stead of three as generally observed for the terminal carbon. Although the extra splitting is small, only a few hertz, this could not be due to the incomplete proton noise decoupling, since, under the same experimental conditions, this phenomenon has not been observed in other compounds such as alanine and serine (pH 11). In addition the number of peaks and their relative intensities of the C_0 multiplet agree with theoretical predictions for the case of one carbon coupled with two others.[9] Figure 1b shows the C_α spectrum of pyroglutamic acid, a case of one carbon coupled with three others. Since the enrichment factor is lower than 100%, there are in all $2^3 = 8$ possible combinations of different ^{13}C or ^{12}C sites giving rise to a multiplet of $3^3 = 27$ peaks! The combination probabilities and their relative intensities as a function of enrichment factor E are plotted in Figure 2. We note that in the case of one carbon coupled with two[9] or three carbons, the intensities of different combinations are comparable when $E = 67\%$. Below this value, the main peaks decrease quickly and will be masked by the increased intensity of peaks due to other submultiplets. This probably explains why Sogn et al.[10] even using an intrinsic resolution of 0.12 Hz did not observe the geminal and vicinal couplings with 45% ^{13}C-enriched amino acids. In our previous papers[8,9] the chosen conditions (1.25 Hz of intrinsic resolution) did not allow, even with a ^{13}C-enrichment ratio of 85%, the good observation of these couplings.

With regard to the data in Table I, three remarks are in order. (1) In amino acids with only four carbons (aspartic acid, threonine) or a maximum of four carbons in the principal chain (valine), a vicinal coupling between C_0 and C_γ is observed. $^3J_{C_0-C_\gamma}$ is relatively small, varying from 1.5 to 3.5 Hz. (2) Amino acids with more than four carbons show vicinal coupling clearly between C_α and C_δ while $^3J_{C_0-C_\gamma}$ is lower than 1.5 Hz. $^3J_{C_\alpha-C_\delta}$ is usually higher than $^3J_{C_0-C_\gamma}$, varying from 3.5 to 7.5 Hz. These two remarks would be useful for assignment of terminal and nonprotonated carbons (aspartic, glutamic, pyroglutamic acids). (3) The geminal coupling constant is small ($\leq$1.5 Hz) in the case of saturated amino acids; however, this is not true for histidine where $^2J_{C_\beta-C_4}$ (5.9 Hz) is higher than $^3J_{C-C}$ ($\leq$1.2 Hz). In the case of tyrosine the peaks of aromatic carbons are broad and unresolved, and the geminal coupling constants between these carbons can therefore not be determined.

Doddrell et al.[7] have already given a theoretical curve for alcohols. We now try to establish with experimental data the same correlation. For that, we follow our investigation on selectively enriched rigid peptide molecules which shall give us information on the dihedral angles from the ^{13}C-^{13}C coupling values.

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Hydrogen Bond Cooperativity. The Methanol–Tri-*n*-octylamine System in *n*-Hexadecane

Sir:

Although the concept of a cooperative effect in formation of multiply hydrogen bonded complexes has gained rather wide popularity, there are very few experimental data from which even a roughly quantitative assessment of the magnitude of cooperativity may be extracted. Thermodynamic data which clearly show cooperativity effects are of potential importance in the formulation of improved theories of associated liquids, such as water.

One early suggestion of cooperativity was made by Frank and Wen with relation to their model for the structure of liquid water.[1] The nearest chemical neighbors of water—the lower alcohols—should also possess a degree of cooperativity in forming hydrogen bonded polymers if this effect is of importance. However, the long controversy over alcohol association still does not permit any absolute conclusions to be reached regarding cooperative effects in alcohol self-association.[2] It has been suggested for a number of years that the different OH frequency shifts in the infrared region for alcohol solutions in organic solvents show that the hydrogen bond strength in higher polymers is much more than that in dimers and/or trimers.[3] No previous thermodynamic data for alcohol association using enthalpies from models involving dimer and higher polymers will directly support the qualitative conclusions from frequency shifts.[2] The additional problem of discerning relative proportions of cyclic and acyclic alcohol polymers complicates the interpretation of self-association data.

One method which may be used to limit the possible structure types of hydrogen bonded species is to study the association of alcohols with a single site proton acceptor such as a tertiary amine. The possibility of forming cyclic alcohol-amine complexes is thereby excluded. With the occurrence of only linear complexes, the problem of examining hydrogen bond cooperativity is reduced to that of obtaining accurate values of equilibrium constants and enthalpies for the reactions.

