TABLE I

EFFECT OF STRUCTURAL CHANGES IN POSITION 4 ON THE PHARMACOLOGICAL ACTIVITIES OF OXYTOCIN

Compound	Activities, units/mg. Depressor (fowl)	Oxytocic (rat)	Milk-ejecting (rabbit)	Pressor (rat)	Antidiuretic (rat)
Oxytocin[3]	507 ± 15	486 ± 5	410 ± 16	3.1 ± 0.1	2.7 ± 0.2
4-Decarboxamido-oxytocin[4] (4-L-α-aminobutyric acid-oxytocin)	108 ± 5	72 ± 2	225 ± 7	~0.1	0.2–0.3
4-L-Alanine-oxytocin[26]	65 ± 3	36 ± 6	240 ± 55	<0.01	<0.01
4-Glycine-oxytocin	5.5 ± 0.2	2.8 ± 0.1	17 ± 1	<0.002	<0.005
4-L-Serine-oxytocin[26]	230 ± 20	195 ± 30	255 ± 45	<0.1	0.06 ± 0.01
Isotocin[27] (4-L-serine-8-L-isoleucine-oxytocin)	320 ± 15	150 ± 12	300 ± 15	0.06 ± 0.01	0.18 ± 0.03

On the other hand, 2-leucine-oxytocin[31] has extremely low activity and 2-serine-oxytocin[32] has practically none. It is therefore not surprising that the 2-glycine-oxytocin was practically inactive in the bioassays performed.

With regard to the 3-position, substitution of the isoleucine residue in this position by a 5- or 6-carbon aliphatic amino acid[30,33,34] and even by the aromatic amino acid phenylalanine (oxypressin)[33,35] gives rise to analogs showing appreciable activity. The lack of appreciable activity in 3-glycine-oxytocin is thus of interest.

Acknowledgments.—The author is greatly indebted to Dr. Vincent du Vigneaud for many helpful suggestions and encouragement. She also wishes to thank the following members of the laboratory for their assistance: Mr. Joseph Albert for the elementary analyses, Mr. Roger Sebbane and Mrs. Caroline Holzhauser for the amino acid analyses, and Mrs. Sherrilyn Goodwin, Mrs. Marilyn Rippe, and Miss Margitta Wahrenburg for the biological assays. The author also wishes to acknowledge the supply of a portion of the synthetic protected pentapeptide used in these studies from Parke, Davis and Company through the courtesy of Dr. Harry M. Crooks, Jr.

(30) R. A. Boissonnas, S. Guttmann, B. Berde, and H. Konzett, *Experientia*, **17**, 377 (1961).

(31) K. Jošt, J. Rudinger, and F. Šorm, *Collection Czech. Chem. Commun.*, **28**, 1706 (1963).

(32) S. Guttmann and R. A. Boissonnas, *Helv. Chim. Acta*, **43**, 200 (1960).

(33) R. A. Boissonnas, S. Guttmann, P.-A. Jaquenoud, and J.-P. Waller, *ibid.*, **39**, 1421 (1956).

(34) J. Rudinger, J. Honzl, and M. Zaoral, *Collection Czech. Chem. Commun.*, **21**, 770 (1956); H. Nesvadba, J. Honzl, and J. Rudinger, *ibid.*, **28**, 1691 (1963).

(35) P. G. Katsoyannis, *J. Am. Chem. Soc.*, **79**, 109 (1957).

COMMUNICATIONS TO THE EDITOR

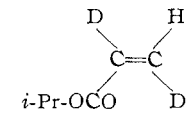
Stereospecificity in the Anionic Polymerization of Isopropyl Acrylate

Sir:

Natta, *et al.*,[1] have observed that the polarized infrared spectra of polymers of *cis*-1-d_1-propene and of *trans*-1-d_1-propene are quite different. Miyazawa and Ideguchi[2] have shown by infrared studies that *cis*-1-d_1-propene yields the *erythro*-diisotactic polymer (D on the opposite side of the planar zigzag from the methyl group) while the *trans*-1-d_1-propene yields the *threo*-diisotactic polymer (D on the same side). These results were interpreted as indicating that with the Ziegler–Natta catalyst employed, *cis* opening of the double bond occurs, as concluded by Natta, *et al.*,[3] for *trans*-propenyl isobutyl ether.

No studies have been reported of the stereospecificity, with respect to the methylene group, of the polymerization of any vinyl or vinylidene monomer other than propene or with any catalyst other than the Ziegler–Natta type. In this communication, we report an investigation by n.m.r. of the stereospecificity of the Grignard-initiated polymerization of isopropyl acrylate.

