tionalized with a fluxional process wherein rotational diffusion proceeds more slowly than the intramolecular rearrangement occurring.[18] This rate condition may very well be satisfied by stereoisomerizations involving limiting polytopal forms for which the degree of deformation required for interconversion is extremely small. On intuitive grounds, Berry pseudorotation is the most attractive mechanism to invoke in this regard since, for TBP molecules having equivalent ligands, it would be anticipated to occur at a very fast rate and does involve a very slightly polar intermediate configuration.[21] Finally, the foregoing explanation given for the origin of the relaxation absorption is also quantitatively consistent with ancillary physical evidence and theoretical expectations relating to this problem; i.e., the $Fe(CO)_5$ axial-equatorial exchange is extremely fast[2,22] (no temperature coalescence of NMR spectral lines can be observed), it is thought to occur down to at least 100 K[23], and is believed to be associated with a barrier certainly <5 kcal mol^{-1}.

In summary, it is realized that the dielectric evidence, considered in isolation, is in no way conclusive. However, the results of this investigation, when contemplated in the light of previous nondielectric studies, appear to be best explained at present by the fluxional mechanism proposed.

Studies dealing with the possible application of microwave dielectric relaxation to the elucidation of extremely rapid polytopal rearrangements are continuing in this laboratory.

References and Notes

(1) B. Beagley, D. W. J. Cruickshank, P. M. Pinder, A. G. Robiette, and G. M. Sheldrick, *Acta Crystallogr., Sect. B*, **25**, 737 (1969).
(2) (a) F. A. Cotton, A. Danti, J. S. Waugh, and R. W. Fessenden, *J. Chem. Phys.*, **29**, 1427 (1958); (b) R. Bramley, B. N. Figgis, and R. S. Nyholm, *Trans. Faraday Soc.*, **58**, 1893 (1962).
(3) E. N. DiCarlo, R. E. Stronski, and C. E. Varga, *J. Phys. Chem.*, **73**, 3433 (1969).
(4) (a) S. K. Garg, H. Kilp, and C. P. Smyth, *J. Chem. Phys.*, **43**, 2341 (1965); (b) E. N. DiCarlo and E. P. Zurbach, *Chem. Phys. Lett.*, **15**, 563 (1972).
(5) Measurements at temperatures above ~40 °C yielded microwave losses variable with time, reflective of sample instability.
(6) Note that the 135-GHz, 4.5-cm^{-1}, measuring frequency is very close to the frequency of maximum absorption, assuming no distribution, i.e., the Debye equations. If the dispersion actually has a distribution associated with it, the 135-GHz point would probably lie on the low frequency side of the absorption maximum, resulting in even shorter relaxation time values which would serve to reinforce the main conclusion that the relaxation is not controlled by a molecular rotational diffusion mechanism (E. N. DiCarlo, E. Watson, Jr., C. E. Vorga, and W. J. Chamberlain, *J. Phys. Chem.*, **77**, 1073 (1973)).
(7) Molecular volume considerations indicate a rotational relaxation time of ~6-8 ps for a molecular the size and shape of $Fe(CO)_5$.
(8) D. H. Whiffen and H. W. Thompson, *Trans. Faraday Soc.*, **42A**, 122 (1946).
(9) D. H. Whiffen, *Trans. Faraday Soc.*, **46**, 124 (1950).
(10) S. K. Garg, J. E. Bertie, H. Kilp, and C. P. Smyth, *J. Chem. Phys.*, **49**, 2551 (1968).
(11) J. Ph. Poley, *J. Appl. Sci., B*, **4**, 337 (1955).
(12) (a) G. W. F. Pardoe, *Trans. Faraday Soc.*, **66**, 2699 (1970); (b) G. J. Davies, J. Chamberlain, and M. Davies, *J. Chem. Soc. Faraday Trans. 2*, **69**, 1223 (1973).
(13) E.N.D.C. is grateful to Professor R. S. Berry for pointing out this interesting possibility.
(14) Although $Fe(CO)_5$ has no permanent dipole moment, rotational transitions can occur in degenerate vibrational states. These transitions have been discussed for molecules of D_{3h} geometry: I. M. Mills, J. K. G. Watson, and W. L. Smith, *Mol. Phys.*, **16**, 329 (1969).
(15) B. J. Dalton, *J. Chem. Phys.*, **54**, 4745 (1971).
(16) As shown by Mills et al.,[14] the effective dipole moment associated with the vibrationally induced rotational absorption can be obtained from the intensity of the IR transition $0-2\nu_6(E')$. The value obtained for PF_5 is ~1.3 × 10^{-3} D.[15]
(17) R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960).
(18) In this regard, a simple site-model analysis wherein fluxional reorientation and molecular rotation have been taken into account will be presented in the future. In terms of the relaxation model employed, i.e., a jump process between two possible dipole positions aligned parallel and antiparallel to the external field direction, it is shown that the Berry exchange mechanism coupled to rotational relaxation leads to $\tau = \tau_f \tau_r / (\tau_f + \tau_r)$ where τ_f is the relaxation time associated with fluxional reorientation. For $\tau_r \gg \tau_f$, the observed τ effectively reflects τ_f.
(19) Formally, the relevant contribution to the static polarization is obtained by averaging over all pseudorotating molecules.
(20) If such a polarization process is operative, the system establishes the distribution of effective dipole axes via the chemical process itself; i.e., the molecule distinguishes between the two alternate ways of pseudorotating.[18] Therefore, thermal considerations will enter even if complete thermal equilibration according to Eyring's absolute rate theory is not attained and the lower barrier to pseudorotation will be favored by a Boltzmann factor with some effective temperature. (H. Fröhlich, "Theory of Dielectrics", Clarendon Press, Oxford, 1958, p 81 ff.) E.N.D.C. is indebted to Professor R. S. Berry for informative discussions regarding this point.
(21) During the course of BPR in $Fe(CO)_5$, (i) the iron atom need not move since it lies at the molecular center of gravity and (ii) the movement required of the carbonyl ligands, the steric hindrance, and the energy change in reaching the intermediate C_{4v} state are all relatively small compared with alternate mechanisms suggested for the fundamental step in the rearrangement.[15]
(22) (a) H. Mahnke, R. J. Clark, R. Rosonske, and R. K. Sheline, *J. Chem. Phys.*, **60**, 2997 (1974); (b) J. K. Burdett, J. M. Grzybowski, M. Poliakoff, and J. J. Turner, *J. Am. Chem. Soc.*, **98**, 5728 (1976); (c) D. L. Lichtenberger and T. L. Brown, *ibid.*, **99**, 8187 (1977).
(23) H. W. Spiess, R. Grosescu, and V. Haeberlen, *J. Chem. Phys.*, **6**, 226 (1974).

