

secondary structure, whose effect would be merely to reduce the measured rate constants in proportion to the amount of such structure present.²⁷ The data in Table II do not show any clear-cut reduction for PBA-S1, but they also are not precise enough to rule out the presence of such a motile structure or other small steric effects such as might arise from branching. It is likewise possible that a small portion of permanently slowly exchanging NH groups (not exceeding 14%) escaped detection due to the fact that the kinetics could not be followed with sufficient accuracy to more than 86% completion in the PBA experiments.

Ultraviolet Spectra. The extinction coefficient for the amide π - π^* transition in PBA-I (Table III) does not show the marked hypochromism apparent in helical poly- α -amino acids. This rules out the possibility of any geometrical arrangement of amide groups approximating that in the α helix, while it permits either a random structure or an amide arrangement comparable to that in β structures. This is the only conformational evidence we have obtained on a high molecular weight, unbranched sample in aqueous solution. The spectrum of the branched sample PBA-S1 is slightly different due to the presence of primary and tertiary amides, and is correspondingly less informative regarding the status of the secondary amides.

Thermodynamic Considerations. The apparent instability of an ordered PBA structure in water may be rationalized by comparison with poly- α -L-alanine, $(\text{NHCH}_2\text{CO})_n$. Recent studies^{28,29} on the latter polymer in water have given the following thermodynamic parameters for helix formation: $\Delta H^\circ \simeq -190$ cal/residue-mol, $\Delta S^\circ \simeq -0.55$ cal deg⁻¹ residue-mol⁻¹, and $\Delta G^\circ \simeq -30$ cal/residue-mol at 25°. We feel justified in drawing a rough analogy between PBA and poly- α -L-alanine because our molecular model

(27) A. Hvidt, *C. R. Trav. Lab. Carlsberg*, **34**, 299 (1964).

(28) R. T. Ingwall, H. A. Scheraga, N. Lotan, A. Berger, and E. Katchalski, *Biopolymers*, **6**, 331 (1968).

(29) H. Sugiyama and H. Noda, *ibid.*, **9**, 459 (1970).

studies show possible PBA helices in which the geometries (and probably the interactions) are rather similar to those in the α helix. A major additional factor in the PBA case is the internal rotation about the C^α - C^β bond. If we assume that this bond has three equally probable conformations in the random chain (as the pmr evidence indicates) and only one in a helix, then there is a contribution to ΔS° for helix formation in the amount $-R \ln 3 = -2.2$ cal deg⁻¹ residue-mol⁻¹. Assuming that the remaining contributions to ΔS° and ΔH° are the same as for poly- α -L-alanine, we find $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ = -190 + 298(0.55 + 2.2) = +630$ cal/residue-mol for PBA at 25°. A PBA helix would then be quite unstable. This estimate is very rough, but it does show the importance of the entropic effect of one additional single bond in the residue backbone. One might also consider that an energetically unfavorable conformation about the C^α - C^β bond in a helix would act to destabilize it. The 3.4 residue/turn poly- β -amino acid helix mentioned elsewhere⁴ places the C^α - C^β bond in a precisely staggered gauche conformation, and in this case the energy contribution from this source would not be significant. The above calculation, while rather oversimplified, provides a convenient rationale for our experimental conclusions.

Acknowledgments. We are indebted to Dr. W. D. Phillips at E. I. du Pont de Nemours & Co., Inc., for helpful consultation on the pmr data and for making available a 220-MHz nmr spectrometer, to Dr. V. Damle for writing a computer program used in the analysis of deuterium exchange data, to Dr. R. W. King for inspiration and advice during the pmr studies, and to Dr. Joan Field for her early exploratory work on deuterium exchange in PBA. This investigation was supported by a research grant (GM-13684) and a predoctoral fellowship (GM-21103) from the National Institute of General Medical Sciences, U. S. Public Health Service.

Communications to the Editor

Lanthanide-Induced Shifts in Proton Nuclear Magnetic Resonance Spectra. I. Europium-Induced Shifts to Higher Fields

Sir:

Much of the work reported in the literature¹ using lanthanide shift reagents (LSR's) to induce large pseudocontact shifts in proton nmr spectra has employed tris(dipivalomethanato)europium(III) $[\text{Eu}(\text{DPM})_3]$. Other lanthanides, notably praseodymium, and other organic ligands have also been investigated.^{1c} The proton nmr shifts induced by these LSR's have been qualitatively discussed, and sometimes at least semiquantitatively rationalized, in terms of a two-

parameter form of the pseudocontact shift equation,² conveniently expressed as

$$\Delta\delta_i = \delta_{i, [\text{Eu} \neq 0]} - \delta_{i, [\text{Eu} = 0]} = k(3 \cos^2 \theta_i - 1)(1/R_i^3) \quad (1)$$

where $\Delta\delta_i$ is the (incremental) shift in parts per million of proton i , δ_i is the chemical shift of proton i (in parts per million from internal TMS), k represents a collection of constants, θ_i is the angle describing the position of proton i relative to the assumed effective symmetry axis of the europium complex, and R_i is taken as the proton-europium distance.

