tion data well leads to nearly equivalent values of Δf_A. The distribution coefficient K_D may additionally be used as a parameter in a more complex fitting process but a sharp minimum in the RMSD in Δf_A is found very near the value we derive from very low concentration MeOH-Hx data. We conclude that these data give convincing direct thermodynamic evidence for a cooperative effect in hydrogen bonding.

As we have noted, most previously reported thermodynamic constants for alcohol self-association reactions are suspect as being strongly model dependent.[2] Solution heteroassociation data for phenol-amine systems at one temperature have been published,[8] but interpretation of these data was limited to calculation of equilibrium constants for 1:1 and 2:1 complexes. Enthalpies supporting the existence of a cooperative effect in formation of methanol-diethylamine complexes have previously been reported by Tucker.[9] Numerous molecular orbital calculations have been published which support the cooperativity concept but there have been essentially no experimental data with which to compare the theoretical hydrogen bond energies. Additionally, there has been some controversy over molecular orbital calculations which, in various degrees of refinement, show predominance of either cyclic or linear hydrogen bonded polymers.[10] Resolution of this problem will be aided by good thermodynamic data for multiply hydrogen bonded complexes whose structures are known with some certainty.

We are currently investigating other systems in an attempt to determine reliable association enthalpies for multiply bonded complexes. By comparing data for alcohol self-association with results for alcohol-base complexes, it may be possible to learn more about the relative importance of cyclic and acyclic alcohol polymers.[2]

Acknowledgment is made to the National Science Foundation (Grant Nos. GP-33519X and GP-43307) for support of this work.

Supplementary Material Available. Vapor pressure data for methanol-*n*-hexadecane and methanol-trioctylamine-*n*-hexadecane solutions will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for \$4.00 for photocopy or \$2.50 for microfiche, referring to code number JACS-75-1269.

References and Notes

(1) H. S. Frank and W. Y. Wen, *Discuss. Faraday Soc.*, **24,** 133 (1957).
(2) E. E. Tucker and E. D. Becker, *J. Phys. Chem.*, **77,** 1783 (1973).
(3) For example, see L. D. Bellamy and R. J. Pace, *Spectrochim. Acta*, **22,** 525 (1966).
(4) E. E. Tucker, S. B. Farnham, and S. D. Christian, *J. Phys. Chem.*, **73,** 3820 (1969).
(5) See paragraph at end of paper regarding supplementary material.
(6) D. W. Marquardt, *J. Soc. Ind. Appl. Math.*, **11,** 431 (1963) (Fortran Share Program No. 1428).
(7) Since the standard state used here is that of unit molarity the enthalpies contain a small nonhydrogen bonding contribution due to thermal expansion of the solvent. For $\Delta H_{11}°$ and $\Delta H_{\infty}°$ this contribution is ca. 0.175 kcal and for $\Delta H_{21}°$ it is ca. 0.35 kcal. These contributions do not affect our conclusions, but it is important to realize their existence. See, for example, E. M. Woolley et al., *J. Phys. Chem.*, **75,** 3591 (1971).
(8) D. Clotman, D. Van Lerberghe, and Th. Zeegers-Huyskens, *Spectrochim. Acta, Part A*, **26,** 1621 (1970).
(9) E. E. Tucker, Ph.D. Dissertation, Oklahoma University, 1969.
(10) B. R. Lentz and H. A. Scheraga, *J. Chem. Phys.*, **58,** 5296 (1973).

Edwin E. Tucker,* Sherril D. Christian
Chemistry Department, Oklahoma University
Norman, Oklahoma 73069

Received June 29, 1974

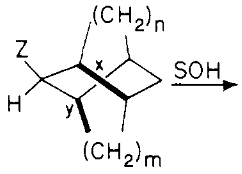
Bond Alignment vs. Product Stability in the Control of Wagner-Meerwein Rearrangements

Sir:

Rearrangements of polycyclic skeletons to more stable ones are well documented;[1a] and enhanced solvolysis rates are frequently attributed to relief of skeletal strain that can accompany a concerted rearrangement.[1b] Understandably, therefore, computer calculations of strain energies and of molecular stability hold great promise for prediction and interpretation of skeletal changes, especially when rearrangement can follow more than one course.[2] For nonreversible shifts an implicit presumption in this approach is that some of the stability of the new skeleton is felt at the transition state.

