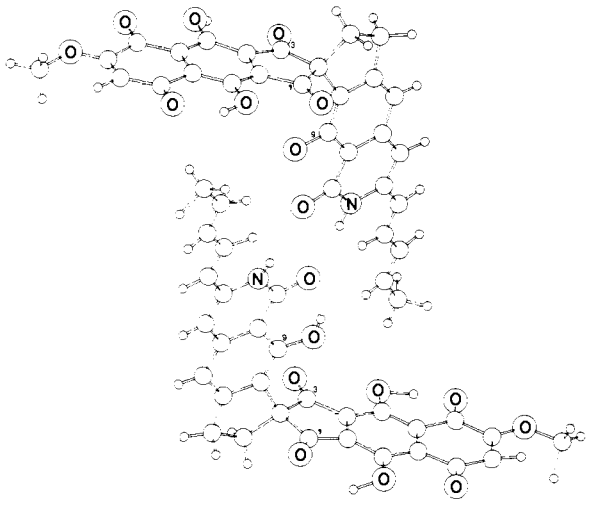

**Figure 1.** Computer-generated perspective view of the two independent molecules in the X-ray structure of fredericamycin A (**1**).

4.08 and 3.37 Å in one molecule and 3.37 and 3.93 Å in the other. The differences are probably due to packing forces and the quite extensive hydrogen bonding.

The spiro[4,4]nonane system found in fredericamycin A has not been observed in any other types of antibiotics. It imposes certain interesting spacial characteristics on the molecule, which may have an important role in determining its biological activity. The spiro ring system is also very interesting from a biogenetic point of view.

Fredericamycin A has been shown to be a potent antitumor agent. Its activity against glioblastoma cells is comparable to that of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU),[2] one of the most potent clinically useful agents. It is also highly cytotoxic[2] against murine leukemias KB, P388, and L1210 cell lines, with $ED_{50}$ values of $7 \times 10^{-1}$, $5 \times 10^{-4}$, and $2 \times 10^{-4}$ $\mu$g/mL, respectively. It has also been shown to be a powerful inhibitor against ovarian tumor growing in a human tumor cloning system.[10]

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**Registry No. 1**, 80455-68-1.

**Supplementary Material Available:** A diagram of the crystallographic nomenclature of fredericamycin A and tables of interatomic distances, bond angles, atomic parameters, and hydrogen atom positions (6 pages). Ordering information is given on any current masthead page.

(10) (a) Von Hoff, D. D., personal communication. (b) Von Hoff, D. D.; Casper, J.; Bradley, E.; Sandbach, J.; Jones, D.; Makuch, R. *Am. J. Med.* **1981**, *70*, 1027-1032.

# Concerning the Mechanism of Ziegler-Natta Polymerization: Isotope Effects on Propagation Rates

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Ziegler-Natta polymerization, a major industrial organometallic process, is poorly understood at the molecular level. Several sets of molecular descriptions have been proposed for this reaction which differ fundamentally from one another.[1-5] The source of this disagreement is the very mode of carbon-carbon bond formation. Before the more subtle distinctions between and within these sets of mechanisms can be elucidated, this most crucial and elementary aspect of the polymerization process must be understood.

Two of the most clearly defined proposals among the many sets suggested are the carbene-to-metallacycle mechanism of Green and Rooney[3] (Scheme I, a) and the direct four-center olefin insertion mechanism of Cossee and Arlman (Scheme I, b).[1] Neither of these schemes is inconsistent with the known kinetic and stereochemical aspects of the process,[6] and known reactions have been cited as models in justifying each step of both proposals.[3,7-10] The important difference between the two suggestions is the involvement of hydrogen migration in a (Scheme I). This mobility implies a large primary kinetic isotope effect on chain propagation in a and related reactions but no such effect in b. In this paper we report our efforts to determine this isotope effect and conclude that if such an effect exists it is quite small.

Earlier workers have examined[11] the rates of polymerization of $C_2D_4$ and $C_2H_4$ and concluded these rates are the same. However, this work allows for $k_H/k_D$ of between 0.7 and 1.4. Since isotope effects on the rate of catalyst generation were also observed even wider variations can not be ruled out.