Hitherto reported europium lanthanide induced shifts (LIS's) have all been to lower applied fields (higher

(1) (a) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969); (b) C. C. Hinckley, *J. Org. Chem.*, **35**, 2834 (1970); (c) J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971).

(2) (a) H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, **29**, 1361 (1958); (b) G. N. La Mar, *ibid.*, **43**, 1085 (1965).

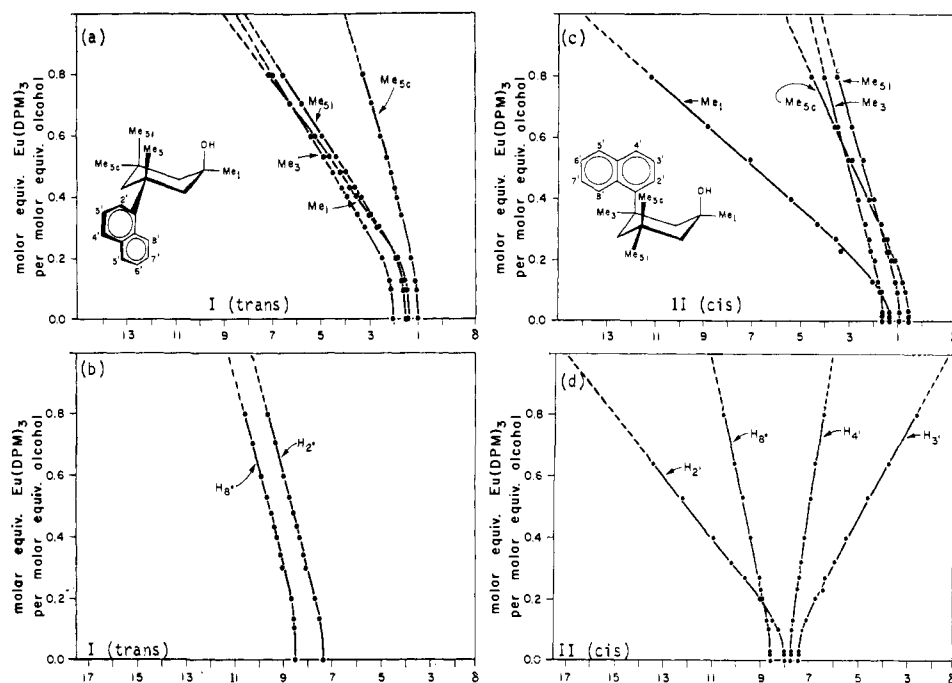


Figure 1. (a) Methyl and (b) aromatic proton shifts of trans isomer I; (c) methyl and (d) aromatic proton shifts of cis isomer II in CDCl_3 solutions as functions of molar equivalents of $\text{Eu}(\text{DPM})_3$ added.

frequencies), *i.e.*, positive shifts as defined by eq 1. This is, however, clearly an accidental consequence of the molecular geometry of the systems studied, for the $(3 \cos^2 \theta - 1)$ term is positive for the more prevalent angles from 0 to 54.736° and from 125.264 to 180° , but negative between 54.736 and 125.264° . For angles in the latter range, a negative $\Delta\delta_i$, *i.e.*, a shift to higher field, should be observed. We report here our initial observations of such upfield shifts, and point out some of the implications for detailed investigations of molecular geometry.

The systems chosen for study were the trans and cis isomers (I and II, respectively) of 3-(1-naphthyl)-1,3,5,5-tetramethylcyclohexan-1-ol.³ Other studies³ indicate that these isomeric alcohols exist highly predominantly in the chairlike conformations shown, and the present report is confined to selected chemical-shift observations.

