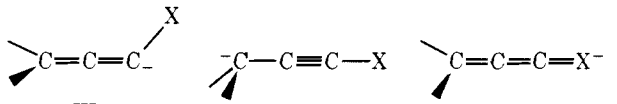
be 17-23. The slower rate of D exchange of II means that its pK_a is in excess of that of the acetylene. The pK_a value of ethylene is 36.5; for II, the inductive effect of α-chlorine substitution (compare water, 16, and hypochlorous acid, 7.5) and the resonance effect of the cumulative double bond (compare ethane, 42, and propene, allylic H, 36) demand corrections that lead us to estimate its value as 22. Since *tert*-butyl alcohol has a pK_a of 19, the barrier to epimerization of the anions at 100 °C is 27-2.3 RT (22-19), or 22 kcal/mol. The precise pK_a values, even those of the analogues chosen, or, for that matter, the simple additivity assumed above, are still far from settled issues,[8] and hence an uncertainty of several kilocalories/mole in this barrier must be accepted. On the other hand, however, it should be emphasized that the mechanism for the epimerization is not known; it *may* occur via inversion of the bent anion, but alternatives—such as rotation, or even carbene



IIIa (bent, planar) IIIb (linear, pyramidal) IIIc (linear, planar)

formation and return of the leaving group—are not ruled out. This means that the result of 22 kcal/mol is the *minimum barrier for inversion.*

It should be noted that, while our results are perhaps most conveniently discussed in terms of bent anions, strictly speaking the conclusion should be couched in terms of the anions' capability of maintaining configuration. Alternately, this capability could be due to some other unequal feature in the environment on the two sides of the molecule; the difference could involve a counterion, or a hydrogen-bonded solvent molecule, for example. The rather severe conditions, however, lead us to consider such possibilities less likely.

Another question that may be raised concerns the shape of unsubstituted allenic anions. Beside the allenic and acetylenic[9] structures (IIIa and IIIb, respectively), structure IIIc surely plays a role when X is chlorine; thus, Brower[10] has attributed the lack of electrostriction of the trichloromethide anion to delocalization of charge into the chlorine d orbitals. On the other hand, chlorine substitution surely increases the weight of structure IIIa over that of IIIb, and so conflicting arguments can be made for the effect of such substitution on the shape. Added to this must be some uncertainty about the effect of the chlorine atom on the hybridization of the unshared pair if it is largely localized as in IIIa. Our own inclination is that the barrier in the parent allenes will be lower; we tend to this conjecture primarily on the known effect of *N*-chlorine substitution on the barrier of inversion in aziridines.[11] However, we also feel that the barrier found in the present work is so large that the replacement of the chlorine atom by hydrogen or an alkyl group will certainly not reduce it to zero.

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Temperature Dependence of Rotational Correlation Times for an Inverse Temperature Transition. A Fundamental Characterization

Sir:

Inverse temperature transitions, for example of polypeptides in aqueous solutions, are commonly discussed in terms of entropy and the Second Law of Thermodynamics. By the Second Law the disorder of the total system, polypeptide plus water, must increase with increases in temperature. Where various physical methods argue for an increase in order of a polypeptide with an increase in temperature, i.e., for an inverse temperature transition, it is inferred that relatively ordered water surrounding exposed hydrophobic groups becomes less ordered bulk water concomitant with association of the hydrophobic side chains.[1-3]

Previous studies on the polytetrapeptide of tropoelastin, HCO-(Val_1-Pro_2-Gly_3-Gly_4)$_n$-Val-OMe, have led to the proposal that at 60 °C a specific additional intramolecular hydrogen bonding occurs.[4] Formation of this hydrogen bond structurally places the hydrophobic Val and Pro side chains in juxtaposition,[5] the implication being that this is the hydrophobic association attending the intramolecular inverse temperature transition. As a means of verifying this proposed association, proton-proton nuclear Overhauser enhancement studies were recently reported which show that the proximity of the Pro_2 δ-CH_2 protons and the Val_1 γ-CH_3 protons becomes dramatically increased at elevated temperature.[6] Thus the nuclear Overhauser effect provided direct experimental evidence for hydrophobic side-chain association attending an inverse temperature transition.

