similar plot for III studied at pH 5.18, 0.2 M NaCl. The b_0 value for PGA at 20° under similar conditions is −200. Thus by the inclusion of greater amounts of L-leucine in the polypeptide backbone of PGA the percentage helix increases at 20° under identical conditions. The observed temperature inversion and increase in helical content begins at lower temperature as the leucine content is increased.

These findings can best be understood by examining the temperature dependence of several interactions assumed responsible for helix stability such as hydrogen bonding, electrostatic interactions, and hydrophobic bonding. The contribution of hydrogen bonding to helical stability in aqueous solution decreases with increasing temperature[15-17] for the peptide hydrogen bonded backbone. It is plausible that a similar temperature effect is operative for hydrogen bonded pairs of un-ionized carboxyls[18] on the side chains, if such interactions play a significant role in conformational stabilization. The electrostatic repulsion between ionized carboxyls causing destabilization of the helix may decrease slightly due to a decrease in ionization upon heating.[18] However, this effect is not apparent in PGA alone. The effect of dilution of the charges in the copolymers as compared to PGA could possibly be responsible for their greater stability. While this is consistent with the greater stability of the copolymers toward heating, it is difficult to account for the increase in helical content at higher temperatures in terms of charge dilution. Thus it seems unlikely that these two forces, hydrogen bonding and electrostatic interactions could be responsible for the behavior of the copolymers in this study.

A third type of interaction, hydrophobic bonding, would be expected to be more important at elevated temperatures. These non-electrostatic side-chain interactions have been shown by Kauzmann[1] and others[2,4] to have a ΔH that is endothermic for the transfer of an aliphatic side-chain from water to a non-polar medium. In the random regions at room temperature the aliphatic side-chains are solvated by water and when the polypeptide becomes helical, this allows for more interactions among side-chains due to their juxtaposition along the helix, the latter occurring at elevated temperatures. In evaluating the role of the forces discussed above to account for the behavior of the copolymers it seems very probable that hydrophobic forces play the most important role.

Similar thermal inversions have been observed previously in non-aqueous solutions[19] and with some proteins in urea solutions.[15,16,20] However, the thermodynamic explanations offered always depend upon the mixed solvent systems used or specific binding which cannot be applied to the present study. A stable helix in aqueous media has been reported for a central block of poly-L-alanine in a block copolypeptide polymer,[21] but it was pointed out that there cannot be side-chain interactions in this case. More recently water soluble derivatives of copolymers of glutamic acid with methionine and alanine have been prepared which maintain their helical structure in aqueous solution.[22]

Acknowledgment.—This work was supported by a grant from the National Institutes of Health (A-5852).

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[19] P. Doty and J. T. Yang, *J. Am. Chem. Soc.*, **78**, 498 (1956).

[20] F. G. Hopkins, *Nature*, **126**, 383 (1930).

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[22] R. K. Kulkarni and E. R. Blout, *J. Am. Chem. Soc.*, **84**, 3971 (1962).

[23] Established Investigator of the American Heart Association.

[24] Contribution No. 169 of the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts.

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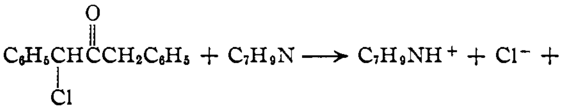
RECEIVED JULY 25, 1962

CAPTURE OF A FAVORSKII INTERMEDIATE BY FURAN

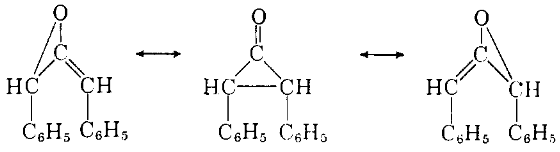
Sir:

An elimination–addition mechanism was proposed recently for the methanolysis of α-chlorodibenzyl ketone (I) promoted by 2,6-lutidine.[1] The kinetics of this reaction suggested that a proton and a chloride ion were lost from I to produce a reactive intermediate. Other lines of evidence were advanced in support of the belief that the intermediate was a delocalized molecule, for which hybrid structure II was proposed, and it was suggested that the Favorskii rearrangement of I[2] proceeds through the same intermediate. New evidence that the reaction of I with 2,6-lutidine produces a delocalized molecule is now reported: when furan is present in the reaction mixture an adduct can be obtained.