Recent studies provide values expected for titanocene systems that involve carbenoid intermediates. The abstraction of an $\alpha$ hydrogen by an aluminum alkyl is modeled by the formation of $Cp_2TiCH_2Al(CH_3)_2Cl$ from $Cp_2TiCl_2$ and $(CH_3)_3Al$.[12] The isotope effect for this reaction is 3. Other related $\alpha$ abstractions fall between 3 and 3.5.[13] Even if the $\alpha$-hydrogen migration is not a part of the rate-determining step, the reverse of eq 3 provides an expected secondary isotope effect for reactions involving titanium carbene intermediates. The secondary isotope effect determined in these systems is large, ranging from 1.2 to 1.4.[14] Since few models exist for direct insertion into a metal-carbon bond, good values are not available. However, since this reaction does not involve hydrogen migration or major hybridization

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(2) McKinney, R. J. *J. Chem. Soc., Chem. Commun.* **1980**, 491-492. This mechanism requires growth by two olefin units/insertion step. Hence, only $C_2$, $C_6$, $C_{10}$, $C_{14}$, $C_{18}$ . . . would be expected. The results presented in Table I ruled out this mechanism.
(3) Ivin, K. J.; Rooney, J. J.; Stewart, C. D.; Green, M. L. H.; Mahtab, R. *J. Chem. Soc., Chem. Commun.* **1978**, 604-606. Green, M. L. H. *Pure Appl. Chem.* **1978**, *50*, 27-35.
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(12) Ott, K., unpublished results.
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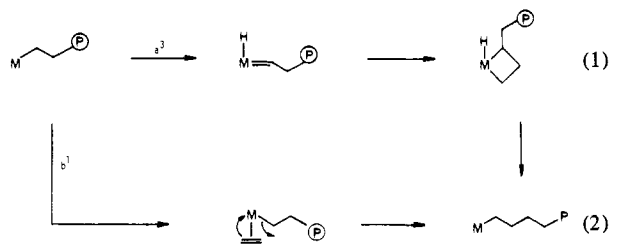
Scheme I.



(1)

(2)

Table I. Relative Concentration of *n*-Alkanes from Ethylene-$d_0$:Ethylene-$d_4$ Mixtures

| *n*-alkane produced | $d_4$:$d_0$ 1:0 | 1.03:1 | 0:1 | 1.03:1 |
|---|---|---|---|---|
| $C_{12}$ | 1.00 | 1.00 | 1.00 | 1.00 |
| $C_{14}$ | 1.43 | 1.34 | 1.06 | 1.19 |
| $C_{16}$ | 2.18 | 1.38 | 1.03 | 1.32 |
| $C_{18}$ | 1.55 | 1.24 | 0.89 | 1.06 |
| $C_{20}$ | 1.21 | 1.08 | 0.87 | 0.81 |
| $C_{22}$ | 1.04 | 0.99 | | 0.67 |

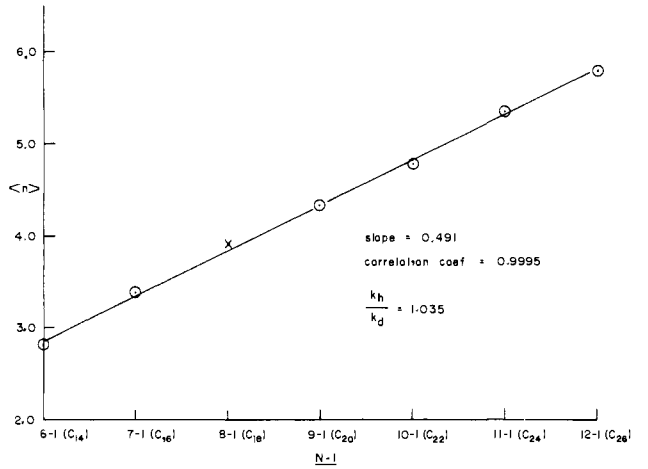
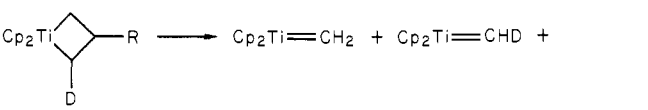


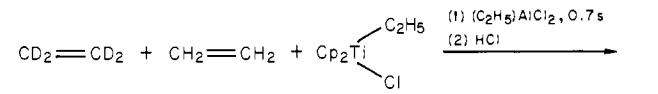

**Figure 1.** Average number of $C_2D_4$ units, $\langle n \rangle$, as a function of total number of monomer units, $N$, in an oligomer.



(3)

changes at the growing polymer terminus, we expect $k_H/k_D \simeq 1$ for this process.