Reagent grade methanol and *n*-hexadecane (Hx) were purified as previously reported.[4] Tri-*n*-octylamine (TNOA) (Aldrich) was purified by two distillations at low pressure through a wiped-film molecular still.

The distribution of methanol between vapor phase and Hx has been reported.[4] New measurements were made for the present study by a slightly different procedure and are fully described in the deposited data.[5] The experimental procedure consists of studying the vapor/solution distribution of MeOH in Hx and in Hx solutions containing added amine. The vapor pressure above these solutions is essentially due only to methanol. Data were taken at two amine concentration levels, ca. 0.07 and 0.18 *M*, at temperatures of 25, 35, and 45°. The thermostat bath temperature was controlled to ±0.005°. Methanol vapor pressure measurements were made using a Texas Instruments fused quartz precision pressure gage with a minimum resolution of 0.003 Torr absolute.

The basic assumption made is that Henry's law is obeyed by monomeric methanol and other solute species in the concentration range of 0–0.2 *M* MeOH in Hx. We additionally assume that the amine does not self-associate at the low concentrations used. The vapor pressure-concentration data are presented in Table I (supplementary material).[5]

The monomer methanol molarity in solution may be expressed as

$$C_A = K_D \frac{P_A}{RT}$$

Table II. RMSD's and Equilibrium Constants for Methanol–Tri-*n*-octylamine Complexes

RMSD ($M \times 10^4$)	T (°C)	K_{11} (M^{-1})	K_{21} (M^{-2})	K_∞ (M^{-1})
0.41	25	2.08 ± 0.01	20.43 ± 0.13	11.64 ± 0.04
0.57	35	1.56 ± 0.01	10.50 ± 0.09	8.92 ± 0.03
1.0	45	1.15 ± 0.01	5.47 ± 0.08	6.82 ± 0.04

Table III. Enthalpies (kcal/mol) and Entropies (cal/(deg mol)) for Methanol–Tri-*n*-octylamine Complexes[a]

$-\Delta H_{11}° = 5.58 \pm 0.20$	$-\Delta S_{11}° = 17.3 \pm 0.6$
$-\Delta H_{21}° = 12.4 \pm 0.2$	$-\Delta S_{21}° = 35.6 \pm 0.7$
$-\Delta H_\infty° = 5.04 \pm 0.11$	$-\Delta S_\infty° = 12.0 \pm 0.3$

[a] See ref 7 for comment.

where

$$\frac{P_A}{RT} = C_A^{\text{vapor}}\ (\text{molarity}) \tag{1}$$

where P_A is monomer alcohol pressure (in Torr) and K_D is the ratio of alcohol concentration in solution to vapor alcohol concentration at infinite dilution and a 1.0 M standard state. At any given methanol activity the formal molarity of alcohol-amine complexes may be generally represented by

$$\Delta f_A = K_{11}C_AC_B + 2K_{21}C_A{}^2C_B + 3K_{31}C_A{}^3C_B + \ldots \tag{2}$$

where C_B is monomer amine concentration and where the reasonable assumption is made that only one amine molecule is present in each heterocomplex. Δf_A is the difference between total alcohol in Hx solution and total alcohol in the Hx-TNOA mixture at a particular MeOH activity. Total amine molarity may similarly be expressed as

$$f_B = C_B + K_{11}C_AC_B + K_{21}C_A{}^2C_B + K_{31}C_A{}^3C_B + \ldots \tag{3}$$

where C_B is monomer amine concentration.

The data may be fit by use of eq 1-3 or modifications thereof. Δf_A is not directly observable but may be obtained to a high degree of precision by subtracting from the total alcohol concentration in the MeOH-TNOA-Hx mixture the alcohol concentration predicted by an adequate self-association model for methanol. Alternatively, an analytical process of interpolation between closely spaced activity-concentration pairs for MeOH-Hx solutions could be used.

A graphic display of the degree of association in the present system is quite instructive. If only a 1:1 alcohol-amine complex were formed then the equilibrium constant for that reaction would be

$$K_{11}{}^{\text{app}} = \frac{\Delta f_A}{(C_A)(f_B - \Delta f_A)} \tag{4}$$

for which values of $K_{11}{}^{\text{app}}$ can be calculated without recourse to model fitting. A plot of $K_{11}{}^{\text{app}}$ vs. C_A should be a horizontal line if only a 1:1 complex is present and a straight line with slope $2K_{21}$ (in the low concentration region) if only 1:1 and 2:1 alcohol-amine complexes exist. Figure 1 is a plot of $K_{11}{}^{\text{app}}$ vs. C_A for our data. It is apparent that not only are 1:1 and 2:1 complexes present but also higher complexes exist. One very interesting fact about Figure 1 is the evidence that there is really no region in which we can safely and with high precision consider only a 1:1 complex.