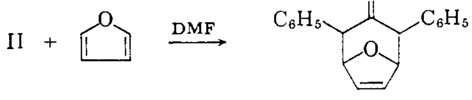


$$C_6H_5CH(Cl)C(=O)CH_2C_6H_5 + C_7H_9N \longrightarrow C_7H_9NH^+ + Cl^- +$$

I



II



III

In a small-scale experiment α-chlorodibenzyl ketone (I), 2,6-lutidine and furan, in a 1:4:2.5

[1] A. W. Fort, *J. Am. Chem. Soc.*, **84**, 2620 (1962).

[2] J. Jullien and P. Fauche, *Bull. soc. chim. France*, [5] **20**, 374 (1953).

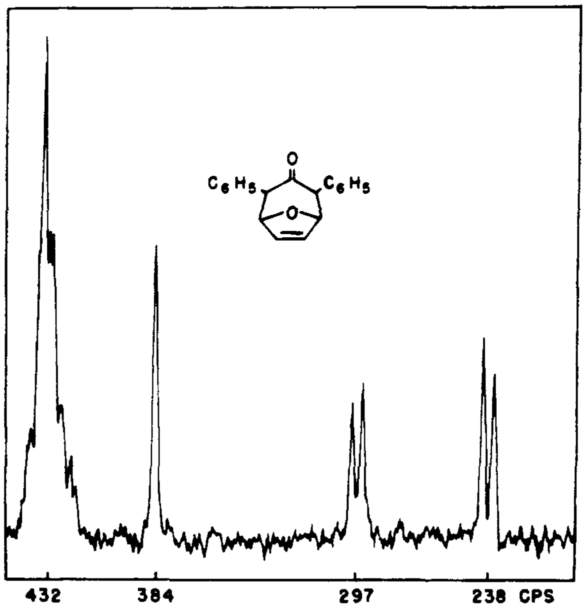


Fig. 1.

molar ratio, were allowed to stand at room temperature in dimethylformamide solution for a period of 96 hours. The reaction mixture was poured into ether and the ether solution was washed successively with water, dilute acid and dilute sodium bicarbonate solution, then ether was replaced by cyclohexane. The cyclohexane solution deposited an adduct,[3] $C_{19}H_{16}O_2$, m.p. 135–136°, 18% yield. The reaction was incomplete as shown by the presence of starting α-chloroketone in the cyclohexane mother liquors (11% recovery).

The infrared spectrum[4] of the adduct showed a characteristic absorption band for a carbonyl group (1733 cm.$^{-1}$) and the expected characteristic bands for monosubstituted benzene. Intense absorption at 1098 cm.$^{-1}$ is consistent with the presence of an oxygen bridge as in III, the proposed structure for the adduct. Weak absorption at 1665 cm.$^{-1}$ and a strong band at 725 cm.$^{-1}$ are compatible with the *cis*-olefin group of III. Structure III for the adduct is strongly supported by its n.m.r. spectrum (Fig. 1).[5] The chemical shifts observed are approximately those expected for the protons of structure III. The relative simplicity of the peak for the ten aromatic protons suggests that the two phenyl groups are in very similar environments. The observation that the benzyl and bridgehead protons form two identical AB systems is compatible with the belief that the molecule has a high degree of symmetry, with the phenyl groups *cis* with respect to each other.

The adduct was allowed to stand at room temperature with fuming hydrobromic acid in ether for a period of 72 hours. The acid treatment produced a new compound,[3] $C_{19}H_{16}O_2$, m.p. 151.5–152.5°, 33% yield. The new compound had an infrared spectrum[4] very similar to that of the original adduct, and the two compounds appeared to be stereoisomers.[6] The n.m.r. spectrum[7] of the compound m.p. 151.5–152.5° indicated the presence of the same relative amounts of each type of proton observed previously, but spin–spin interactions were different. In the n.m.r. spectrum of the compound m.p. 151.5–152.5° the peak for ten aromatic protons was relatively complicated, indicating that the two phenyl groups were no longer in very similar environments. In agreement with this interpretation the n.m.r. spectrum showed an AB pattern for only one of the benzyl and one of the bridgehead protons, indicating that one of the α-benzyl carbon atoms had been inverted by the acid treatment (*cf.* Table I).