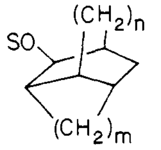
The transition state energy for a Wagner-Meerwein shift can also be influenced by the effectiveness of orbital overlap, which in turn can depend on the initial alignment of relevant bonds. For a rearrangement that is concerted with ionization the migrating group should ideally be antiplanar to the leaving group ("sp^3 alignment factor"), and for rearrangement to a carbocation site (i.e., nonconcerted) the migrating group and the receptor p orbital should ideally be in one plane ("sp^2 alignment factor").[3,4] Therefore, to the extent that bond alignments are important, the geometry prior to rearrangement can influence transition state energy in ways that are not revealed by static, enthalpy considerations. When a polycycle can rearrange nonreversibly to more than one new ring system, a fundamental question arises. Is the path predictably determined by the relative enthalpies of the possible products (i.e., stability factor) or can the direction be controlled by geometry in the reactant (i.e., bond alignment factor)? The relative influence of these two factors could differ for each circumstance but, because no definitive case has been studied where they clearly oppose each other, we do not know whether they can be of comparable importance or whether one always dominates.

The situation is typified in tricyclic molecules like **1**[5,6] in which bonds "y" and "x" are both formally trans to the departing group Z and can shift to produce, respectively, the new skeletons **2** and **3**. The alignment factors for "y" and "x" and the relative stability of products **2** and **3**[7] depend on the values of *n* and *m*. Although some of these systems have

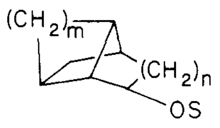


1

4a, $n = m = 1$; Z = OBs
b, $n = m = 1$; Z = Cl
7, $n = 2$; $m = 2$; Z = OTs
10a, $n = 1$; $m = 2$; Z = OBs
b, $n = 1$; $m = 2$; Z = OAc
c, $n = 1$; $m = 2$; Z = OH



+



2

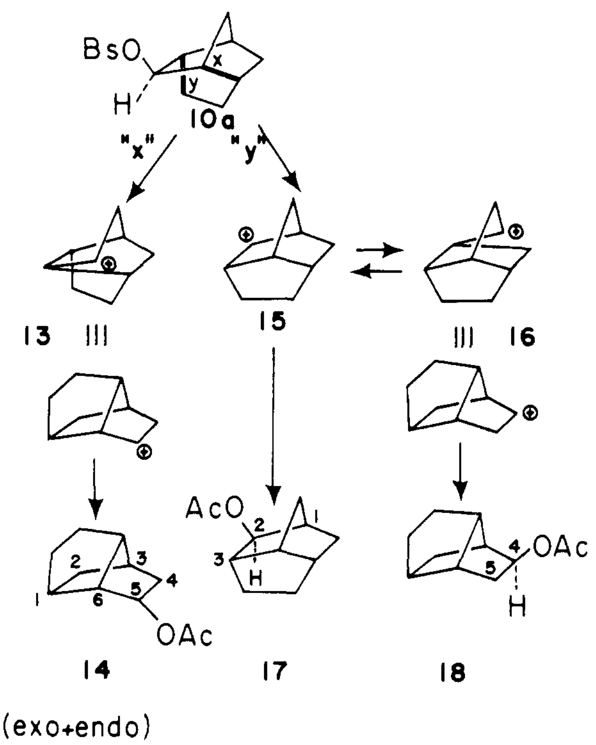
5, $n = m = 1$: S = Ac or H
8, $n = m = 2$; S = H
11, $n = 1$; $m = 2$; S = Ac

3

6, $n = m = 1$; S = Ac or H
9, $n = m = 2$; S = H
12, $n = 1$; $m = 2$; S = Ac

been reported ($n = m = 1$ and $n = m = 2$), the desired information is not extractable either because the "alignment" and "stability" factors favor the same product (i.e., **5** from systems **4a**[5] and **4b**[6]) or because the products were not identified (system **7**[8]).