It is obvious from the shape of the curves in Figure 1 that if these data are fit on the basis of specific complexes with uncoupled equilibrium constants a minimum of three constants is required. However, we have been unable to fit these data to a high degree of precision by assuming only three specific complexes. In an effort to obtain a realistic fit of data with a limited number of parameters, we use a model with specific constants K_{11} and K_{21} and a constant equilibrium quotient for the addition of alcohol monomer to heterotrimer and higher polymers. These assumptions result in the equations

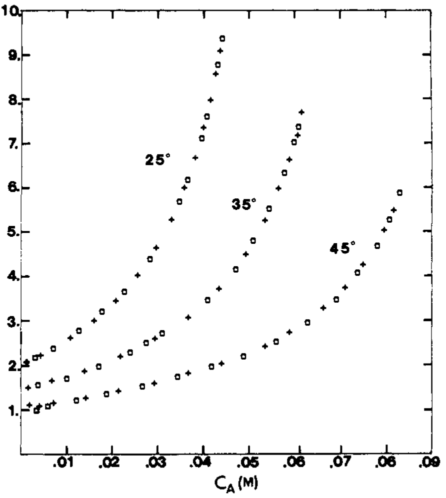

Figure 1. Apparent equilibrium constant ($K_{11}{}^{\text{app}}$) for formation of a 1:1 complex of methanol and tri-*n*-octylamine in hexadecane solution vs. monomeric methanol concentration (C_A) at three temperatures and two fixed amine concentrations (□ ~ 0.07 M; + ~0.18 M amine). For clarity, approximately half the data points measured are plotted.

$$\begin{aligned} A + B &= AB \quad K_{11} \\ 2A + B &= A_2B \quad K_{21} \\ A_nB + A &= A_{n+1}B \quad K_\infty \text{ for } n \geq 2 \end{aligned} \tag{5}$$

$$\Delta f_A = K_{11}C_AC_B + K_{21}C_A{}^2C_B\frac{(2 - K_\infty C_A)}{(1 - K_\infty C_A)^2} \tag{6}$$

$$f_B = C_B + K_{11}C_AC_B + \frac{K_{21}C_A{}^2C_B}{(1 - K_\infty C_A)} \tag{7}$$

The best least-squares values of K_{11}, K_{21}, and K_∞ for each data set which minimize the root mean square deviation (RMSD) between Δf_A (obsd) and Δf_A (calcd) were found using a modified version of a multiparameter least-squares program developed by Marquardt.[6] Values of the equilibrium constants and their standard errors are listed in Table II along with the RMSD of the fit. Least-squares values of $\Delta H°$ and $\Delta S°$ for the complexes are given in Table III.

The parameters in Tables II and III offer dramatic evidence of a cooperative effect. Even allowing for generous errors in the enthalpies it is apparent that the electron donor property of the methanol oxygen in the 1:1 complex has at least been increased to the level of the amine nitrogen, since $\Delta H_{21}°$ is more than twice $\Delta H_{11}°$. Thus, the 1:1 amine-alcohol complex is a significantly stronger base than the uncomplexed amine molecule.

We do not wish to claim that the model used in fitting these data is unique, but the extreme goodness of fit of the heterodata (an average RMSD of 6.6×10^{-5} M for Δf_A values ranging from 0 to 0.056 M) is reassuring. Our fundamental Henry's law assumption is given strong support by the coincidence of the $K_{11}{}^{\text{app}}$ vs. C_A curves in Figure 1 for different amine concentrations at the same temperature and MeOH activity. Correction for MeOH self-association is no problem since use of any model which fits the self-association 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]

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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.

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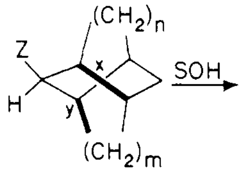
Bond Alignment vs. Product Stability in the Control of Wagner-Meerwein Rearrangements

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.

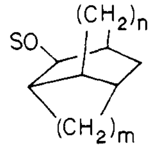
The transition state energy for a Wagner-Meerwein shift can also be influenced by the effectiveness of orbital overlap, which in turn can depend on the initial alignment of relevant bonds. For a rearrangement that is concerted with ionization the migrating group should ideally be antiplanar to the leaving 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



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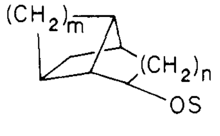

2

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