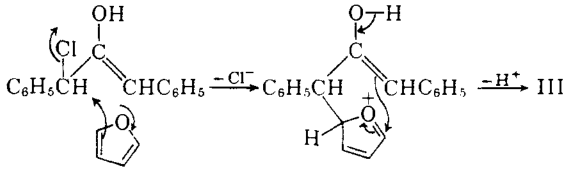
TABLE I

THE N.M.R. SPECTRUM OF THE ISOMER, M.P. 152°, IN $CDCl_3$ SOLUTION AT 60 MC.

Chemical shift,[a] c.p.s.	Number of protons	Assignment
207 singlet	1	α-Benzyl[b]
247 doublet[c]	1	α-Benzyl
299 doublet[c]	1	Bridgehead
318 singlet	1	Bridgehead
388 singlet	2	Olefinic
433[d] multiplet	10	Aromatic

[a] Tetramethylsilane was used as an internal standard. [b] This proton appears to be shielded, probably by virtue of its close proximity to the carbon–carbon double bond. [c] Coupling constant about 5 c.p.s. [d] Extent of shift at highest peak of the multiplet.

The structure of the adduct (III) is suggestive of a reaction, similar to a Diels–Alder reaction, involving the delocalized intermediate (II) and furan. Another possible mode of reaction[8] attributes strongly nucleophilic character to furan:



However, furan apparently is not alkylated in the absence of catalysts,[9] and of the two general modes of reaction suggested here for formation of III, only the first has ample precedents in the literature.

Acknowledgment.—The author is indebted to Professor D. E. Applequist of the University of Illinois and to Dr. Roy W. King of Iowa State Uni-

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(3) A satisfactory analysis for carbon and hydrogen was obtained for this compound.

(4) A Perkin-Elmer model 21 spectrophotometer was used with a sodium chloride prism to examine solutions of the sample in carbon tetrachloride and in carbon disulfide.

(5) A Varian Associates model A60 spectrometer was used.

(6) Intense bands were found at 1730 cm.$^{-1}$ and 720 cm.$^{-1}$, indicating carbonyl and *cis*-disubstituted olefin, respectively. Weak absorption near 2895 cm.$^{-1}$ for *tert* C–H stretching, and near 1665 cm.$^{-1}$ for C=C stretching was found in this spectrum, as in the spectrum of the original adduct. The intense band attributed to a heterocyclic ring vibration was shifted slightly in the new compound to near 1122 cm.$^{-1}$. In the spectra of both compounds characteristic absorption for monosubstituted benzene was found at 755 cm.$^{-1}$ and 696 cm.$^{-1}$.

(7) A Varian Associates model HR60 spectrometer was used.

(8) This alternative reaction path was pointed out by a referee.

(9) A. P. Dunlap and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p. 32.

versity for the n.m.r. spectra and for assistance in the interpretation of the n.m.r. spectra.

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RECEIVED OCTOBER 15, 1962

HIGH RESOLUTION NUCLEAR MAGNETIC RESONANCE SPECTRA OF VARIOUS POLYISOPRENES

Sir:

There has been some controversy recently as to whether hevea and balata (or gutta-percha) macromolecules comprise 100% 1,4 units, or whether they are predominantly *cis* and *trans* structures, respectively, with minor amounts of isopropenyl or 3,4 units. Binder[1] contends, on the basis of a small absorption peak at 11.25 μ in the infrared spectrum of each of these polymers, that the hevea and balata macromolecules contain 2.2 and 1.3% 3,4 units, respectively. This has been disputed by Fraga[2] who showed that there was no evidence for isopropenyl groups in the near infrared spectra; he therefore concluded that the natural polyisoprenes are essentially pure 1,4-type polymers. Another interesting question which has never been resolved is whether the 1,4 units in hevea (or balata) are exclusively *cis* (or *trans*) or whether these polymers contain a small amount of the opposite isomer as an impurity. Recent developments in high resolution n.m.r. work on polymers,[3] and in particular, the application of n.m.r. to an analysis of butadiene–isoprene copolymer compositions,[4] have prompted us to examine these questions with the aid of this tool. The present communication reports the results of an investigation of hevea and balata microstructure using a Varian high resolution 100 Mc. n.m.r. spectrometer as well as a Mnemotron Computer of Average Transients (C.A.T.) attached to a Varian A-60 spectrometer.