A crucial test substrate is *exo*-twistbrendan-2-ol brosylate (**10a**) in which $n = 1$ and $m = 2$. Molecular models as well as computer calculations[9] indicate that the sp^3 alignment factor clearly favors "x" migration (to produce the brexyl system **13**), whereas product stability favors "y" shift (to give the brendyl skeleton **15**, which is more stable than the brexyl skeleton by 2.24–3.13 kcal/mol).[10] The twistbrendyl system **10a** also has the unusual feature[4] that the best-aligned bonds are different for concerted and nonconcerted rearrangements. Thus the "sp^2 alignment factor" would favor migration of "y" over "x" and would act synergistically with the stability factor. Table I summarizes the four possible situations and shows that an experimental preference for "x" shift would uniquely support bond alignment control (situation A) whereas a preference for "y" shift (situations B, C, or D) would be less informative, especially for high y/x ratios.



In acetolysis, migration of "x" produces the brexyl-5 cation (**13**), which terminates with solvent to give a mixture of exo and endo acetates **14** plus a small amount of brexene-4. Migration of "y" initially produces the brendyl-2 cation (**15**) which is known from independent studies[11-14] to convert partially to the brexyl-4 cation (**16**) prior to solvent capture and to produce a mixture of *exo*-brendan-2-ol acetate (**17**) and *exo*-brexan-4-ol acetate (**18**), plus a small amount of deltacyclane.[12] We showed that each product is stable to our reaction conditions.[15] Therefore the amount of **14** (plus olefin brexene-4) compared to the sum of **17** and **18** (plus hydrocarbon deltacyclane) represents the migration ratio of bonds x/y.

We synthesized brosylate **10a** from the known acetate **10b**[16] via the alcohol **10c**. And we obtained each of the epimeric brexyl-5-acetates (**14**) by conventional reactions on brexan-5-one, which was prepared from brexan-4-one by a reported ketone transposition sequence.[17,18] Authentic samples of all other acetates were prepared as reported earlier.[11-13] Solvolysis of **10a** in acetic acid buffered with potassium acetate gave *exo*-**14** (21%), *endo*-**14** (41.5%), **17** (15.5%), **18** (13%), deltacyclane (2%), brexene-4 (4%), and *endo*-twistbrendyl acetate (3%). These products correspond to an x/y migration ratio of 2.2/1 and uniquely support situation A (Table I). For the present case, therefore, bond alignment in the reactant is more important than product stability, and this finding suggests that, in general, both factors must be evaluated for prediction of Wagner–Meerwein rearrangements.[19]

Table I. Competitive Shift of x and y in Solvolysis of *exo*-Twistbrendan-2-ol Brosylate (10a)

Situation	Timing	Controlling factor	Bond favored
A	Concerted	Bond alignment (sp^3)	x
B	Concerted	Product stability	y
C	Nonconcerted	Bond alignment (sp^2)	y
D	Nonconcerted	Product stability	y

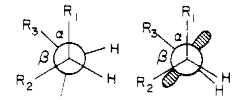
References and Notes

(1) (a) J. A. Berson in "Molecular Rearrangements", P. de Mayo, Ed., Interscience, New York, N.Y., 1963, Chapter 3; R. C. Bingham and P. v. R. Schleyer, *Top. Current Chem.*, **18,** 1 (1971); W. Hanstein, H. J. Berwin, and T. G. Traylor, *J. Am. Chem. Soc.*, **92,** 829 (1970); N. A. Clinton, R. S. Brown, and T. G. Traylor, *ibid.*, **92,** 5228 (1970); (b) W. G. Dauben, J. L. Chitwood, and K. V. Scherer, Jr., *ibid.*, **90,** 1014 (1968); D. Lenoir and P. v. R. Schleyer, *Chem. Commun.*, 941 (1970); K. B. Wiberg, V. Z. Williams, Jr., and L. E. Friedrich, *J. Am. Chem. Soc.*, **92,** 564 (1970); K. B. Wiberg, R. A. Fenoglio, V. Z. Williams, Jr., and R. W. Ubersax, *ibid.*, **92,** 568 (1970).

