1-methylsulfinyl-2-undecene (IV), b.p. 131° (0.2 mm.). *Anal.* Calcd. for $C_{12}H_{24}OS$: C, 66.5; H, 11.2; S, 14.8. Found: C, 66.2; H, 11.3; S, 14.4. Neither 1-methylsulfinyl-1-undecene (V) nor 1-methylsulfinyl-2-*t*-butoxyundecane was isolated, although a minor amount of V was present in IV (*vide infra*).

$$\underset{\text{III}}{C_9H_{19}CHCH_2\overset{\uparrow}{S}CH_3} \xrightarrow[t\text{-BuOH}]{t\text{-BuO}^-} \underset{\text{IV}}{C_8H_{17}CH{=}CHCH_2\overset{\uparrow}{S}CH_3} \quad (2)$$

The position of the double bond in IV was assigned on the basis of its n.m.r. spectrum (10% solution in carbon tetrachloride on a Varian A-60 spectrometer) which showed the presence of methylene protons between the double bond and the sulfinyl group (multiplet centered at 6.65 τ, relative area 1.9), as well as methylsulfinyl protons (sharp band at 7.58 τ, area 3.0), and allylic protons (multiplet centered at 7.9 τ, area 2.0). Other features of the spectrum resulted from the vinyl protons (complex multiplet centered at 4.4 τ, area 1.9) and protons of the alkyl chain (multiplet at 8.7 τ, area 12.0, and multiplet centered at 9.0–9.1 τ, area 3.0). The band at 6.65 τ is at lower field than that observed for protons adjacent to either a sulfinyl group or a double bond. Shifts due to adjacent groups are known to be approximately additive,[10] and this peak is shifted from the absorption region for unactivated methylene protons by an amount about equal to the sum of the shifts produced by the carbon–carbon double bond and the sulfinyl group.

To compare the n.m.r. spectrum of IV with that of an α,β-unsaturated sulfoxide a sample of 1-methylsulfinyl-1-dodecene (VI) (mixture of *cis* and *trans* isomers), b.p. 132° (0.15 mm.) (*Anal.* Calcd. for $C_{13}H_{26}OS$: C, 67.7; H, 11.37; S, 13.9. Found: C, 67.6; H, 11.6; S, 13.6) was prepared by the free radical addition of methyl mercaptan to 1-dodecyne and subsequent oxidation of the sulfide. The n.m.r. spectrum of VI differed from that of IV in two important respects. VI did not absorb in the 6.6 τ region, while its olefinic proton absorption was centered at 3.7 τ (compared with 4.4 τ for IV) with none above 3.9 τ. Thus, by comparison of the peak area at 3.5–3.9 with that at 3.9–4.8 τ, we estimate that the maximum percentage of V present in the equilibrium mixture of IV and V is 4%. Treatment of 0.043 mole of VI with 0.012 mole of potassium *t*-butoxide in 200 ml. of *t*-butyl alcohol for 5 hr. at room temperature converted it to 1-methylsulfinyl-2-dodecene containing 4% of VI, demonstrating that equilibrium had been attained during the elimination reaction.

That the β,γ-isomer is favored under equilibrium conditions was shown independently by deuterium exchange experiments. When 1.0 g. of IV was stirred for 24 hr. at room temperature with 1.0 g. of potassium *t*-butoxide in 10 ml. of *t*-butyl alcohol-O-*d*, exchange occurred at both the α- and γ-positions to yield $C_8H_{17}CD{=}CHCD_2SOCD_3$ (n.m.r. spectrum indicated relative area of 1.0 at 4.4 τ and virtual elimination of 6.65 and 7.58 τ bands). A sample of IV treated with potassium *t*-butoxide in *t*-butyl alcohol under identical conditions was unchanged as shown by its n.m.r. spectrum. These results demonstrate that equilibrium between IV and V is readily established, since deuterium in the γ-position must arise from formation of the α,β-unsaturated isomer followed by conversion to the β,γ-unsaturated isomer. It follows that IV is the predominating product in the elimination reaction because it is thermodynamically more stable than V, not because it is the kinetically favored product. It seems quite probable that elimination first yields V, which then isomerizes to IV (eq. 3). Russell has reported[11] the similar formation of an α,β-unsaturated compound from 1-methylsulfinyl-2-phenyl-2-hydroxyethane, but in that system a β,γ-unsaturated isomer does not exist.