E. N. DiCarlo,* E. P. Zurbach
Department of Chemistry, Saint Joseph's College
Philadelphia, Pennsylvania 19131
Received March 13, 1978

Solvent Effects on Protomeric Equilibria: Quantitative Correlation with an Electrostatic Hydrogen-Bonding Model

Sir:

The possibility of developing a quantitative model for the effect of molecular environment on protomeric equilibria is offered by our recent work which provides the energy difference between isolated heterocyclic protomers in the gas phase and in solution.[1,2] The energy of transfer of such an equilibrium from the gas phase to solution may be discussed in terms of the energies of (1) the interaction of the electrostatic reaction field of the solvent with the different dipoles of the protomeric isomers (ΔE_{ele}), (2) hydrogen-bond acceptance by and donation to the solute from the solvent ($\Delta E_{H_{do}}$ and $\Delta E_{H_{ac}}$), (3) solvent cavitation (ΔE_{cav}), and (4) van der Waals interactions (ΔE_{vdW}).[3,4] Previous analyses of protomeric equilibrium constants have focused on ΔE_{ele},[1,5] a combination of $\Delta E_{H_{ac}}$ and $\Delta E_{H_{do}}$,[6] ΔE_{cav},[7] or on correlation with empirical Z values.[8] We wish to report that solvent effects on the protomeric equilibrium of 6-chloro-2-hydroxypyridine (**1a**)-6-chloro-2-pyridone (**1b**), 2-hydroxypyridine (**2a**)-2-pyridone (**2b**), 4-hydroxypyridine (**3a**)-4-pyridone (**3b**), 2,6-di-*tert*-butyl-4-hydroxypyridine (**4a**)-2,6-di-*tert*-butyl-4-pyridone (**4b**), 6-chloro-2-thiolpyridine (**5a**)-6-chloro-2-thiopyridone (**5b**), 2-thiopyridine (**6a**)-2-thiopyridone (**6b**), and 4-thiolpyridine (**7a**)-4-thiopyridone (**7b**) can be quantitatively analyzed in
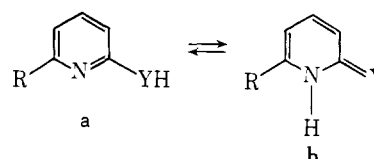

