is approximately the inverse of the ratio of the slopes of the gas vs. Me_2SO and gas vs. H_2O correlation lines in Figures 1 and 2, consistent with the differences in the solvation of the phenoxide ion center.[9]

These comparisons of gas-phase and solution acidities reveal that the solvent plays a dominant role not only in controlling reactivity at the phenoxide ion reaction center but also in modifying the effects of substituents on this reactivity. It is clear from Figures 1 and 2 that modifications due to substituent solvation change significantly the order of substituent effects on acidity (and no doubt on reactivity[2]) from *p*-$SOCH_3$, *p*-CO_2CH_3, *p*-CF_3 < *p*-$COCH_3$, *p*-SCF_3 < *p*-CHO < *p*-CN < *p*-SO_2CH_3 < *p*-NO < *p*-NO_2 < *p*-SO_2CF_3 for nonsolvated substituents (gas phase) to *p*-CF_3, *p*-$SOCH_3$ < *p*-SCF_3 < *p*-CO_2CH_3 < *p*-$COCH_3$ < *p*-SO_2CH_3 < *p*-CN < *p*-NO_2, *p*-SO_2CF_3 < *p*-NO with certain substituents involving SSAR solvation (Me_2SO solution) to *p*-CF_3 < *p*-SCF_3 < *p*-CO_2CH_3 < *p*-$SOCH_3$ < *p*-$COCH_3$, *p*-CN < *p*-SO_2CH_3 < *p*-CHO < *p*-NO_2, *p*-SO_2CF_3 < *p*-NO with SSSAF and SSSAR solvation effects included (aqueous solution, the Hammett σ_p^- order).

These results indicate that we can expect to see SSSAF and SSSAR effects for strong HBA +R substituents[11] in all strong HBD (solvent HBD parameter α[5] $\geq$ 0.5) media and expect to see SSAR effects for charge localized +R para substituents in dipolar nonhydroxylic or non-HBD ("aprotic") solvents[12] for which α = 0 and π^* > 0.75.

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(9) With the more weakly solvated anilide or benzyl ion centers in Me_2SO solution, even larger SSAR effects of appropriate +R para substituents are observed, cf. ref 10 and a preliminary report in ref 2.

(10) Bordwell, F. G.; Olmstead, W. N.; Mashima, M.; Fujio, M.; Taft, R. W., manuscript in preparation.

(11) As substituent–solvent complexing weakens, its acidity effects are expected to suddenly disappear for reasons considered in detail in ref 1 and 2.

(12) Most solvents now commonly referred to as "dipolar aprotic" (Me_2SO, DMF, NMP, HMPA, CH_3CN, CH_3CN, CH_3NO_2, etc.) are *not* aprotic. Since these solvents are frequently used in reactions employing strong bases, it is important that their protic character be recognized. (In Me_2SO solution the pK_a values are, for CH_3NO_2, 17.2, CH_3CN, 31.3, Me_2SO, 35, NMP, ~35, and HMPA, ~45 or above.) For this reason we urge that the "dipolar aprotic" designation for these solvents be abandoned and replaced by "dipolar nonhydroxylic" or "dipolar non-hydrogen-bond donor".

Asymmetric Alkylation of α-Alkyl β-Keto Esters

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The development of new methodologies for asymmetric alkylation and their practical utility in the synthesis of biologically active natural products have been the subjects of intensive investigation,[1] and several approaches have been recently reported.[2] In this communication we report our results for diastereoselective alkylation of lithio enamines **3** derived from α-alkyl β-keto esters **1** (Scheme I).[3] Furthermore, use of various additives have shown that the facial selectivity may be reversed to provide either optical antipode.