Isopropyl α-*cis*-β-d_2-acrylate was prepared by *trans* addition of deuterium to isopropyl propiolate.[4] The



structure was confirmed by n.m.r. (7.5% (w./v.) solution in toluene; Varian DP-60 spectrometer) which showed in the vinyl region a 1:1:1 triplet at τ 4.71, the spacing of which (*ca.* 1.6 c.p.s.) corresponds to *cis*-H^1–H^1 coupling (10.4 c.p.s.); the geminal coupling was, as expected, too small to observe. There were indications of some residual α- and *cis*-β-protons. Polymerization was carried out at *ca.* −78° (seven volumes of toluene, one volume of monomer, 8 mole % of phenylmagnesium bromide), the Grignard reagent being added under high vacuum; no ether was present. The polymer was purified by reprecipitation with petroleum ether and ethanol and freeze-drying from benzene. Nondeuterated polymer was prepared in the same manner.

The polymer prepared under these conditions is believed to be highly isotactic.[5] This was confirmed by the n.m.r. spectra, obtained on 14.0% (w./v.) solutions in chlorobenzene at 150°. In Fig. 1, the septet of the carbinyl proton (τ 4.96) and the doublet of the methyl protons (τ 8.76, J = 6.14) of the side chain are not shown. The observed backbone proton

(1) G. Natta, M. Farina, and M. Peraldo, *Atti. Acad. Nazl. Lincei, Rend. Classe Sci. Fis Mat. Nat.*, [8], **25**, 424 (1958); M. Peraldo and M. Farina, *Chim. ind. (Milan)*, **42**, 1349 (1960).

(2) T. Miyazawa and Y. Ideguchi, *J. Polymer Sci.*, **B1**, 389 (1963).

(3) G. Natta, M. Farina and M. Peraldo, *Chim. ind.* (Milan), **42**, 255 (1960).

(4) C. E. Castro and R. D. Stevens, Abstracts, 143rd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1962, the authors thank Dr. Castro for further details on this preparation given in personal communication.

(5) B. A. Garrett, *et al.*, *J. Am. Chem. Soc.*, **81**, 1007 (1959).

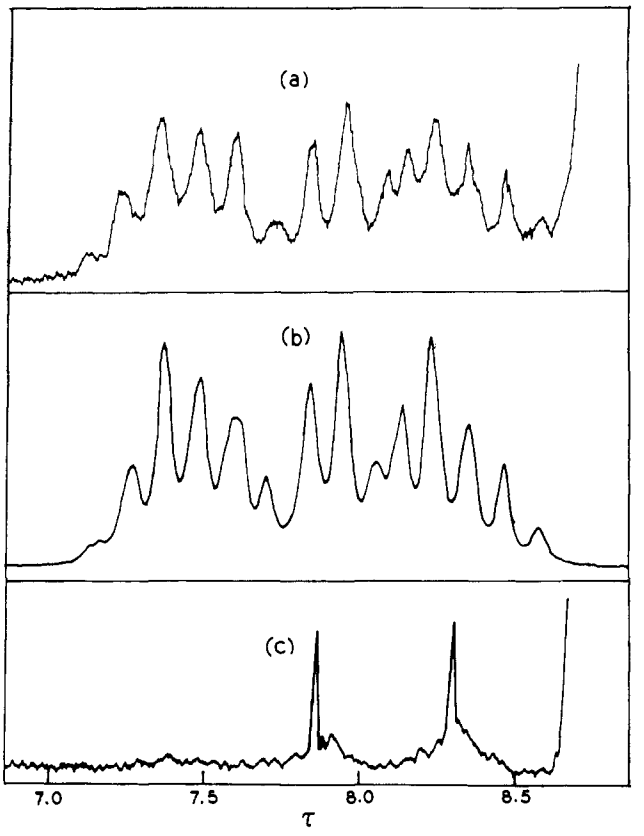


Fig. 1.—(a) Backbone proton spectrum of isotactic polyisopropyl acrylate; (b) calculated backbone proton spectrum of isotactic polyisopropyl acrylate; (c) backbone proton spectrum of polyisopropyl-α-*cis*-β-d_2 acrylate with deuterium irradiation.