As the molecular expression of temperature is motion—vibrational, rotational, and translational—an increase in temperature means an increase in molecular motion. A corollary, therefore, of an inverse temperature transition would, in this fundamental sense, be a decrease in molecular motion with an increase in temperature. We report that spin-lattice relaxation studies on the polytetrapeptide of tropoelastin, the molecular structure referred to above, clearly demonstrate a decrease in mobility of the polytetrapeptide on going from 60 to 70 °C.

The ^{13}C spin-lattice relaxation times were measured on a JEOL FX-100 pulse Fourier transform NMR spectrometer using the inversion recovery method (180°-τ-90° pulse sequence). A 44-μs pulse width was used for 180° tilt of the ^{13}C magnetization vector and a 22-μs pulse width for 90° tilt. Spectra were collected on the spectrometer using the deuterium signal from coaxial D_2O as an internal lock and broad band

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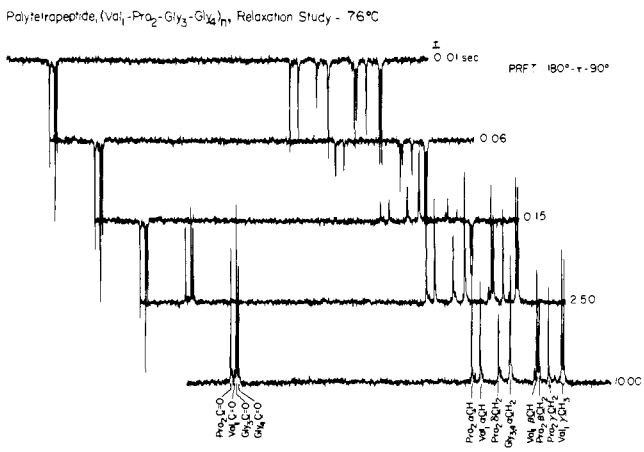

Figure 1. A representative set of partially relaxed Fourier transform (PRFT) spectra of the polytetrapeptide of tropoelastin, HCO-(Val$_1$-Pro$_2$-Gly$_3$-Gly$_4$)$_n$-Val-OMe, taken at 76 °C. The pulse sequence was 180°–τ–90° with the value of τ in seconds given at the right-hand side of each spectrum. Note the narrow lines even though this is a high polymer, $n > 40$, which has undergone an inverse temperature transition to a state of increased order.

decoupling of the proton signal. A Texas Instruments 980-B computer with 16K memory was used to operate the spectrometer using the Fourier transform method during accumulation of the T_1 data. The T_1 values were calculated by the computer using at least four points in the least-squares method. Temperatures in the probe were regulated by a JEOL VT-3B variable-temperature controller with an accuracy of ±2 °C. The polypeptide H-(L-Val-L-Pro-Gly-Gly)$_n$-L-Val-methyl ester ($n > 40$) was synthesized in this laboratory[7] and dissolved in H_2O at a concentration of ~150 mg/mL. D_2O was not chosen as a solvent as H-D exchange of the amide proton affects the relaxation of the carbonyl carbon.[8] The sample was placed in a microcell and dissolved oxygen was removed by passing argon gas through the solution for 20 min.

A representative set of spectra from which the T_1 values were derived are given in Figure 1 taken at 76 °C. The assignments were published previously.[9,10] A plot of log T_1 vs. T^{-1} (K) is given in Figure 2A where the points for each carbonyl are seen to be fairly linear with an abrupt transition between 60 and 70 °C. The other carbons in the polytetrapeptide also show the transition, though less dramatically. Assuming dipole-dipole coupling, isotropic motion, the extreme narrowing condition, and the proximal protons of the preferred conformation (which in the $\Sigma_j r_j^{-6}$ are dominated by the conformationally independent protons of the same residue α proton(s) and the subsequent residue NH proton), the rotational correlation times, τ_c, were calculated[11,12] at each temperature and are plotted in Figure 2B. These qualitative rotational correlation times are in the nanosecond range whereas the nuclear Overhauser enhancements,[13] which, on going from 40 to 70 °C vary from 60 to 80% (with 1.99 taken as 100%), suggest that the correct mobilities are of the order of 10^{-8} s/rad or slower. It appears that the standard assumptions made in calculating the values of τ_c, e.g., the assumption of isotropic motion, lead to an interpretation of motion that is too rapid. Furthermore, as these studies characterize an inverse temperature transition to a state of increased order and as that state is represented by T_1-derived rotational correlation times of 10^{-9} s, it would seem that similarly calculated values of $\tau_c \simeq 10^{-9}$ (an all the more so for values of 10^{-8} s) should not incautiously be used to argue for the absence of order. What can be obtained from Figure 2B are approximate relative barriers to mobility, i.e., $\tau = \tau_0 e^{-\Delta E/RT}$ where ΔE goes from an average of 2.5 kcal/mol to 5.2 kcal/mol. These are likely minimal barriers as other mechanisms of relaxation than di-