(2) F. H. Westheimer in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, Chapter 12; J. B. Hendrickson, *J. Am. Chem. Soc.*, **83,** 4537 (1961); K. B. Wiberg, *ibid.*, **87,** 1070 (1965); S. Lifson and A. Warshel, *J. Chem. Phys.*, **49,** 5116 (1968); R. H. Boyd, *ibid.*, **49,** 2574 (1968); J. D. Williams, P. J. Stang, and P. v. R. Schleyer, *Annu. Rev. Phys. Chem.*, **19,** 531 (1968); M. J. S. Dewar and E. Haslback, *J. Am. Chem. Soc.*, **92,** 590 (1970); N. L. Allinger, M. T. Tribble, M. A. Miller, and D. W. Wertz, *ibid.*, **93,** 1637 (1971); E. M. Engler, M. Farcasiu, A. Seven, J. M. Cense, and P. v. R. Schleyer, *ibid.*, **95,** 5769 (1973).

(3) D. M. Brouwer and H. Hogeveen, *Recl. Trav. Chim. Pays-Bas*, **89,** 211 (1970), and references cited.

(4) Importantly, in a rigid polycycle where the dihedral angles α and β are substantially fixed by the interconnection of R_1, R_2, and R_3, the alignment factors for two migrating groups could change according to whether migration proceeds toward an sp^3 or an sp^2 center. Thus R_1 is better aligned than R_2 for a shift that is concerted with Z loss (i), whereas R_2 is oriented better than R_1 if the nucleofugal carbon becomes sp^2 prior to rearrangement (ii). For illustration we show R_1 and R_2 on the same carbon; cf. J. A. Berson, *Angew. Chem., Int. Ed. Engl.*, **7,** 79



i ii

(1968). More typically, in bridged polycycles they are on different carbons, each of which is adjacent to the nucleofugal site (e.g., as in **10a**).

(5) (a) R. R. Sauers and B. R. Sickles, *Tetrahedron Lett.*, 1067 (1970); (b) R. R. Sauers, K. W. Kelly, and B. R. Sickles, *J. Org. Chem.*, **37,** 537 (1972).

(6) P. K. Freeman, R. B. Kinnel, and T. D. Ziebarth, *Tetrahedron Lett.*, 1059 (1970).

(7) E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95,** 8005 (1973).

(8) H. W. Whitlock and M. W. Siefken, *J. Am. Chem. Soc.*, **90,** 4928 (1968).

(9) According to computer calculations,[7] the relevant dihedral angles (ϕ) in twistbrendane (**10,** $Z = H$) are 152° for bond y and 166° for bond x, representing deviations from ideality ($\Delta\phi$) of 28° and 14°, respectively. For $Z = CH_3$ the $\Delta\phi$'s are 38° for bond y and 6° for bond x. When Z is lost and the nucleofugal carbon is sp^2, the $\Delta\phi$'s are 1.5° for bond y and 41.2° for bond x. We thank Professor P. v. R. Schleyer and D. Khoury for unpublished data and Professor T. J. Kistenmacher for assistance in the calculation of the last two angles.

(10) For example, direct acid equilibration of brendyl-2 acetate (**17**) and brexyl-4 acetate (**18**) at 25° gave 2.24;[11] computer calculations[7] on the parent hydrocarbons brendane and brexane gave 2.90; and on 2-*exo*-methylbrendane and 4-*exo*-methylbrexane gave 3.13. Twistbrendane is considerably less stable (ca. 8.7 kcal/mol) than brexane. (Private communication from P. v. R. Schleyer and D. Khoury.)

(11) T. Swartz, Ph.D. Thesis, The Johns Hopkins University, 1966.

(12) A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, *J. Am. Chem. Soc.*, **87,** 1615 (1965).

