to more closely related pentadentate derivatives[15,19] which give rhombic signals. ESR spectrum of hexamethylene derivative: $g_\perp$, 1.977; $g_\parallel$, 2.096; $a_\perp$, 15.0; $a_\parallel$, 20.5 G. The value of $a_\parallel$ is consistent with the large dioxygen affinity.[15,19-21]

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(19) Niswander, R. H.; Taylor, L. T. *J. Magn. Reson.* **1977**, *26*, 491.

(20) Niswander, R. H.; Taylor, L. T. *Inorg. Chem.* **1976**, *15*, 2360.

(21) We are grateful to the Calouste Gulbenkian Foundation (Lisbon, Portugal) for financial support.

A Priori Calculations of pK_a's for Organic Compounds in Water. The pK_a of Ethane

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The enduring fascination of organic chemists with acidities and basicities reflects the fundamental importance of these concepts in understanding organic reactivity.[1] Developing scales of aqueous acidities for weak organic acids is challenging in view of the need for extrapolations from organic solvents to water, ion-pairing and aggregation effects for organometallic compounds, and the derivation of thermodynamic quantities from kinetic measurements.[1-4] The problems are reflected in the experimental ranges for the pK_a's of the simplest alkanes, methane and ethane, which cover from 40 to 60.[1a,e,3,4] In the present communication, we demonstrate how simulation methodology can be used to obtain a priori predictions for the relative pK_a's of organic compounds in water. The first applications are for the pK_a's of acetonitrile and ethane relative to methanethiol.

Consideration of the cycle below yields eq 1 where the aqueous

$$\begin{tikzcd}
\mathrm{AH} \arrow[r, "\Delta G_{gas}"] \arrow[d, "\Delta G^{hyd}(\mathrm{AH})"] & \mathrm{A}^- \arrow[d, "\Delta G^{hyd}(\mathrm{A}^-)"] & + & \mathrm{H}^+ \arrow[d, "\Delta G^{hyd}(\mathrm{H}^+)"] \\
\mathrm{AH} \arrow[r, "\Delta G_{aq}"] & \mathrm{A}^- & + & \mathrm{H}^+
\end{tikzcd}$$

pK_a for AH is related to free energies of hydration and the gas-phase acidity. A similar expression for BH and subtraction provides eq 2 which shows that the difference in pK_a's has three

$$\Delta G_{aq} = 2.3RT\,\mathrm{p}K_a(\mathrm{AH}) = \Delta G^{hyd}(\mathrm{A}^-) + \Delta G^{hyd}(\mathrm{H}^+) - \Delta G^{hyd}(\mathrm{AH}) + \Delta G_{gas} \quad (1)$$

$$2.3RT[\mathrm{p}K_a(\mathrm{BH}) - \mathrm{p}K_a(\mathrm{AH})] = \Delta\Delta G^{hyd}(\mathrm{B}^- - \mathrm{A}^-) - \Delta\Delta G^{hyd}(\mathrm{BH{-}AH}) + \Delta\Delta G_{gas}(\mathrm{BH{-}AH}) \quad (2)$$

components: the differences in free energies of hydration for the anions and for the neutrals and in the gas-phase acidities. These quantities can all be obtained with high precision by using modern theoretical methods, Monte Carlo or molecular dynamics simulations for the $\Delta\Delta G^{hyd}$'s,[5-9] and ab initio quantum mechanics for $\Delta\Delta G_{gas}$.[10-12]

Table I. Potential Function Parameters for the Anions

site	q (e$^-$)	σ (Å)	ϵ (kcal/mol)
		CH_3S^-	
C	−0.40	4.20	0.30
H	0.10	2.50	0.05
S	−0.90	4.25	0.50
		CH_2CN^-	
C1	−1.07	4.20	0.30
H	0.19	2.50	0.05
C2	0.51	3.65	0.15
N	−0.82	3.40	0.25
		$CH_3CH_2^-$	
C2	−0.40	4.20	0.30
H2	0.08	2.50	0.05
C1	0.00	4.20	0.30
H1	0.07	2.50	0.05
M[a]	−0.98	0.0	0.0

[a] M is a point in the plane of the HC1H bisector with r(C1–M) = 0.35 Å and ∠C2C1M = 117.75°

Table II. Computed and Experimental Free Energy Differences (kcal/mol) and pK_a's at 25 °C[a]