1a-1b, R = Cl; Y = O
2a-2b, R = H; Y = O
5a-5b, R = H; Y = S
6a-6b, R = Cl; Y = S

© 1978 American Chemical Society

Table I. Comparisons of Experimental and Calculated Free Energies of Solution[a]

Solvent	Equilibrium							
	1a–1b		5a–5b		6a–6b		7a–7b	
	$\Delta G°_{calcd}$[b]	$\Delta G°_{exptl}$	$\Delta G°_{calcd}$[c]	$\Delta G°_{exptl}$	$\Delta G°_{calcd}$	$\Delta G°_{exptl}$	$\Delta G°_{calcd}$	$\Delta G°_{exptl}$
Cyclohexane	1.6	1.6	1.2	1.2			2.2	2.0
Dioxane	2.3	2.3	−0.13	0.57			0.8	0.96
Carbon tetrachloride	1.5	1.6	1.0	0.84				
Benzene	1.5	1.5	0.8	0.57			1.9	1.4
Chloroform	1.0	0.5	−0.3	−0.48	−2.4	1.7	0.8	0.72
Diethyl ether	2.4	≥2.3	−1.0	−0.3			−0.75	−0.36
Ethyl acetate	2.2	2.1	−1.5	−0.9	−2.2	1.5		
Tetrahydrofuran	2.3	2.3	−2.0	−1.1			−0.8	−0.53
Dichloromethane	0.9	0.9	−0.8	−0.63	1.0	0.67	0.22	0.36
1,2-Dichloroethane	0.9	0.93	−0.9	−0.84	1.0	0.71	0.2	0.31
tert-Butyl alcohol	1.5	1.0			1.0	0.28		
n-Butyl alcohol	0.77	0.8			0.3	0.18		
Isopropyl alcohol	0.96	0.95			0.5	0.21	−3.2	−2.0
n-Propyl alcohol	0.8	0.82			−0.3	0.18		
Ethyl alcohol	0.76	0.80	−3.2	−2.0	−0.5	0.14		
Methane alcohol	−0.3	0.6			−0.6	0		
Hexamethylphosphortriamide	3.0	≥2.3						
N,N-Dimethylacetamide	2.3	2.3			2.1	1.3		
Dimethyl sulfoxide	2.4	≥2.3						
Water	−1.9	−1.7	−5.7	−5.8			−4.1	−5.4

[a] In kilocalories/mole. [b] Calculated by expression 2. [c] Calculated by expression 3.

3c–3d, R = H; Y = O
4c–4d, R = C(CH$_3$)$_3$; Y = O
7c–7d, R = H; Y = S
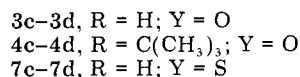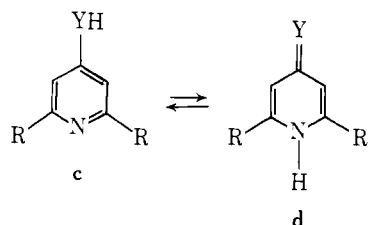
terms of the electrostatic and hydrogen-bonding effects as described in eq 1.

$$\Delta G°_{soln} - \Delta G°_{vapor} = \Delta E_{ele} + \Delta E_{H_{do}} + \Delta E_{H_{ac}} \quad (1)$$