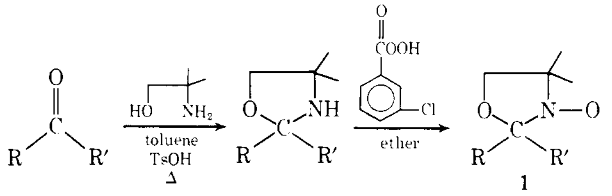
(13) A. Nickon, G. P. Pandit, and R. O. Williams, *Tetrahedron Lett.*, 2851 (1967).
(14) R. S. Bly, R. K. Bly, A. O. Bedenbaugh, and O. R. Vail, *J. Am. Chem. Soc.*, **89**, 880 (1967).
(15) We also generated the brexyl-5 cation by acetolysis of exo and endo brexyl-5 brosylate to produce exo-endo acetates **14** and brexene-4 (<6%). Separately we established that cation **13** does not convert to **15** or **16** (and vice versa) even under equilibrating conditions.
(16) R. R. Sauers and J. A. Whittle, *J. Org. Chem.*, **34**, 3579 (1969).
(17) A. Nickon, F. Huang, R. C. Weglein, K. Matsuo, and H. Yagi, *J. Am. Chem. Soc.*, **96**, 5264 (1974).
(18) All new compounds (**10a**, **10c**, *exo*-**14**, *endo*-**14**) were characterized spectroscopically and gave satisfactory elemental analyses.
(19) An additional view that emerges from this study is that *changes* in migration ratio (e.g., as a function of solvent, departing group, etc.) might be used to probe the subtleties of timing in Wagner-Meerwein rearrangements for systems where the sp^2 and sp^3 alignment factors favor different bonds.
(20) Supported by the National Institutes of Health (Grant GM-06304) and by the National Science Foundation.

Alex Nickon,* Raymond C. Weglein
Department of Chemistry, The Johns Hopkins University[20]
Baltimore, Maryland 21218
Received July 22, 1974

A Versatile Synthesis of Doxyl Spin Labels Bypassing the Usual Ketone Precursors

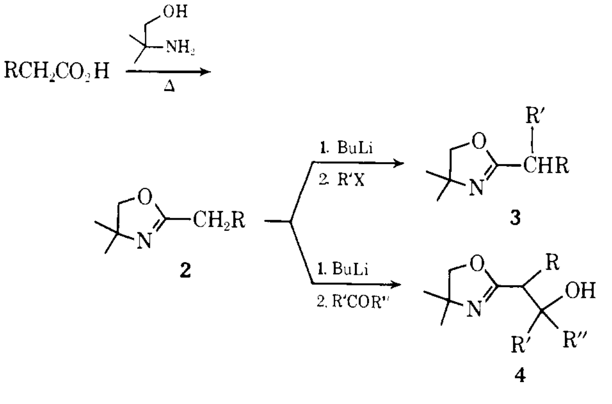
Sir:

Doxyl (4,4-dimethyloxazolidine-*N*-oxyl) spin labels, since their inception in 1967,[1] have proven highly productive in studies of anisotropic motion, orientation, polarity, and diffusion within biological systems.[2] Heretofore, the doxyl group was prepared by condensation of an appropriate ketone with 2-amino-2-methyl-1-propanol followed by oxidation of the resulting oxazolidine with *m*-chloroperoxybenzoic acid (MCPA) (eq 1).[1] We now describe a new versatile method for assembling doxyl spin labels which does not depend on the availability of the ketone and which permits facile synthesis of doxyl derivatives containing unsaturation in the carbon chain, for example.



(1)

In this method advantage is taken of the availability of an impressive variety of 4,4-dimethyloxazoline derivatives **2–4** (eq 2) stemming from the elegant work of Meyers.[3-5] It occurred to us that if these oxazolines could be converted into the corresponding nitrones, the latter might be susceptible to attack by an organometallic reagent[6] leading to an *N*-hydroxyoxazolidine, mild oxidation of which would produce the corresponding doxyl derivative.