AH	$\Delta\Delta G^{hyd}(A^-)$	$\Delta\Delta G^{hyd}(AH)$	$\Delta\Delta G_{gas}$	pK_a
CH_3SH	0.0	0.0	0.0	(10.3)[b]
CH_3CN	5.2 ± 0.4	−1.3 ± 0.2	18.5	28.6 ± 0.3
	(4.3 ± 2)[c]	(−2.6)[c]	(11.7)[d]	(25 ± 1)[e]
CH_3CH_3	−6.4 ± 0.2	3.9 ± 0.1	65.3	50.6 ± 0.2
		(3.1)[c,f]	(60.8)[d,g]	(42–60)[h]

[a] Experimental values in parentheses. Error estimates for the computed values obtained as in ref 5. [b] Reference 1e. [c] Reference 17. [d] Reference 15. [e] Reference 24. [f] Reference 25. [g] Reference 16. [h] References 1a,e, 3, 4.

Briefly, the computations for the present three acids proceeded as follows. The ab initio calculations all employed the 6-31+G(d) basis set which includes d-orbitals and diffuse s- and p-orbitals on the non-hydrogen atoms.[13,14] Complete geometry optimizations were carried out for the three isolated anions and their conjugate acids, followed by calculations of the vibrational frequencies.[10] Correlation energies were computed with Møller–Plesset perturbation theory to third order, i.e., the calculations are denoted MP3/MP2/6-31+G(d)//6-31+G(d).[10] The ehthalpies, entropies, and free energies for ionization were then calculated in the usual way.[10,12] The results for ΔG_{gas}^{298} are 349.2, 367.7, and 414.5 kcal/mol for CH_3SH, CH_3CN, and CH_3CH_3 which agree well with the experimental values 352.7,[15] 364.4,[15] and 413.5,[16] respectively.

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(1) For reviews, see: (a) Cram, D. J. *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965. (b) Bordwell, F. G. *Pure Appl. Chem.* **1977**, *49*, 963. (c) Streitwieser, A., Jr.; Juaristi, E.; Nebenzahl, L. L. In *Comprehensive Carbanion Chemistry, Part A*; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1980; Chapter 7. (d) Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247. (e) Stewart, R. *The Proton: Applications to Organic Chemistry*; Academic Press: New York, 1985. (f) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; Chapter 3.

(2) Streitwieser, A., Jr. *Acc. Chem. Res.* **1984**, *17*, 353.

(3) Juan, B.; Schwarz, J.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 5741.

(4) Butin, K. P.; Beletskaya, I. P.; Kashin, A. N.; Reutov, O. A. *J. Organometal. Chem.* **1967**, *10*, 197.

(5) Jorgensen, W. L.; Ravimohan, C. *J. Chem. Phys.* **1985**, *83*, 3050.

(6) (a) Lybrand, T. P.; McCammon, J. A.; Wipff, G. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 833. (b) Wong, C. F.; McCammon, J. A. *J. Am Chem. Soc.* **1986**, *108*, 3830.

(7) Straatsma, T. P.; Berendsen, H. J. C.; Postma, J. P. M. *J. Chem. Phys.* **1986**, *85*, 6720.

(8) (a) Singh, U. C.; Brown, F. K.; Bash, P. A.; Kollman, P. A. *J. Am. Chem. Soc.* **1987**, *109*, 1607. (b) Bash, P. A.; Singh, U. C.; Langridge, R.; Kollman, P. A. *Science (Washington, D.C.)* **1987**, *236*, 564.

(9) Jorgensen, W. L.; Buckner, J. K.; Huston, S. E.; Rossky, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 1891.

(10) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(11) Chandrasekhar, J.; Andrade, J. G.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5609, 5612.

(12) Gao, J.; Garner, D. S.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1986**, *108*, 4784.

(13) Binkley, J. S.; Whiteside, R. A.; Raghavachari, K.; Seeger, R.; DeFrees, D. J.; Schlegel, H. B.; Frisch, M J.; Pople, J. A.; Kahn, L. R. GAUSSIAN 82 *Release H*; Carnegie-Mellon University: Pittsburgh, 1982.

(14) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294.

(15) Bartmess, J. E.; McIver, R. T., Jr. In *Gas Phase Ion Chemistry, Volume 2*; Bowers, M. T.; Ed.; Academic Press: New York, 1979; p 87.

(16) DePuy, C. H.; Bierbaum, V. M.; Damrauer, R. *J. Am. Chem. Soc.* **1984**, *106*, 4051. The reported $\Delta H°_{acid}$ was converted to ΔG_{gas}^{298} by subtracting 7.5 kcal/mol.[17] These values are somewhat ambiguous since the ethyl anion is unbound in the gas phase. See also: Schleyer, P. v. R.; Spitznagel, G. W.; Chandrasekhar, J. *Tetrahedron Lett.* **1986**, *27*, 4411.

