

may be joined and from which the final product may be removed, and (c) possess a structure that will permit diffusion of reagents into the reactive sites and the product out into solution.

We selected styrene-divinylbenzene "popcorn" polymer³ since insoluble polymers of this type may be obtained which have a very low degree of cross linking. Diffusion problems should therefore be less serious than with conventional resins, which must have a relatively high degree of cross linking to be suitable as a support. The experiments herein described were carried out with polymer 99.5% in styrene and 0.5% in divinylbenzene.⁴ More recently, insoluble, low swelling polymer of excellent quality has been obtained which contains only 0.1% divinylbenzene.⁵ Although unnecessary insofar as the chemical reactions are concerned, it was found convenient to cut the low density popcorn polymer into small particles with a Waring blender. In this form the polymer can be packed to give a rapid draining column and may be separated from liquid suspensions readily by filtration.

Carboxyl groups (0.33 mequiv./g.) were introduced by treating the polymer, suspended in nitrobenzene, with diphenylcarbonyl chloride and aluminum chloride and hydrolyzing the resulting amide with a mixture of sulfuric acid, acetic acid, and water. In these and subsequent steps the polymer product was recovered quantitatively simply by filtration. Transformations at the side chains were followed by changes in the infrared absorption bands arising from the carbonyl groups. Thus, the diphenylcarboxamido polymer exhibited a strong band at 6.02 μ whereas the carboxy-polymer absorbed at 5.90 μ . Chemically, the functional groups joined to the polymer behaved normally. Carboxy polymer was converted quantitatively to a hydroxymethyl polymer by reduction with lithium aluminum hydride in ether, to the acid chloride (λ 5.58 μ) by treatment with thionyl chloride, and to a methyl ester (λ 5.90 μ) on reaction with diazomethane in ether. Reaction of the acid chloride with *p*-phenylenediamine and ethylenediamine afforded amides (λ 6.00 μ).

As a test of the synthetic applicability of the support, the hydroxymethyl derivative was used in the preparation of leucylglycine. Phosgene in benzene converted the hydroxymethyl polymer to the chloroformyl derivative (λ 5.62 μ), which with L-leucine ethyl ester hydrochloride in dimethylformamide in the presence of triethylamine afforded \oplus -leucine ethyl ester⁶ (λ 5.78 μ). Alkaline hydrolysis at room temperature yielded \ominus -leucine (λ 5.80 μ ; 0.25 mequiv. of acid/g. of polymer by titration). On successive treatment of the leucine derivative with (a) isobutyl chlorocarbonate and triethylamine in toluene and (b) glycine benzyl ester *p*-toluenesulfonate and triethylamine in dimethylformamide, \oplus -leucylglycine benzyl ester was formed. The dipeptide was cleaved from the polymer with 15% hydrobromic acid in acetic acid and was precipitated as the hydrobromide by addition of ether to the solution of cleavage products. Neutralization in methanol solution with Amberlite CG-400 (OH⁻) yielded leucylglycine. For characterization of the

products from the popcorn polymer, the hydrobromide salt was chromatographed on paper (descending) with 1-butanol-ethanol-water (5:1:4), which gave two faint spots corresponding to glycine hydrobromide (R_f 0.25) and leucine hydrobromide (R_f 0.71) and a major spot corresponding to leucylglycine hydrobromide (R_f 0.61). Elution of the last, hydrolysis with acid, and paper chromatography of the products revealed leucine and glycine as the constituents of the dipeptide. As further confirmation, the mixture of hydrobromide salts from the ether precipitation was analyzed⁷ on a Beckman/Spinco Model 120 B amino acid analyzer according to the method of Moore, *et al.*⁸ Leucylglycine, glycine, and leucine were found in the relative amounts 89.2, 7.2, and 3.6 mole %.

Experiments aimed at utilization of polymer supports in the synthesis of relatively large peptides and of oligonucleotides are in progress.

(7) The analysis was performed by K. A. Thompson.

(8) S. Moore, D. H. Spackman, and W. H. Stein, *Anal. Chem.*, **30**, 1185 (1958); D. H. Spackman, W. H. Stein, and S. Moore, *ibid.*, **30**, 1190 (1958).