spectrum of the nondeuterated polymer (Fig. 1a) was closely matched by a six-spin machine calculation (treating the polymer in effect as a cyclic dimer[6]) employing the following parameters: H_α τ 7.43; H_{β_1} τ 7.86; H_{β_2} τ 8.32; $J_{gem}(H_{\beta_1}\text{–}H_{\beta_2})$: −13.6 c.p.s.; $J_{vic}(H_\alpha\text{–}H_{\beta_1}, H_\alpha\text{–}H_{\beta_2})$ 6.50 c.p.s.; more distant couplings 0 c.p.s.; line width 2.5 c.p.s. The calculated spectrum is shown in Fig. 1b. (Methylene groups in syndiotactic sequences necessarily have equivalent protons and so give an entirely different spectrum[7]; it is believed that even a relatively small proportion of syndiotactic sequences, *i.e.*, more than *ca.* 5%, could have been detected.) In Fig. 1c, the spectrum of the β-deutero polymer is shown.[8] The peaks corresponding to *erythro* (τ 7.86) and *threo* (τ 8.32) methylene protons[9] appear to be nearly equal in intensity. (The resonance of residual α- and β-CH_2 protons makes exact measurement somewhat difficult.) Thus, in contrast to what is observed for polypropene, *the configuration of the polyacrylate chain is random with respect to the CHD groups and stereoregular with respect to the* $CHCO_2R$ *groups.*[10] This result seems to us to make it necessary to re-examine existing proposals for the mechanism of stereospecific anionic polymerization.[11] A possible interpretation is that "*cis*" and "*trans*" opening of the double bond are equally probable. Steric considerations, however, make it appear likely that the actual direction in space along which the active chain end and monomer approach each other is always *trans*; apparent "*cis*" addition must then result from a rotation of the newly formed chain end under the influence of the magnesium counter ion. These ideas, as well as the present experimental results, will be described in greater detail elsewhere. We are now extending these studies to other monomers and initiators.

In the accompanying communication by Yoshino, *et al.*,[12] it is shown that in the anionic polymerization of methyl acrylate with lithium aluminium hydride addition to the monomer double bond is stereospecific, in contrast to our findings; if our assignment of methylene peaks is correct, the addition must be *trans*, in contrast to the conclusions of Natta, *et al.*[3] The stereospecificity with regard to the ester groups, however, is not so high as with the Grignard initiator. Thus, different anionic initiators exert varying degrees of control at the CHR and CHD groups.

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(6) W. C. Tincher, private communication.

(7) F. A. Bovey and G. V. D. Tiers, *J. Polymer Sci.*, **44**, 173 (1960); *Fortschr. Hochpolymer. Forsch.*, **3**, 139 (1963).

(8) This spectrum shows the appearance of the peaks when decoupled from deuterium by irradiation at 9.1 Mc. sec., using double resonance equipment manufactured by Nuclear Magnetic Resonance Specialties, Inc.; narrowing of the peaks upon decoupling is appreciable but much less than expected because the multiplet arising from H–D couplings is already partially collapsed. Evidently, deuterium nuclei on a polymer chain experience particularly effective quadrupole relaxation because of the relatively slow tumbling of the molecular framework.

(9) This assignment, although very probable, is not entirely certain; it is based on measurements reported for related small molecules. See L. M. Jackman, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon Press, London, 1959, pp. 121–125.

(10) The alternate possibility that the polymer may actually be *syndiotactic* with respect to the CHD groups should perhaps not be entirely dismissed, but is not considered here because it would be very difficult to construct a rational reaction mechanism to account for it.

(11) See C. Schuerch, *Ann. Rev. Phys. Chem.*, **13**, 195 (1962); C. E. H. Bawn and A. Ledwith, *Quart. Rev.* (London), **16**, 361 (1962).

(12) T. Yoshino, J. Komiyama, and M. Shinomiya, *J. Am. Chem. Soc.*, **86**, 4482 (1964).

COLLEGE OF FORESTRY
SYRACUSE UNIVERSITY
SYRACUSE, NEW YORK
C. SCHUERCH
W. FOWELLS
A. YAMADA

BELL TELEPHONE LABORATORIES, INC.
MURRAY HILL, NEW JERSEY
F. A. BOVEY
F. P. HOOD
E. W. ANDERSON

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On the Propagation Steps of Free-Radical and Anionic Polymerization

Sir:

Many theories[1,2] have been proposed in regard to the propagation steps of free-radical and anionic polymerization. Although some of these theories conflict with others, they have not been proved or disproved because of lack of sufficient experimental bases. One of the most important and fundamental things required for considering the reaction mechanisms is whether or not monomer double bonds open in a definite mode of *cis* or *trans* in free-radical or anionic polymerization. For the purpose of confirming this point, methyl acry-

(1) Most of these theories are summarized by C. E. H. Bawn and A. Ledwith, *Quart. Rev.* (London), **16**, 361 (1962).

(2) C. E. H. Bawn, W. H. Janes, and A. M. North, *J. Polymer Sci.*, **C4**, 427 (1963).