On addition of $\text{Eu}(\text{DPM})_3$, the proton nmr spectra⁴ of trans isomer I showed the usual downfield shifts for the signals from all 18 different proton types (in contrast to the pattern arising from cis isomer II (*vide infra*)). The

(3) A mixture of the two alcohols is obtained in quantitative yield from the reaction of 3-(α -naphthyl)-3,5,5-trimethylcyclohexanone (see B. L. Shapiro, *et al.*, *Tetrahedron Lett.*, 219, 223 (1971)) with excess ethereal methylmagnesium bromide. The alcohols (I, mp 55° ; II, mp 57 – 58°) were separated by column chromatography and fully characterized by elemental analysis, infrared spectra, detailed nmr studies, and their *p*-toluenesulfonic acid-benzene dehydration to fully characterized isomeric cyclohexenes. The nmr evidence for the structures of these alcohols is analogous to that already presented for the parent ketone; the most important point is the observation of a methyl (Me) resonance for cis isomer II at δ 0.48, *i.e.*, a highly shielded position, whereas the corresponding methyl resonance in the trans isomer I is at a normal value of δ 0.92. The axial positions of the hydroxyl groups in both isomers are strongly required on the grounds of minimal steric interaction and are, in fact, demonstrated in detail by the LIS data presented here. These data are clearly incompatible with equatorial hydroxyl groups in either of the isomers, and the present results also serve to exclude any significant contribution of a twist-boat conformation to the structures of I and II.

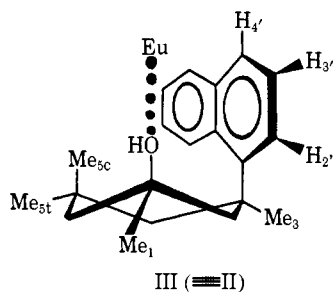
(4) Proton nmr spectra were determined on either a Varian HA-100 (sample temperature 31°) or HR-220 (at 18°) nmr spectrometer with 4 wt/vol % solutions in CDCl_3 . Shifts are accurate to ± 0.01 ppm.

relative magnitudes of these shifts serve to confirm the gross structure of the trans alcohol, as well as requiring the axial disposition of the hydroxyl group, the trans (and therefore equatorial) relationship of the 1-naphthyl substituent, and the chairlike conformation of this highly substituted cyclohexane ring. The methyl shifts (see Figure 1a) serve to exemplify these points. The assignments, which do not depend on these LIS observations, are consistent in detail with expectation if the $\text{Eu}(\text{DPM})_3$ complexes to the top side of the structure as written, thus placing the europium atom such as to influence three methyl groups (Me_1 , Me_3 , and Me_{5t}) strongly and the more remote Me_{5c} to a lesser extent. The close parallelism of the dilution lines for Me_3 and Me_{5t} underlines the expected similarity of their spatial orientations with respect to the hydroxyl oxygen and the europium atoms. The complex set of absorptions arising from the seven naphthyl ring protons is simplified somewhat by (small) downfield shifts of the patterns from five of the protons and the much larger downfield shifts from $\text{H}_{2'}$ and $\text{H}_{6'}$ (Figure 1b). Examination of models indicates the consistency of these observations with the distance relationships implied by formula I.

These observations contrast markedly with analogous results obtained for the cis alcohol II (see Figure 1c,d). Here only one strongly affected methyl group, *viz.*, Me_1 , is seen, while Me_3 , Me_{5c} , and Me_{5t} are much less strongly shifted, all consistent with the structure and conformation shown in II. Again, the very similar and cleanly parallel dilution lines obtained for Me_3 and Me_{5t} may be noted, as well as the good agreement between the slopes of these lines and that obtained for the (structurally analogous) equatorial Me_{5c} of the trans isomer I. Again the structure and conformation are confirmed in detail, and these conclusions are further supported by LIS data obtained for all six of the cyclohexane ring hydrogens for each isomer.

Of greatest interest, however, are the shifts observed

for the *aromatic hydrogen resonances* of the cis isomer (Figure 1d). Large positive (*i.e.*, downfield) shifts are again observed for $H_{2'}$ and $H_{3'}$, but *substantial negative shifts, i.e., to higher applied fields*, are seen for $H_{3'}$ and $H_{4'}$. The $H_{3'}$ shift is very substantial, and the gross, first-order triplet observed for this proton is in fact the highest field absorption in the spectrum at $\text{Eu}(\text{DPM})_3$ levels above *ca.* 0.5 molar equiv, and shows a chemical shift at the 0.8-equiv level of δ 2.62. These LIS values observed for cis alcohol II are clearly rationalized by inspection of eq 1 and examination of the relevant distances and angles as depicted in stereoformula III. In the latter, the $\text{OEuH}_{2'}$ angle is seen to be sharply acute, and hence the $(3 \cos^2 \theta - 1)$ angle