The protomeric equilibrium constant (K_T = [NH]/[OH]) for **1a–1b** has been determined in 20 solvents by ultraviolet spectroscopy.[9,10] Attempted correlations of log K_T with previously suggested solvent parameters are not satisfactory.[11] However, when expression 2 is used the results shown in Table I are obtained.[11] The second term in the equation is the gas-phase free-energy difference, the third term is the electrostatic field effect as defined by Onsager,[12] and the terms containing α and β are hydrogen-bonding acceptor and hydrogen-bonding donor terms, both as defined by Taft.[13] The constants associated with α and β, which reflect the influence of hydrogen-bond acceptance and donation by the solvent to the stability of the isomers, are chosen to provide the best fit to the data. However, it should be noted that the right side of expression 2 independently and correctly predicts the gas-phase energy difference,[14] and the coefficient of the dielectric constant term.[15]

$$\Delta G°_{soln} + 2.2 = 3.1 \left(\frac{\epsilon - 1}{2\epsilon + 1}\right) - 2.3\beta + 2.8\alpha \text{ kcal/mol} \quad (2)$$

Since hydrogen-bonding interactions similar to those of **1a–1b** might be expected for the systems **2a–2b**, **3c–3d**, and **4c–4d**, the constants for the fourth and fifth terms from expression 2, along with a calculated third term,[15] and the estimated equilibrium constants in water were used in an analysis of those systems. The available data are quite limited and the success of the approach is judged by comparison of the calculated gas-phase energy differences with the independent esti-

mates available for the first two cases. The results are as follows (isomers, $\Delta G°_{calcd}$, $\Delta G°_{exptl}$ (kcal/mol)): **2a–2b**, 0.6, 0.5;[1] **3a–3b**, 5, 7.[3,16] For **4a–4b**, a $\Delta G°_{calcd}$ of 5 kcal/mol is obtained.

Extension of this approach to the equilibrium constants for the protomers **5a–5b**, **6a–6b**, and **7c–7d** provide a test in a system with potentially very different hydrogen-bonding effects. For example

$$\Delta G°_{soln} - 2.9 = 8.5 \left(\frac{\epsilon - 1}{2\epsilon + 1}\right) - 3.2\beta - 3.9\alpha \text{ kcal/mol} \quad (3)$$

is obtained for **5a–5b**.[11] The close agreement between calculated and experimental values for 30 points for the three systems and the agreement between the estimated gas-phase energy difference of ca. −3 kcal/mol for **5a–5b** with that of an estimate of ca. −2 kcal/mol from gas-phase basicities[16] provide support for this analysis. However, it should be noted that the two points for **6a–6b** in chloroform and ethyl acetate which do not correlate well suggest the assumed transferability of coefficients for the hydrogen-bonding terms needs to be examined further. If it is assumed for that case that those terms have opposite signs, the calculated points are brought within 0.7 kcal/mol of the experimental values and the other points are unaffected.

This analysis of solvent effects on protomeric equilibria provides a physically based model which quantitatively correlates the effect of molecular environment on molecular energies. It appears to be useful in estimating gas-phase equilibria and in assessing both the effect of the electric field and of hydrogen-bond donation and acceptance of the solvent on isomer stability. While the model is clearly rudimentary,[17] the prospect of understanding solvent effects on protomeric equilibria in terms of these specific interactions is intriguing and subject to further testing.

References and Notes

(1) P. Beak, F. S. Fry, J. Lee, and F. Steele, *J. Am. Chem. Soc.*, **98**, 171 (1976).
(2) P. Beak, J. B. Covington, and S. G. Smith, *J. Am. Chem. Soc.*, **98**, 8284 (1976); P. Beak, J. B. Covington, and J. M. Zeigler, *J. Org. Chem.*, **43**, 177 (1978).
(3) For a summarizing discussion, see P. Beak, *Acc. Chem. Res.*, **10**, 186

(1977). This article notes that ΔE_{cav} and ΔE_{vdw} are not likely to be significant factors in the present systems.

(4) For discussion of solvation of ionic species, see D. H. Aue, H. Webb, and M. T. Bowers, *J. Am. Chem. Soc.*, **98**, 311, 318 (1976); E. M. Arnett, B. Chawla, L. Bell, M. Taagepera, W. J. Hehre, and R. W. Taft, *ibid.*, **98**, 5729 (1976); J. F. Wolf, R. H. Staley, I. Koppel, M. Taagepera, R. T. McIver, J. L. Beauchamp and R. W. Taft, *ibid.*, **98**, 5417 (1976), and reference cited therein.