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The differences in free energies of hydration were obtained from Monte Carlo simulations by using the same procedures described in detail previously for the interconversion of methanol and ethane in water.[5] Statistical perturbation theory[18] allowed computation of $\Delta\Delta G^{\text{hyd}}$ as one solute was progressively mutated into another. Three steps were used for the interconversion of the neutral molecules and four for the anions with double-wide sampling.[5] The simulations were run at 298 °C and 1 atm for the solute plus 216 water molecules in a cube with periodic boundary conditions. Metropolis and preferential sampling were employed along with an 8.5-Å cutoff for the intermolecular interactions, feathered between 8.0 and 8.5 Å,[9] and based on roughly the center-of-mass separations. Each step in a mutation had an equilibration phase of ca. 10^6 configurations followed by averaging over an additional 1.5×10^6 or 2×10^6 configurations. Convergence of the $\Delta\Delta G^{\text{hyd}}$'s was rapid and was verified by running several of the perturbations forwards and backwards.

The critical input to the simulations is the intermolecular potential functions. The well-proven TIP4P model was used for water,[19] and parameters for CH_3SH,[20] CH_3CH_3,[21] and CH_3CN[22] were available from prior extensive studies of the corresponding pure liquids. Coulomb and Lennard-Jones interactions are included acting between sites located mostly on the nuclei. The parameters for the anions were derived by fitting to geometrical and energetic results from ab initio 6-31+G(d) calculations on low-energy forms of anion-water complexes, as in previous studies.[9,23] This basis set has been shown to perform extremely well in reproducing experimental anion-water interaction energies.[12] The resultant atomic charges and Lennard-Jones parameters for the anions are summarized in Table I. The latter are quite standard and transferable, so most of the fitting involved the charges. All atoms are explicit for the anions and an additional interaction site was found to be needed in a lone-pair location for $C_2H_5^-$. It should be noted that these three anions were chosen in part because they all have optimal interactions with a water molecule weaker than 20 kcal/mol: CH_3S^- (12), CH_2CN^- (13), and $CH_3CH_2^-$ (18). This helps limit potential errors in the perturbation calculations.

The key results are summarized in Table II. For acetonitrile, the computed $\Delta\Delta G^{\text{hyd}}$'s for both the anion and acid agree well with the experimental data. The error in the ab initio gas-phase acidity is also not large, so the resultant prediction for the pK_a (28.6) is close to the experimental value (25 ± 1)[24] and supports the viability of the computational procedure. If the ab initio $\Delta\Delta G_{\text{gas}}$ is replaced by the experimental finding (11.7), the predicted pK_a is 23.7.

For ethane, the experimental $\Delta\Delta G^{\text{hyd}}$ for the acids is well reproduced, and the ethyl anion is predicted to be better hydrated by 6.4 kcal/mol than methanethiolate. Combination with the ab initio $\Delta\Delta G_{\text{gas}}$ yields an a priori predicted pK_a of 50.6 which would be reduced to 47.3 with use of the experimental $\Delta\Delta G_{\text{gas}}$.[16] These are direct estimates in water, uncomplicated by aggregation and ion-pairing effects or use of nonaqueous solvents.[2] The largest uncertainty in the calculations is in the choice of potential function parameters and lack of explicit polarization in the functions themselves. However, the parameters were obtained in a uniform manner from the 6-31+G(d) calculations, and the perturbation method is conducive to some cancellation of errors for the polarization problem, consistent with the excellent results for acetonitrile. The favorable hydration of $CH_3CH_2^-$ may be somewhat overestimated owing to the stronger anion-water interactions than for CH_3S^-. The effect should not amount to more than a few pK_a units, so our best estimate for the pK_a of ethane in water is still about 50. The a priori computation of this elusive quantity illustrates the power and versatility of modern theoretical methodologies.[26]

Supplementary Material Available: Geometrical and energetic details for the anions and anion-water complexes obtained from the ab initio calculations and potential functions (5 pages). Ordering information is given on any current masthead page.

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(17) Pearson, R. G. *J. Am. Chem Soc.* **1986**, *108*, 6109.

(18) Zwanzig, R. W. *J. Chem. Phys.* **1954**, *22*, 1420.

(19) (a) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, *79*, 926. (b) Jorgensen, W. L.; Madura, J. D. *Mol. Phys.* **1985**, *56*, 1381. (c) Speedy, R. J.; Madura, J. D.; Jorgensen, W. L. *J. Phys. Chem.* **1987**, *91*, 909. (d) Neumann, M. *J. Chem. Phys.* **1986**, *85*, 1567. (e) Tse, J. S.; Klein, M. L. *J. Phys. Chem.*, in press. (f) Reddy, M. R.; Berkowitz, M. *J. Chem. Phys.*, in press.