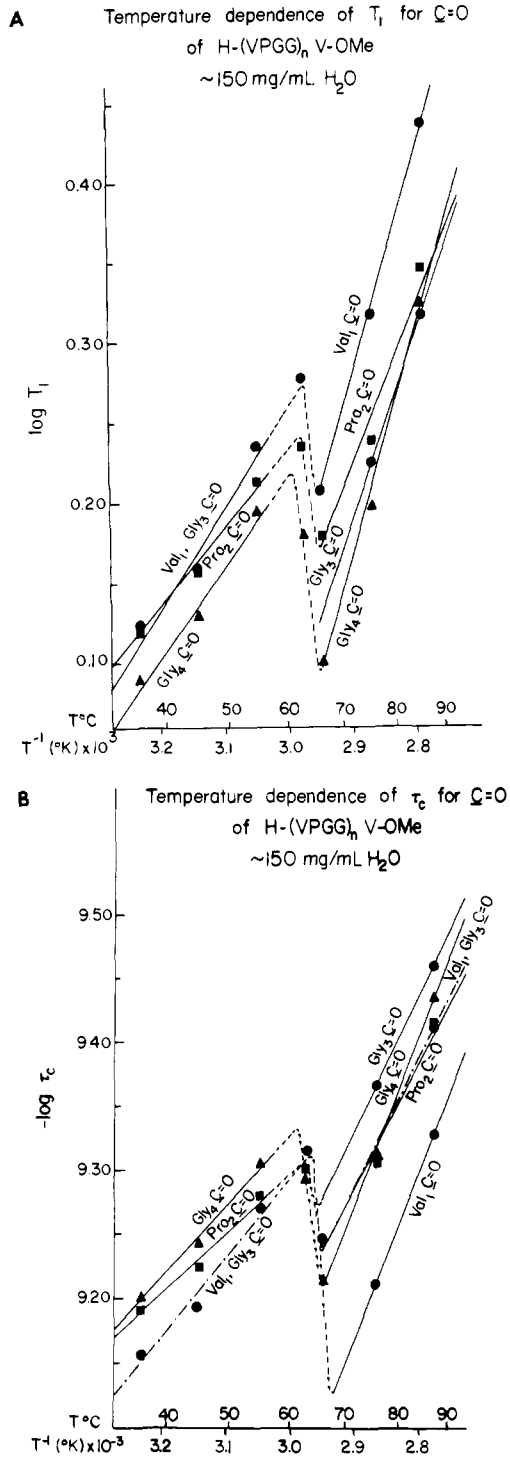

Figure 2. Relaxation studies as a function of temperature on the peptide carbonyls of the polytetrapeptide, HCO-(Val$_1$-Pro$_2$-Gly$_3$-Gly$_4$)$_n$-Val-OMe. (A) A plot of relaxation times vs. T^{-1} (K). Note the precipitous drop in T_1 values on raising the temperature from 60 to 70 °C. The Val$_1$ C=O and Gly$_3$ C=O resonances overlap before the transition but are resolved (at an expanded scale) after the transition. (B) Semilog plot of the temperature dependence of τ_c, the rotational correlation times. There is clearly demonstrated a drop in mobility on increasing the temperature which provides a fundamental characterization of an inverse temperature transition. (Before the transition the values of τ_c for the overlapping Val$_1$ C=O, Gly$_3$ C=O, –·–·–, were calculated using the arithmetic mean of the sum of the proton distances. For comparison after the transition a mean was also calculated, -·-·-, with T_1 for the two resonances averaged.) See text for discussion.

pole-dipole, such as spin rotation, would tend to decrease the slope.