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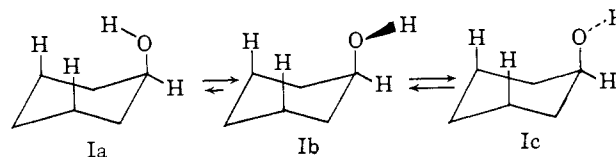
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Direct Conformational Assignment of the Hydroxyl Group

Sir:

Physical methods which may be used for conformational assignment of the hydroxyl group are of extreme importance.¹ Thus, infrared spectroscopic correlations of C-O stretching frequencies have been examined² and, more recently, n.m.r. spectroscopy has been applied.³ Exceptions to both methods, however, have been noted.^{2,4} A third, though seemingly neglected, correlation is based on the observation⁵ that an axial hydroxyl group has a fundamental free O-H stretching absorption about 5 to 10-cm.⁻¹ higher than that of its equatorial epimer. Cole and co-workers have suggested⁶ that this is a result of an increase in the force constant of the O-H stretching vibration due to steric opposition of the axial hydrogens (Ib or c).



That the fundamental free O-H stretching absorption of alcohols generally results in an unsymmetrical band has been discussed by Oki and Iwamura,⁷ who attribute this phenomenon to the presence of isomers corresponding to the rotational conformations of the hydroxyl group. The unsymmetrical bands were separated into two symmetrical ones corresponding to conformers designated as types II (hydroxyl hydrogen staggered between the carbinol hydrogen and an adjacent carbon,

(1) W. Hückel, *Bull. soc. chim. France*, **1** (1963).

(2) E. A. Braude and F. S. Waight in W. Klyne, "Progress in Stereochemistry," Vol. I, Butterworths Publications, Ltd., London, 1954, p. 167.

(3) E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, **No. 17**, 741 (1962); J. I. Musher, *J. Chem. Phys.*, **35**, 1159 (1961).

(4) (a) I. L. Allsop, A. R. H. Cole, D. E. White, and R. L. S. Willix, *J. Chem. Soc.*, 4868 (1956); (b) J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4610 (1962).

(5) A. R. H. Cole, P. R. Jefferies, and G. T. A. Müller, *J. Chem. Soc.*, 1222 (1959), and preceding papers.

(6) A. R. H. Cole, G. T. A. Müller, D. W. Thornton, and R. L. S. Willix, *ibid.*, 1221 (1959).

(7) M. Oki and H. Iwamura, *Bull. Chem. Soc. Japan*, **32**, 950 (1959).

(3) For discussion of the chemistry of popcorn polymers see J. L. Amos, K. E. Coulter, and F. M. Tennant in "Styrene," edited by R. H. Boundy and R. F. Boyer, Reinhold Publishing Corp., New York, N. Y., 1952, p. 729; E. H. Immergut, *Makromol. Chem.*, **10**, 93 (1953); R. L. Letsinger and S. B. Hamilton, *J. Am. Chem. Soc.*, **81**, 3009 (1959).

(4) Some of the polymerization reactions were studied in these Laboratories by Dr. Merlin Guinard.

(5) Merrifield (ref. 2) used resin beads that were 2% in divinylbenzene. His attempts to use 1% cross-linked resin were unsuccessful due to fracturing of the beads, whereas with 8 and 10% cross-linked beads the reaction rates were too slow to be practical.

(6) For simplicity, the insoluble blocking group for the amino function is designated here by the symbol \oplus .

e.g., Ib and c, $\bar{\nu}$ about 3625 cm.^{-1}) and III (hydroxyl hydrogen staggered between two adjacent carbon atoms, *e.g.*, Ia, $\bar{\nu}$ about 3617 cm.^{-1}) for secondary alcohols. Based on these observations, the increase in the frequency of the absorption maximum in going from an equatorial to an axial hydroxyl epimer may be explained by the absence of the contribution of the type III conformation (*e.g.*, Ia), the population of which would be negligible due to diaxial steric interactions. This situation does not exist for the equatorial epimers. If this theory is correct, *direct conformational assignment of the hydroxyl group may be made on the basis of its band shape: a symmetrical band for an axial, an unsymmetrical band for an equatorial hydroxyl group.*

We have examined a series of epimeric alcohols of simple carbocyclic, azabicyclic, and steroid systems in dilute carbon tetrachloride solution ($<0.02 M$) using a high resolution grating spectrophotometer. The free O-H stretching band was very slowly scanned on an expanded abscissa (5 $\text{cm.}^{-1}/\text{cm.}$). Absorbancy correction factors⁸ due to the spectral slit width used (less than 2 cm.^{-1}) were considered to be negligible and were not applied. The absorption bands thus obtained may be characterized as being either symmetrical or unsymmetrical merely by inspection, although even the symmetrical bands tend to possess certain minor features of asymmetry. For quantitative characterization the symmetry of the band may be expressed as the α/β ratio which results from measurements of the segments of the half band width⁹ ($\Delta\nu_{1/2}$) on the high (α) and low (β) frequency sides of $\bar{\nu}_{\text{max}}$. Thus, the band symmetry should decrease as α/β departs from unity. The results summarized in Table I reveal that an α/β ratio which deviates from unity by less than 10% would appear to be a firm indication of an axial hydroxyl conformation.