factor is positive; together with the small $\text{EuH}_{2'}$ distance in the naphthyl rotamer shown in III, this should result in a large, positive shift for $H_{2'}$, as is observed. In the case of $H_{3'}$, however, although the $\text{EuH}_{3'}$ distance is still relatively small (actually, very similar to that for $H_{2'}$) the OEuH angle has opened up to a value estimated from models to be somewhere in the range 60 – 75° . Thus $(3 \cos^2 \theta - 1)$ for $H_{3'}$ is negative, and a large, negative shift is in fact observed for this proton. For $H_{4'}$, the OEuH angle is opened up still further, to a value in the 80 – 95° range. Now, however, the distance factor is smaller, due to $H_{4'}$ being more remote from the europium than either $H_{2'}$ or $H_{3'}$; the resulting shift, although again negative, is thus much smaller than for $H_{3'}$. Finally, $H_{3'}$ gives the modest sized, downfield shift consonant with its again sharply acute OEuH angle and the relatively greater distance.

The above arguments hold for any reasonable location of the europium atom, *i.e.*, for any OEu bond length above *ca.* 2.5 \AA and for any C_1OEu angle and $\text{C}_2\text{C}_1\text{OEu}$ dihedral angle which places the europium outside the perimeter of the cyclohexane ring. The necessary angle and distance relationships to give the above-described behavior are provided by the cis parallel, diaxial disposition of the $\text{C}_1\text{--O}$ and the $\text{C}_3\text{--naphthyl}$ bonds together with predominance of the pictured rotational orientation of the naphthalene ring.

The present results, then, underline the theoretically expected importance of the angle factor⁵ as well as the distance dependence of these striking and very useful shifts, and tend to support the view that these LIS's are of a clearly pseudocontact nature describable by eq 1. We further believe that this type of system can be used to make a detailed study of the quantitative

(5) The importance of the angle factor has, of course, been pointed out by several authors, *e.g.*, R. R. Fraser and Y. Y. Wigfield, *Chem. Commun.*, 1471 (1970), and J. Briggs, F. A. Hart, and G. P. Moss, *ibid.*, 1506 (1970). These authors have also made important first contributions toward the detailed and quantitative incorporation of the angle factor into incremental shift calculations.

aspects of the pseudocontact equation and to put the distance and steric requirements of the lanthanide on a firm quantitative basis, as well as providing numerical values for distance and angle relationships among the constituents of these and other cyclohexanol systems. Such studies are in progress.

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(7) Undergraduate research fellow of The Robert A. Welch Foundation.

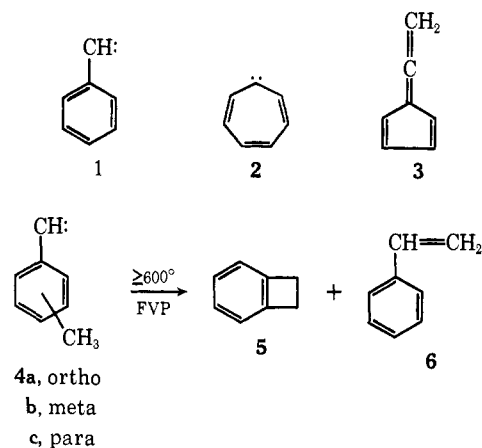
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The Thermal Rearrangement of *p*-Tolylcarbene to Benzocyclobutene and Styrene. A Carbon-13 Labeling Study¹

Sir:

We earlier reported that phenylcarbene (**1**) generated in the gas phase from phenyldiazomethane rearranged either to cycloheptatrienyldiene^{2a,b} at temperatures $\leq 600^\circ$ or ring contracted to fulvenallene (**3**) at temperatures $\geq 600^\circ$.^{2a} In contrast, we found that the high-temperature rearrangement for similarly generated *p*-, *m*-, and *o*-tolylcarbenes **4** resulted in benzocyclobutene and styrene in the ratios listed in about 50% overall yields at 700° under flash vacuum pyrolysis (FVP) conditions³ (**5**:**6**:**4a**, 3; **4b**, 0.80; **4c**, 0.83).



This remarkable conversion must involve isomerization of *p*- or *m*-tolylcarbene to *o*-tolylcarbene which, in part, undergoes C-H insertion to give **5**. Styrene

(1) Flash Vacuum Pyrolysis. IX. Part VIII: E. Hedaya and M. E. Kent, *J. Amer. Chem. Soc.*, **92**, 2149 (1970).

(2) (a) P. O. Schissel, M. E. Kent, D. J. McAdoo, and E. Hedaya, *ibid.*, **92**, 2147 (1970); (b) R. C. Joines, A. B. Turner, and D. M. Jones, *ibid.*, **91**, 7754 (1969).

(3) Similar results were recently reported: W. J. Baron, M. Jones, Jr., and P. P. Gaspar, *ibid.*, **92**, 4739 (1970).