The dramatic drop in the curves beginning at ~60 °C and the difference in slopes (barriers) before and after the transi-

tion clearly exemplify the decreased mobility attending an inverse temperature transition. The loss of segmental motion demonstrated by the transition in Figure 2, on the basis of previous secondary structural studies,[4] is reasonably taken to be due to the addition of a hydrogen bond between the Val_1 NH and the Gly_4 C-O, which as noted above occurs concomitantly with the Val_1 γ-CH_3-Pro_2 δ-CH_2 hydrophobic side-chain association.[6]

The proposed biological role of the inverse temperature transition in the elastin system is in the mechanism of elastic fiber formation and the transition is fundamental to the molecular pathology of vascular and pulmonary tissues. In the vascular wall, varices occur at lower temperatures (at the surface of the extremities) where fiber formation is impaired; and the elastic fiber, because it is a hydrophobic construct, is a primary site of lipid deposition.[14] In lungs challenged by toxic atmospheres, a proline hydroxylating enzyme system is activated which hydroxylates the repeat peptides of elastin[15] and impairs the hydrophobic association required in fiber formation.[16] The histological result in lungs is fragmented and nonfunctional elastic fibers. The specific role of the polytetrapeptide within the precursor protein is thought to be one of raising the temperature of fiber formation. Wherein the other repeat peptides undergo temperature transitions below 37 °C, addition of the polytetrapeptide raises the temperature to the physiological range.

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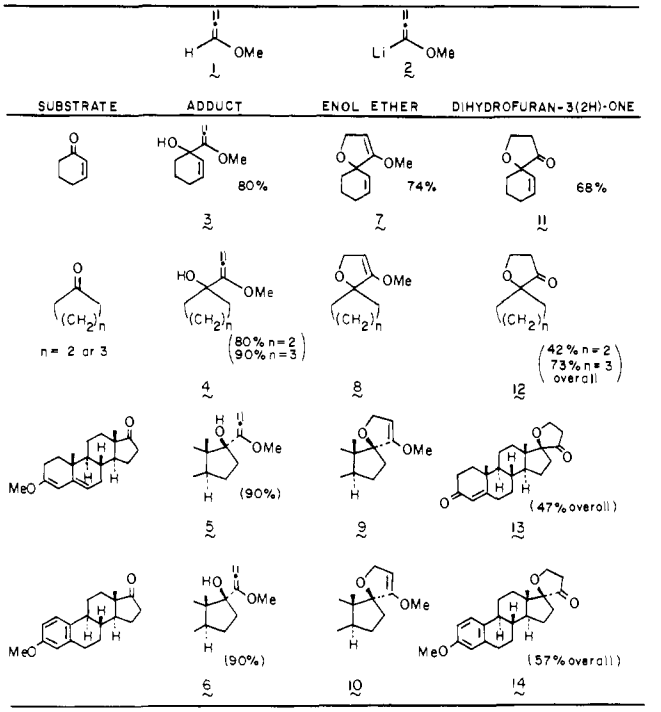
Table I