In these catalytic systems, as well as many other, comparisons between different polymerization runs are dangerous, owing to a lack of *absolute* reproducibility from one preparation to the next. Furthermore, the concentration of the active sites can be affected by the monomer (as in Shilov's study), and in some systems the catalytic activity is diffusion limited. Consequently, experiments designed for precise isotope-effect measurements must be copolymerizations. Due to the ease of analysis and the availability of homogeneous catalyst systems, the polymerization of ethylene and perdeuterioethylene was chosen for study. So that precise measurements on the copolymers could be obtained, the reaction was studied by using a stopped-flow apparatus similar to that developed by Fink and co-workers.[15] Suitable conditions were developed to obtain sufficient material of the $C_8H_{18}$ to $C_{28}H_{58}$ molecular weight range for GC/MS–CI analysis.[16]



(4)

If the catalyst activation is fast and the chain transfer slow relative to chain propagation, then the results for the copolymerization can be analyzed precisely. It can be shown that the average number of deuterated units, $\langle n \rangle$, in a chain is related to the total number of units, $N$, by the following expression:[17]

$$\langle n \rangle = (N-1)\left(\frac{c\alpha}{1+c\alpha}\right) + \frac{c}{1+c}$$

where $c = k_{cD}[C_2D_4]/(k_{cH}[C_2H_4])$ and $\alpha = k_{pD}/k_{pH}$, $k_c$ = rate of complexation, and $k_p$ = rate of propagation.

The distribution of products in Table I shows a bell-shaped curve.[18] This demonstrates that the catalyst is formed at a much faster rate than polymer growth. Only traces of olefin are formed in the reaction, i.e., little chain transfer is taking place.[19] Hence the two boundary conditions are met. The plot of $\langle n \rangle$ vs. $(N-1)$ in Figure 1 shows an excellent agreement with eq 2 (correlation factor 0.9996) with a slope of 0.49, which corresponds to a $k_{pH}/k_{pD}$ of $1.04 \pm 0.03$.

Although this is derived from only one catalyst system which is not a propylene polymerization catalyst,[20] these data strongly support an insertion mechanism that does not involve a hydrogen migration during the rate-determining step of propagation. It is possible that the growing alkyl chain is interacting with a bridging Lewis acid center which does not leave the catalyst site during reaction or that the $\alpha$-CH bonds are always distorted toward the metal center. Such cases would not necessarily show an isotope effect but could have a pronounced influence on the stereoselectivity. Such systems are now under investigation.

**Registry No.** Ethylene, 74-85-1; ethylene-$d_4$, 683-73-8.

(14) Lee, B.; Ott, K.; Grubbs, R. H., unpublished results.
(15) Schnell, D.; Fink, G. *Angew. Makromol. Chem.* **1974**, *39*, 131.

(16) Typically, the experiments were carried out by mixing 50 mL of a solution of $Cp_2Ti(C_2H_5)Cl$ (1 mmol in toluene) saturated with the desired monomer with an equal volume of $Al(C_2H_5)Cl_2$ (10 mmol in toluene) saturated with the same monomer in a stop-flow tube. After leaving the initial chamber, the reaction stream was delivered to a solution of HCl, $CH_3OH$, and toluene in a second mixing chamber. The contact time for the reaction was 0.7 s. The reaction mixture was washed with aqueous base (1M NaOH), dried, and concentrated by using a spinning band column to remove most of the toluene. The product was analyzed by capillary GC (10 m SE-30 column) and GC/MS–CI (methane). The monomer mix was ethylene-$d_0$/ethylene-$d_4$ = 1/1.033 (high-resolution MS). The ethylene mixture recovered after reaction showed no deuterium scrambling.

(17) Given the assumptions mentioned in the text, the probability of producing (in the given reaction time) a polymer chain $N$ units long, $n$ of which are deuterated units, is proportional to

$$F(N,n) = \frac{(ck_D)^{n-1}(k_H)^{N-n-1}}{(k_H + ck_D)^{N-1}}\left\{k_H\left(\frac{c}{1+c}\right)\left(\frac{N!}{(n-1)!(N-n-1)!}\right) + \left(\frac{1}{1+c}\right)(ck_D)\left(\frac{(N-1)!}{n!(N-n-1)!}\right)\right\}$$

Then $\langle n \rangle$ is given by

$$\langle n \rangle = \frac{\sum_n F(N,n)}{\sum F(N,n)} = (N-1)\left(\frac{c\alpha}{1+c\alpha}\right) + \frac{c}{1+c}$$

(18) As seen in Table I, the average carbon number is similar for each monomer mix, while the spread in variance changes with monomer. The average is related to propagation rate while the spread is a function of catalyst formation rate. Both molecular and macroscopic factors will influence catalyst formation.

(19) Lack of chain transfer was demonstrated by the following: (a) polymerizing pure ethylene-$d_0$ and $-d_4$ resulted in no detectable alkenes (capillary GC, authentic standards); (b) from the polymerization of ethylene-$d_4$ only those oligomers of formula $C_nD_{2n-4}H_6$ were produced. None of the $H_1$ or $H_5$ isomers were observed by GC–MS.

(20) Boor, John., Jr. "Ziegler-Natta Catalysts and Polymerizations"; Academic Press: New York, 1979.