TABLE I

FREE O-H STRETCHING INFRARED ABSORPTION DATA^a FOR CYCLIC ALCOHOLS

Equatorial alcohols	$\bar{\nu}_{\text{max}}$, cm.^{-1}	α/β
Pseudotropine	3623	0.38
<i>cis</i> -2,10-H-2-Hydroxyquinolizidine ^b	3624	.43
<i>trans</i> -1,10-H-1-Hydroxyquinolizidine ^b	3636	.57
<i>trans</i> -3,10-H-3-Hydroxyquinolizidine ^b	3628	.63
3 β -Cholestanol	3624	.57
Epiandrosterone	3623	.70
Cholesterol	3624	.64
<i>trans</i> -4- <i>t</i> -Butylcyclohexyl alcohol	3624	.64
Menthol	3628	.55
Axial alcohols		
Tropine	3626	1.08
<i>trans</i> -2,10-H-2-Hydroxyquinolizidine ^b	3627	0.90
3 α -Cholestanol	3627.5	.94
Androsterone	3627.5	.92
<i>cis</i> -4- <i>t</i> -Butylcyclohexyl alcohol	3628	.98

^a Perkin-Elmer Model 421 spectrophotometer, slit program 1000 \times 1. ^b For conformational assignments of the hydroxyquinolizidines, see C. P. Rader, G. E. Wicks, Jr., and H. S. Aaron, Abstracts of the 144th National Meeting of the American Chemical Society, March 31-April 5, 1963, Los Angeles, Calif., p. 40M; F. Bohlmann, E. Winterfeldt, O. Schmidt, and W. Reusche, *Chem. Ber.*, **94**, 1767 (1961).

This simple correlation may not hold in the case of a vicinally substituted axial alcohol. The spatial environment of each of the type II conformers (*e.g.*, Ib or c) will no longer be identical upon unsymmetrical vicinal substitution. Neomenthol, for example, gives an over-all symmetrical band, but with a doublet

($\bar{\nu}_{\text{max}}$ values of 3628 and 3632 cm.^{-1}) of near equal intensities. A strict application of the method used for the quantitative characterization of band symmetry would result in an equatorial assignment (α/β , 0.60) to a known axial hydroxyl group. When an instrument of lower resolving power is used, neomenthol gives a symmetrical free O-H stretching band which corresponds to an axial alcohol.

Piccolini and Winstein¹⁰ examined the first overtone of the hydroxyl stretching frequency for a series of compounds, discussed their results from the standpoint of singlet *vs.* doublet character of the bands, and attempted to establish the structural variations which lead to doublet (*i.e.*, unsymmetrical) band character due to steric interactions. They have observed neomenthol to give a symmetrical band in the first overtone, a result confirmed by the present authors. The scope of the steric effect in this phenomenon, however, has not been delineated. Effects of vicinal substitution upon shifts in the frequency of type II and type III conformations have been noted in non-cyclic systems.^{7,11} The presence of functional moieties which can lead to intramolecular hydrogen bonding¹² may also result in an unsymmetrical band for an axial hydroxyl epimer (*e.g.*, epicholesterol¹³).

The noted exceptions notwithstanding, the analysis of the shape of the O-H stretching band constitutes a powerful tool for direct conformational assignment in a rigid six-membered ring system. More subtle applications of the phenomenon are foreseen in the projected areas of conformational analysis and stereochemical assignments in other ring systems.¹⁴ For these purposes both the fundamental and first overtone spectral bands appear to be useful. A recent study of the shape of hydroxyl absorption bands has yielded results from the first overtone which are similar to those from the fundamental.¹⁵ Further comparisons of these two spectral bands are desirable.

Additional and more detailed reports on the applications of this phenomenon will be made at a later date.

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Sulfur Monofluoride: The Microwave Spectrum of a Second Isomer¹

Sir:

Three recent communications have been published concerning sulfur monofluoride. Kuczowski and Wilson² using mass and microwave spectroscopy showed

(1) This work was supported by a grant extended Harvard University by the Office of Naval Research.

(2) R. Kuczowski and E. B. Wilson, Jr., *J. Am. Chem. Soc.*, **85**, 2028 (1963).

(8) D. A. Ramsay, *J. Am. Chem. Soc.*, **74**, 72 (1952).

(9) R. N. Jones and C. Sandorfy in W. West, "Chemical Applications of Spectroscopy," Interscience Publishers, Inc., New York, N. Y., 1956, p. 272.