[a] A typical experimental procedure is as follows. To a stirred solution of *n*-BuLi (27.7 mL, 1.6 M in hexane) in THF (20 mL) under N_2, at −78 °C, was added methoxyallene (3.0 g). The mixture was stirred for 0.5 h and 3-methoxyandrost-3,5-dien-17-one (4.29 g) in THF (5 mL) added. After stirring for 3 h at −78 °C, the mixture was worked up by quenching with saturated aqueous ammonium chloride solution, extraction (CH_2Cl_2), drying ($MgSO_4$), and evaporation which gave **5** (5.03 g, TLC, NMR, and IR show this material to be at least 95% pure). The adduct **5** (2.0 g) in dry *t* BuOH (15 mL) was treated with KO-*t*-Bu (3.03 g) and dicyclohexyl-18-crown-6 (100 mg). The mixture was heated at reflux for 4 h. Workup by quenching in 6 N HCl (10 mL), extraction (CH_2Cl_2), drying ($MgSO_4$), evaporation, and chromatography of the residue over silica gel, eluting with ether–pentane (1:1), gave **13**, mp 167–168 °C (from MeOH–pentane) (0.86 g, 47%). [b] **3**: ν_{max}^{tf} 3440, 1954 cm^{-1}; τ 7.7–8.5 (6 H, m), 7.47 (1 H, s, D_2O, exchange), 6.58 (3 H, s), 4.53 (2 H, s), 4.28 (2 H, d). **4** (*n* = 2): ν_{max}^{tf} 3440, 1950 cm^{-1}; τ 8.22 (8 H, br s), 7.25 (1 H, s, D_2O, exchange), 6.58 (3 H, s), 4.53 (2 H, s). **4** (*n* = 3): ν_{max}^{tf} 3440 and 1950 cm^{-1}; τ 8.4 (10 H, br m), 7.25 (1 H, s, D_2O, exchange), 6.60 (3 H, s), 4.51 (2 H, s). **7**: ν_{max}^{tf} 1664 cm^{-1}; τ 7.9–8.4 (6 H, m), 6.5 (3 H, s), 5.58 (2 H, br s), 4.0–5.0 (3 H, m). **8** (*n* = 2): ν_{max}^{tf} 1668 cm^{-1}; τ 8.32 (8 H, s), 6.38 (3 H, s), 5.56 (3 H, s). **8** (*n* = 3): ν_{max}^{tf} 1665 cm^{-1}; τ 8.5 (10 H, m), 6.4 (3 H, s), 5.52 (3 H, s). **11**: bp 80 °C (0.75 mmHg); ν_{max}^{tf} 1750 and 1060 cm^{-1}; τ 8.48 (4 H, m), 8.06 (2 H, m), 7.58 (2 H, t, *J* = 8 Hz), 5.96 (2 H, t, *J* = 8 Hz), 4.73 (1 H, d, *J* = 11 Hz), 4.08 (1 H, m). **12** (*n* = 2): ν_{max}^{tf} 1750, 1060 cm^{-1}; τ 8.38 (8 H, s), 7.66 (2 H, t, *J* = 7 Hz), 6.06 (2 H, t, *J* = 7 Hz). **12** (*n* = 3): ν_{max}^{tf} 1750, 1060 cm^{-1}; τ 8.5 (10 H, m). 7.72 (2 H, t, *J* = 7 Hz), 6.08 (2 H, t, *J* = 7 Hz). **13**: mp 167–168 °C; ν_{max}^{Nujol} 1740, 1675, 1620, 1085, 1060, 885 cm^{-1}; τ 9.0 (3 H, s), 8.78 (3 H, s), 7.62 (4 H, m), 5.90 (2 H, t, *J* = 7 Hz), 4.28 (1 H, s), 8.0–8.8 (17 H, m); anal. C, H. **14**: mp 118–119 °C; ν_{max}^{Nujol} 1745, 1600, 1040 cm^{-1}; τ 9.1 (3 H, s), 8.9–8.0 (13 H, m), 7.57 (2 H, t, *J* = 7 Hz), 7.22 (2 H, m), 6.30 (3 H, s), 5.94 (2 H, t, *J* = 7 Hz), 3.48 (1 H, br s), 3.39 (1 H, d, *J* = 10 Hz), 2.92 (1 H, d, *J* = 10 Hz); anal. C, H.

An Unusual New Allene Cyclization Reaction. Synthesis of Dihydrofuran-3(2*H*)-ones

Sir:

The readily available C_3 unit, methoxyallene[1] (**1**), has found a number of useful applications in organic synthesis over the past decade.[2] Our interest in β-acyl anion equivalents (homoenolates),[3] and the potential of **1** to serve in this capacity, decided us to examine some of the synthetic chemistry of **1**. Here are reported some unexpected and useful results from this investigation.

Deprotonation of methoxyallene in tetrahydrofuran at −78 °C using *n*-butyllithium gave the α-lithio-α-methoxyallene unit (**2**). Treatment of cyclohex-2-enone with **2** gave the 1,2 adduct **3** (see Table I). We were interested in either the alkoxide-accelerated [3,3]-sigmatropic shift[4] or the [1,3]-sigmatropic shift[5] of the adduct **3**. The terminal π orbitals of the allene are in the same plane as the cyclohexene π orbitals, and

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