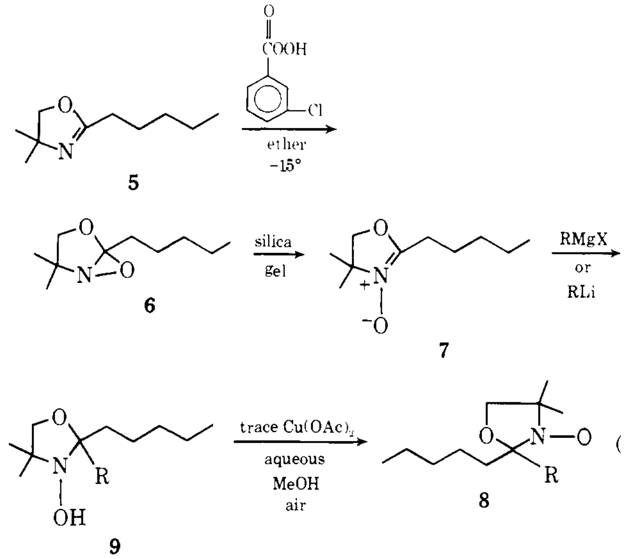
(2)

Table I. Summary of Experimental Conditions and Results

Doxyl derivative 8	Organometallic reagent	Temp, °C	Reaction time	% yield[d]
R = CH_3–[a]	CH_3MgI	–15	5 min	30
R = CH_3CH_2–[b]	CH_3CH_2MgBr	–15	5 min	27[e]
R = $CH_3(CH_2)_6$–[b]	$CH_3(CH_2)_6MgBr$	–15	5 min	27[e]
R = CH_2=CH–[b]	CH_2=CHLi[c]	–78	2 hr	29[e]

[a] Identical by ir with sample prepared by eq 1.[1] [b] A satisfactory C, H, and N elemental analysis was obtained. All doxyl derivatives showed the expected mass spectral fragmentation patterns[12] and each (10^{-4} *M* in EtOAc) showed the typical three-line nitroxide ESR spectrum. [c] Alfa Chemical Co. [d] Isolated yield, based on starting nitrone. [e] Analytical sample obtained by preparative VPC on a 2 ft 5% SE 30/Firebrick column.

To this end 2-pentyloxazoline (**5**) (eq 3) was prepared in 80% yield from hexanoic acid and 2-amino-2-methyl-1-propanol by the method of Allen and Ginos.[7] Dropwise addition of an ether solution of 1.0 equiv of MCPA to an ether solution of **5** at −15° followed by a 24-hr period at 8° produced, after washing the ether solution with cold 10% Na_2CO_3 and drying (K_2CO_3), oxaziridine **6** as an oil (stable when stored at −20°) (90% yield, >97% pure by NMR).[8] A $CHCl_3$ solution (0.5 ml) of crude **6** (150 mg) was adsorbed onto a dry silica gel column (1 × 15 cm) and $CHCl_3$ was added to the top of the column such that after 1 hr the $CHCl_3$ eluant containing the impurities present with **6** arrived at the bottom. Subsequent elution with MeOH afforded nitrone **7**[9] (140 mg (95%), solvent removal <25°) as an oil which is best used immediately as it is slowly converted into a hydrate upon standing at 25°.



(3)

Reaction of nitrone **7** (100 mg) with a two–three-fold excess of the Grignard or alkyllithium reagent in ether (10 ml) at low temperatures gave, after cold aqueous workup, the corresponding *N*-hydroxyoxazolidine **9** (by NMR).[10] Crude **9** was dissolved in MeOH-H_2O (9:1) (10 ml) containing ~2 mg of $Cu(OAc)_2{\cdot}H_2O$[11] and the solution was stirred under air for 2 hr at 25°. Dilution with H_2O and extraction of the product with ether afforded, after chromatography over silica gel, the pure nitroxide **8** (see Table I). The isolated yield of nitroxide **8** (R = CH_3) compares favorably to that obtained via the route outlined in eq. 1.[1] Vinyl nitroxide **8** (R = vinyl) is the first doxyl molecule incorporating an olefinic linkage in the doxyl chain. Unsaturated doxyl molecules will undoubtedly become important in assessing the role of unsaturation in biological systems using the spin labeling technique.[2]