(20) Jorgensen, W. L. *J. Phys. Chem.* **1986**, *90*, 6379.

(21) Jorgensen, W. L.; Madura, J. D.; Swenson, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 6638.

(22) Jorgensen, W. L.; Briggs, J. M. *Mol. Phys.*, in press.

(23) Jorgensen, W. L.; Gao, J. *J. Phys. Chem.* **1986**, *90*, 2174.

(24) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439.

(25) Dec, S. F.; Gill, S. J. *J. Solution Chem.* **1984**, *13*, 27. Ben-Naim, A.; Marcus, Y. *J. Chem. Phys.* **1984**, *81*, 2016.

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Haller-Bauer Cleavage of Open-Chain and Cyclic α-Phenyl Ketones Proceeds with Retention of Configuration

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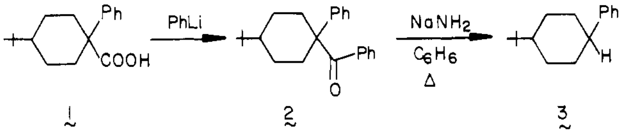
Originally, the Haller-Bauer reaction was designed to provide a means for amide synthesis via cleavage of nonenolizable ketones by $NaNH_2$.[1] In more recent times, the process has seen its greatest use as a tool for effecting the replacement of a carboxyl group by hydrogen as in the conversion of **1** to **3**.[2] C-C bond cleavage is particularly effective when the incipient carbanion is stabilized, e.g., in benzylic[3] and cyclopropyl situations.[4] Walborsky has made particularly elegant use of Haller-Bauer decarboxylation in demonstrating that anionic centers on three-membered rings are configurationally stable.[4a-d] However, the inability of cyclopropyl anions to undergo inversion of configuration is intrinsic to these systems[5] and sheds no light in general terms on the stereochemical course of this useful reaction. We have now examined the Haller-Bauer cleavage of several open-chain and cyclic α-phenyl ketones and herein provide evidence showing conclusively that the *bond scission does not lead to racemic benzyl carbanions*



---

(1) (a) Hamlin, K. E.; Weston, A. W. *Org. React.* **1957**, *9*, 1. (b) Kaiser, E. M.; Warner, C. D. *Synthesis* **1975**, 395.

(2) Ra, C. S., unpublished observations.

(3) (a) Cram, D. J.; Langemann, A.; Allinger, J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 5740. (b) Calas, M.; Calas, B.; Giral, L. *Bull. Soc. Chim. Fr.* **1976**, 857. (c) Alexander, E. C.; Tom, T. *Tetrahedron Lett.* **1978**, 1741.

(4) (a) Walborsky, H. M.; Impastato, F. J. *Chem. Ind.* (*London*) **1958**, 1690. (b) Walborsky, H. M. *Rec. Chem. Prog.* **1962**, *23*, 75. (c) Impastato, F. J.; Walborsky, H. M. *J. Am. Chem. Soc.* **1962**, *84*, 4838. (d) Walborsky, H. M.; Allen, L. E.; Traenckner, H.-J.; Powers, E. J. *J. Org. Chem.* **1971**, *36*, 2937. (e) Piehl, F. J.; Brown, W. G. *J. Am. Chem. Soc.* **1953**, *75*, 5023. (f) Hamlin, K. E.; Biermacher, U. *Ibid.* **1955**, *77*, 6376. (g) Gassman, P. G.; Lumb, J. T.; Zalar, F. V. *Ibid.* **1967**, *89*, 946. (h) Paquette, L. A.; Uchida, T.; Gallucci, J. C. *Ibid.* **1984**, *106*, 335.

(5) (a) Walborsky, H. M.; Impastato, F. J. *J. Am. Chem. Soc.* **1959**, *81*, 5835. (b) Walborsky, H. M.; Young, A. E. *Ibid.* **1961**, *83*, 2595; **1964**, *86*, 3288. (c) Pierce, J. B.; Walborsky, H. M. *J. Org. Chem.* **1968**, *33*, 1962. (d) Walborsky, H. M.; Johnson, F. P.; Pierce, J. B. *J. Am. Chem. Soc.* **1968**, *90*, 5222. (e) Webb, J. L.; Mann, C. K.; Periasamy, M. P. *Ibid.* **1974**, *96*, 3711. (f) Hoell, D.; Schneiders, C.; Mullen, K. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 243.

0002-7863/87/1509-6858$01.50/0