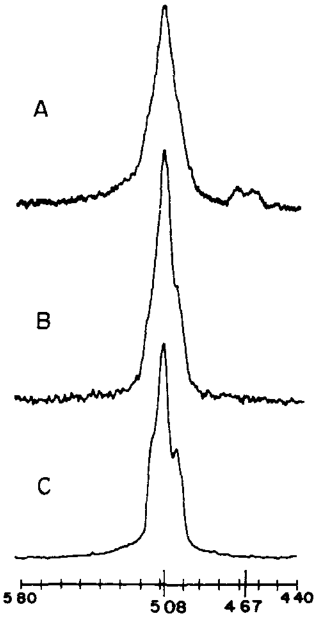

Fig. 1.—Proton n.m.r. spectra of various polyisoprenes at 100 Mc. in the olefinic proton region: (A) synthetic *cis;* (B) natural *cis* or hevea; and (C) natural *trans* or balata.

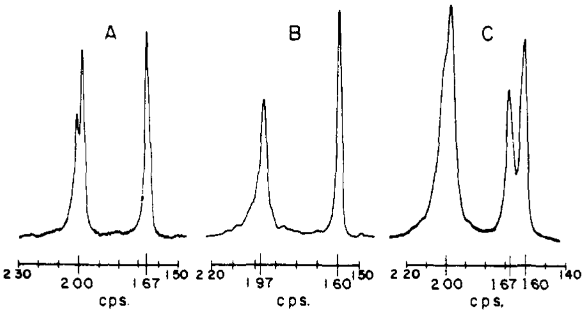

Fig. 2.—Proton n.m.r. spectra of natural *cis* (A) and natural *trans* (B) polyisoprenes and an isomerized polyisoprene (C) at 100 Mc. The peaks around 200 c.p.s. correspond to methylene protons while the 167 and 160 c.p.s. peaks correspond to methyl protons on *cis* and *trans* double bonds.

The broad resonance at 508 c.p.s. (4.92 τ) in the 100 Mc. spectra of hevea, balata and a synthetic *cis* polyisoprene[5,6] (Fig. 1) undoubtedly corresponds to $-\mathrm{C(CH_3)}{=}\mathrm{C}H-$ protons while the doublet at 467 c.p.s. (5.33 τ) (Fig. 1A) corresponds to $>\mathrm{C}{=}\mathrm{C}H_2$ protons. The ratio of areas for these two kinds of protons in the synthetic polymer, *viz.*, 10.9, indicates that this polymer contains 4.4% 3,4 units, which agrees with the value from infrared analysis.[6] The important thing to note, however, is that there is no evidence for any 3,4 units in the n.m.r. spectra of the natural polyisoprenes (Figs. 1B and 1C). This was confirmed by detailed examination of the olefinic proton resonance obtained with the C.A.T.which afforded spectra with considerably greater signal-to-noise ratio than that shown in Fig. 1. Thus, from an analysis of the spectrum of a 9:1 balata-synthetic *cis* polyisoprene mixture, the minimum isopropenyl content which could be detected with the C.A.T. was found to be about 0.3% of the monomer units. Moreover, the corresponding spectra of hevea and balata showed even less than this amount. This finding thus corroborates the conclusions reached by Fraga.[2]

It is seen in Fig. 2 that the methyl proton resonances in the *cis* and *trans* polyisoprenes occur at

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[1] J. L. Binder, *Rubber Chem. and Technol.*, **35**, 57 (1962); J. L. Binder and H. C. Ransaw, *Anal. Chem.*, **29**, 503 (1957).

[2] D. W. Fraga, *J. Polymer Sci.*, **41**, 522 (1959).

[3] F. A. Bovey and G. V. D. Tiers, paper presented at the 142nd Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, Polymer Division Preprint Booklet, p. 115*, and references therein.

[4] H. Y. Chen, *Anal. Chem.*, **34**, 1134 (1962).

[5] The spectra in Figs. 1 and 2 were obtained at room temperature on CCl_4 solutions containing 1% tetramethylsilane as internal standard. The polymer concentrations ranged from about 2% in the high *cis* solutions to about 10% in the high *trans* solutions.

[6] Hevea and balata were obtained through the courtesy of J. J. Shipman, The B. F. Goodrich Company Research Center, Brecksville, Ohio. The synthetic polyisoprene was obtained from Shell Chemicals Company, Torrance, California, and was considered to have 4.7% 3,4 content based on infrared analysis.