Chiral enamines **2a–c** were prepared from the corresponding β-keto esters **1** and (*S*)-valine *tert*-butyl ester.[4,5] By direct analogy with earlier studies of the alkylation of enamines derived from simple ketones,[5] chiral enamine **2a** was lithiated with $LiN(i\text{-}C_3H_7)_2$ (LDA) (1.2 equiv) and methylated with methyl iodide (2 equiv) in tetrahydrofuran (THF) (−78 °C). Subsequent hydrolysis and purification afforded **5a** (R^4 = Me) with an *S* configuration in 58% ee (77% chemical yield).[6] By changing the solvent from THF to toluene (−5 °C),[7] alkylation afforded **4a** (R^4 = Me) with the opposite *R* configuration in 50% ee (57% chemical yield).

The fact that the stereochemical course of the alkylation was strongly influenced by the nature of the solvent[8] led us to the assumption that, if the lithium cation in **3** is ligated to the enamine nitrogen and two ester carbonyl oxygens, its fourth coordination site will be occupied by an external ligand (L in **3**), which may thus affect the stereochemical course of the reaction.[9] For the alkylation studies summarized in Table I, toluene was employed as the solvent and hexamethylphosphoric triamide (HMPT), THF, dioxolane, and trimethylamine were used as the external ligands.

The alkylation conditions involved successive treatment of a 0.1–0.5 M solution of enamine **2** (1–5 mmol) with LDA (1.2 equiv) in toluene at −78 °C for 1 h, then with 1–3 equiv of an additive at −78 °C for 1 h, and finally with 1–5 equiv of an alkylating agent at −55 to −78 °C for 3–25 h. After acidic hydrolysis and purification by silica gel column chromatography (or bulb-to-bulb distillation), the alkylated β-keto ester (**4** or **5**) was obtained. The chiral auxiliary reagent, (*S*)-valine *tert*-butyl ester, was recovered for reuse without any loss of optical purity. Since no keto esters except **4** (R^1 = R^2 = Me, R^3 = Et, R^4 = $CH_2CH{=}CH_2$) were known in optically pure form, the degree of asymmetric induction and the absolute configuration were determined by converting them into known compounds[6] and also

(1) For recent reviews, see: (a) Meyers, A. I. *Pure Appl. Chem.* **1979**, *51*, 1225. (b) ApSimon, J. W.; Seguin, R. P. *Tetrahedron* **1979**, *35*, 2797. (c) "*Asymmetric Reactions and Process in Chemistry*"; Eliel, E. L., Otsuka, S., Eds.; American Chemical Society: Washington, DC, 1982.

(2) For example, see: (a) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *Ibid.* **1982**, *104*, 1737. (c) Saigo, K.; Kasahara, A.; Ogawa, S.; Nohira, H. *Tetrahedron Lett.* **1983**, *24*, 503. (d) Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117.

(3) Leading references for asymmetric alkylation reactions of β-keto esters: (a) Colonna, S.; Re, A.; Wynberg, H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 547. (b) Cram, J. D.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625. (c) Yamamoto, K.; Tsuji, J. *Tetrahedron Lett.* **1982**, *23*, 3089. (d) Enders, D., "*Asymmetric Synthesis*"; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 225.

(4) Satisfactory analytical and spectral data were obtained for all new compounds.

(5) Hashimoto, S.; Koga, K. *Chem. Pharm. Bull.* **1979**, *27*, 2760.

(6) For the absolute configuration and enantiomeric excess, see Table I.

(7) In toluene **3a** does not react with methyl iodide below −55 °C.

(8) Enders also reported a similar influence of the solvent in the diastereoselective alkylation reactions of chiral hydrazones.[3d]

(9) Tetravalency for the lithium cation has been reported. (a) Jackman, L. M.; Lange, W. B. *J. Am. Chem. Soc.* **1981**, *103*, 4494. (b) Amstutz, R.; Schweizer, W. B.; Seebach, D., *Helv. Chim. Acta* **1981**, *64*, 2617. (c) Seebach, D.; Amstutz, R.; Dunnitz, J. D. *Ibid.* **1981**, *64*, 2622.

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