(5) J. Powling and H. J. Bernstein, *J. Am. Chem. Soc.*, **73**, 4353 (1951).

(6) R. J. Highet and I. E. Chou, *J. Am. Chem. Soc.*, **99**, 3539 (1977).

(7) R. C. Reeves, M. S Maggio, and L. S. Costa, *J. Am. Chem. Soc.*, **96**, 6917 (1974).

(8) A. Gordon and A. R. Katritzky, *Tetrahedron Lett.*, 2767 (1968).

(9) The equilibrium constants were determined by ultraviolet analyses for solutions which are monomeric in solute.

(10) This system has been extensively investigated previously because both isomers can be detected in a wide range of solvents: E. M. Peresleni, L. N. Yakhontov, D. M. Krasnokutskaya, and Y. N. Sheinker, *Dokl. Akad. Nauk. SSSR*, 177, 592, 1070 (1967); A. R. Katritzky, T. D. Rowe, and S. K. Roy, *J. Chem. Soc. B*, 758 (1967); E. S. Levin and G. N. Rodionova, *Dokl. Akad. Nauk. SSSR*. 189, 900 (1969); G. Simchen, *Chem. Ber.*, 103, 398 (1970).

(11) For a complete discussion, see J. B. Covington, Ph.D. Thesis, University of Illinois, 1978, available from University Microfilms, Ann Arbor, Mich. The errors for each term in the expressions follow: for eq 2, second term ±0.3, third term ±0.5, fourth term ±0.3, fifth term ±1; for eq 3, second term ±0.6, third term ±1.2, fourth term ±1.2, fifth term ±1.9.

(12) L. Onsager, *J. Am. Chem. Soc.*, **58**, 1686 (1936).

(13) R. W. Taft and M. T. Kamlet, *J. Am. Chem. Soc.*, **98**, 376, 2886 (1976). Since hydrogen-bond donation and acceptance is possible for each isomer of a pair, the net result will be a balance of competing effects. The assumption of the present analysis, that these effects will be in the same direction for similar bond types, will have to be examined as further data become available.

(14) This value is obtainable by extrapolation to $\epsilon = 1$.

(15) This term is $u_x{}^2/a_x{}^3 - u_y{}^2/a_y{}^3$ from the Onsager reaction field model.

(16) M. J. Cook, A. R. Katritzky, M. Taagepera, T. D. Singh, R. W. Taft, *J. Am. Chem. Soc.*, **98**, 6048 (1976); C. B. Theissling, N. M. M. Nibbering, M. J. Cook, S. El-Abbady, and A. R. Katritzky, *Tetrahedron Lett.*, 1777 (1977); D. H. Aue, L. D. Betowski, W. R. Davidson, M. T. Bowers, P. Beak, and J. Lee, *J. Am. Chem. Soc.*, submitted for publication.

(17) Variation of the dipoles with changes in solvent and different energies of hydrogen bonding for different isomers could prove important on further analyses.

Peter Beak,* Johnny B. Covington

Roger Adams Laboratory, University of Illinois
Urbana, Illinois 61801

Received February 20, 1978

Sphingolipid Base Metabolism.
Concerning the Origin of the Oxygen Atom at
Carbon Atom 4 of Phytosphingosine[1]

Sir:

Sphingolipid bases are major constituents of a variety of biologically important classes of complex lipids of eukaryotes including ceramides, sphingomyelins, gangliosides, and other complex glycosphingolipids. One of the major sphingolipid bases, from which these complex sphingolipids are derived, is phytosphingosine[2] (I). The great majority of studies of the biosynthesis of this compound have utilized *Hansenula ciferrii* (II), a yeast which excretes large quantities of I in the form of its tetraacetyl derivative.[3,4] The precise nature of the enzymatic reactions leading to the formation of I are unclear. Some possible modes of formation of I[5] are illustrated in Figure 1. Greene et al.[6] have demonstrated the incorporation of the label of [9,10-³H]palmitic acid (III) and of [3-¹⁴C]serine into I by II. Under the same conditions, the label of [9,10-³H]-α-hydroxypalmitic acid was not efficiently incorporated into I. The enzymatic formation of I in a cell-free preparation has not been reported. However, it has been shown that microsomal preparations of II catalyze the pyridoxal phosphate-dependent condensation of serine and palmityl coenzyme A to yield 3-ketosphinganine which is then reduced, in an NADPH-dependent reaction, to give dihydrosphingosine[7,8] (IV). While the formation of sphingosine[9] (V) has been shown to occur in this system when 2,3-*trans*-hexadecenoyl coenzyme A was used as the substrate, no formation of I could be detected when
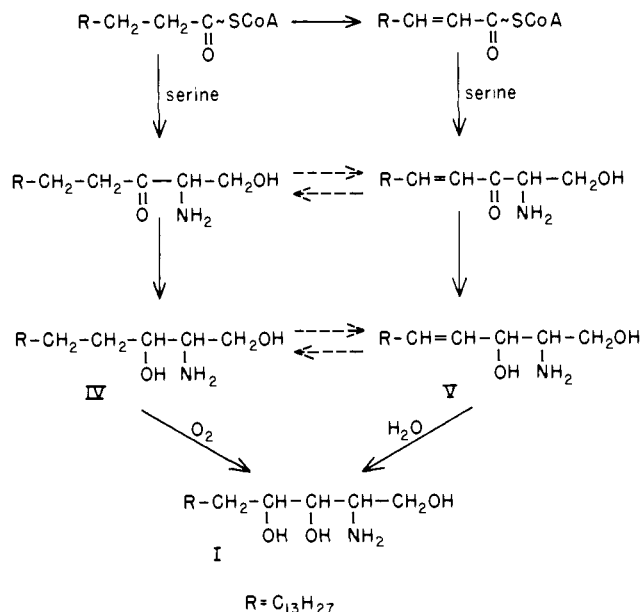

Figure 1.

α-hydroxypalmityl coenzyme A was used as the substrate.[8] It has been suggested that I of II is formed via a hydroxylation of IV.[10] The combined results of two laboratories[10,11] have indicated that the major, if not exclusive, pathway involved in the incorporation of III, by II, into I occurs with the loss of only one hydrogen atom (from C-2) of III and that this hydrogen has the *pro R* configuration. These findings appear to preclude a mechanism which involves the formation of I by hydration of the double bond of V (or an unsaturated precursor of V) but are compatible with a mechanism which involves a stereospecific hydroxylation at C-4 of IV (or a precursor of IV). However, the latter mechanism has appeared to have been excluded by the results of two laboratories which have indicated that the oxygen at C-4 of I was not derived from molecular oxygen.[11,12] The purpose of this communication is to report the results of a reinvestigation of the possible incorporation of molecular oxygen into the hydroxyl function at C-4 of I in its formation in II.

The tris(*O*-trimethylsilyl)-*N*-acetyl derivative of I was chosen as a suitable compound on which to base the assay of the extent of incorporation and localization of labeled oxygen in I. This selection was based upon the results of mass spectral analyses of the above derivative of authentic I, the same compound containing perdeuterated trimethylsilyl functions, and of [(4*R*)-¹⁸O]-I. The latter compound was synthesized from tribenzoyl-V by a modification of an approach described by two laboratories[13,14] (Figure 2). This synthesis involves epoxidation of tribenzoyl-V, reduction of the resulting product with lithium aluminum hydride, and subsequent hydrogenolysis of the resulting *N*-benzyl derivative to give the free base. Our results indicate that the procedure yields four compounds (as shown in Figure 2) which could be resolved from each other by medium-pressure chromatography of the *N*-acetyl derivatives on silicic acid columns.[15] These compounds were characterized by melting point determination and low and high resolution mass spectral, infrared, optical rotation, chromatographic, and chemical degradation studies[15]. The corresponding compounds labeled with ¹⁸O in either the 4 or 5 positions were prepared as outlined in Figure 2 except that ¹⁸O-labeled *m*-chloroperbenzoic acid[16] was used.

The mass spectrum of the tris(*O*-trimethylsilyl)-*N*-acetyl derivative of I did not show a significant molecular ion but did show an ion of high abundance at *m/e* 560. The results of high resolution mass spectral analysis of this derivative of I and the results of low resolution analyses of the corresponding M_3Si-d_9