$$\text{III} \xrightarrow[t\text{-BuOH}]{t\text{-BuO}^-} \underset{\text{V}}{C_8H_{17}CH_2CH{=}CH\overset{\uparrow}{S}CH_2} \rightleftharpoons \underset{\text{IV}}{C_8H_{17}CH{=}CHCH_2\overset{\uparrow}{S}CH_3} \rightleftharpoons C_8H_{17}C{\equiv}C{-}\overset{\uparrow}{S}CH_3 \quad (3)$$

In equilibria between allyl (I, R = H) and propenyl (II, R = H) compounds, determination of the effect of a substituent is complicated by the simultaneous change of two substituents on the double bond, *i.e.*, the double bond of I holds three hydrogens and a $-CH_2X$ group, whereas that of II holds two hydrogens, a methyl group, and an X group. However, in the equilibrium between IV and V, if we make the reasonable assumption that the effects of the C_8H_{17} and C_9H_{19} groups are essentially identical, then the difference in thermodynamic stability between IV and V is due solely to the difference between the stabilizing effects of the $-CH_2SOCH_3$ group and the $-SOCH_3$ group. Thus, the $-SOCH_3$ group has a destabilizing effect compared to that of $-CH_2SOCH_3$.

This result strongly suggests that ground-state resonance between the sulfur atom and the adjacent unsaturated system is unimportant, since conjugation would favor the α,β-unsaturated isomer.[1,3] Further discussion will await completion of the studies now in progress.

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(10) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, pp. 59–60.

(11) G. A. Russell, E. G. Janzen, H. Becker, and F. J. Smentowski, *J. Am. Chem. Soc.*, **84**, 2652 (1962).

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Popcorn Polymer as a Support in Multistep Syntheses[1]

Sir:

The recent publication by Merrifield[2] describing the synthesis of a tetrapeptide on polymer beads prompts us to report at this time experiments carried out independently which demonstrate the feasibility of using a modified "popcorn" polymer as a supporting matrix in repetitive-step syntheses.

In principle it appears that the manipulations involved in the stepwise synthesis of polypeptides and polynucleotides may be materially reduced, thereby rendering possible the construction of more complex substances, if the polymer is held to a solid support throughout the synthetic sequence. To function properly the support should (a) be insoluble in the solvents and inert to the reagents employed, (b) contain a functional group to which the initial monomer unit

(1) This research was supported by the National Science Foundation, grant G25069, and by the Division of General Medical Sciences of the National Institutes of Health, grant GM 10265-01.

(2) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963).

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" polymer[3] for study 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 blendor. 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 diphenylcarbamyl 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 carboxypolymer 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 Ⓟ-leucine ethyl ester[6] (λ 5.78 μ). Alkaline hydrolysis at room temperature yielded Ⓟ-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, Ⓟ-leucylglycine benyzl 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 leucyl glycine 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 analyzed[7] 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.

(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 Ⓟ-.

(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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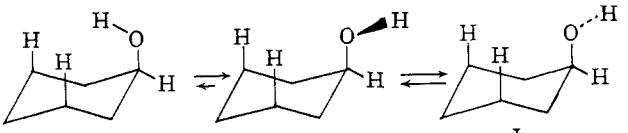
Direct Conformational Assignment of the Hydroxyl Group

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 examined[2] 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 observation[5] 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 suggested[6] 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).



Ia Ib Ic

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).