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.

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), one of the most potent clinically useful agents. It is also highly cytotoxic against murine leukemias KB, P388, and L1210 cell lines, with ED₅₀ values of 7 × 10⁻¹ to 5 × 10⁻⁴ and 2 × 10⁻⁴ μg/mL, respectively. It has also been shown to be a powerful inhibitor against ovarian tumor growing in a human tumor cloning system.¹⁰

Acknowledgment. We thank Dr. John Douros of the National Cancer Institute for his interest and encouragement of this work. Our special thanks are due to Professor K. L. Ridehert, Jr., and Mr. J. C. Cook, Jr., University of Illinois, for FDMS, FABMS, and helpful discussions, to Dr. P. P. Roller, National Cancer Institute, National Institute of Health, for HRFBMS, and to Dr. B. D. Hilton, Chemical Carcinogenesis Program, NCI-Frederick Cancer Research Facility, for IH NMR spectra. We also thank Drs. M. G. Hanna, Jr., C. J. Michejda, M. C. Flickinger, R. M. Stroshane, and J. A. Chan of NCI-Frederick Cancer Research Facility, and Dr. H. M. Fales of the National Institute of Health, for their interest, helpful discussions, and encouragement of this work. We also thank Dr. A. Bavoso of the Laboratory of Chemistry, National Heart, Lung and Blood Institute, for making preliminary measurements on the crystals and Dr. K. L. Loening, Chemical Abstracts Service, for the advice on the nomenclature. This research was sponsored by the Public Health Service, National Cancer Institute under Contract No. NO-1-CO-75380 with Litton Bionetics, Inc.

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.


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

Jorge Soto, Michael L. Steigerwald, and Robert H. Grubbs

Contribution No. 6591 from the Laboratories of Chemistry
California Institute of Technology
Pasadena, California 91125

Received January 25, 1982

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-metalacyclic mechanism of Green and Rooney¹ and the direct four-center olefin insertion mechanism of Cossee and Arlman (Scheme 1, 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.⁷⁻¹⁰ The important difference between the two suggestions is the involvement of hydrogen migration in a (Scheme 1). This mobility implies a 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 examined¹ the rates of polymerization of C₆H₆ and C₅H₄ and concluded these rates are the same. However, this work allows for a wide range 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 α-hydrogen by an aluminum alkyl is modeled by the formation of Cp₂TiCH₂Al(CH₃)₂Cl from Cp₂TiCl₂ and (CH₃)₂Al.¹² The isotope effect for the formation is 3. Other related α-abstractions fall between 3 and 3.5.¹² Even if the α-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 carbenoid intermediates. The secondary isotope effect is determined in these systems is large, ranging from 1.2 to 1.4.¹³ 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

(2) McKinney, R. J. J. Chem. Soc., Chem. Commun. 1980, 491–492. This mechanism requires growth by two olefin units insertion step. Hence, only C₆H₆ C₅H₄ C₄H₄ C₃H₃ ... would be expected. The results presented in Table I ruled out this mechanism.
(4) Bank, R., unpublished results. Ruled out by experiments in ref 5.
(12) Ott, K., unpublished results.
molecular weight range for GC/MS-CI analysis.16 Of homogeneous catalyst systems, the polymerization of ethylene between different polymerization runs are dangerous, owing to a lack of polymerizations. Due to the ease of analysis and the availability of catalystic activity is diffusion limited. Consequently, experiments designed for precise isotope-effect measurements must be co-developed to obtain sufficient material of the CsHls to CZsHSs developed by Fink and co-worker~.14 Suitable conditions were produced in a stopped-flow apparatus similar to that used by Fink and co-workers.10

Table I. Relative Concentration of n-Alkanes from Ethylene-d4:Ethylene-d8 Mixtures

<table>
<thead>
<tr>
<th>n-alkane produced</th>
<th>d4/d8</th>
<th>1:0</th>
<th>1.03:1</th>
<th>0:1</th>
<th>1.03:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>C7</td>
<td>1.43</td>
<td>1.34</td>
<td>1.06</td>
<td>1.19</td>
<td>1.19</td>
</tr>
<tr>
<td>C8</td>
<td>2.18</td>
<td>1.38</td>
<td>1.03</td>
<td>1.32</td>
<td>1.32</td>
</tr>
<tr>
<td>C9</td>
<td>1.55</td>
<td>1.24</td>
<td>0.89</td>
<td>1.06</td>
<td>1.06</td>
</tr>
<tr>
<td>C10</td>
<td>1.21</td>
<td>1.08</td>
<td>0.87</td>
<td>0.81</td>
<td>0.81</td>
</tr>
<tr>
<td>C11</td>
<td>1.04</td>
<td>0.99</td>
<td>0.87</td>
<td>0.67</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Figure 1. Average number of C2D units, (n), as a function of total number of monomer units, N, in an oligomer.

changes at the growing polymer terminus, we expect $k_{HH}/k_{HD} \approx 1$ 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 catalytic systems, the polymerization of ethylene and perdeuterioethyene 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 C6H13 to C32H65 molecular weight range for GC/MS-CI analysis.16

(16) Typically, the experiments were carried out by mixing 50 mL of a solution of Cp2Ti(CH3)Cl (1 mmol in toluene) saturated with the desired monomer with an equal volume of Al(C2H5)Cl (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, CH3OH, 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 (1 M 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-d4, ethylene-d8, and a-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.

Registy No. Ethylene, 74-85-1; ethylene-d8, 683-73-8.

Communications to the Editor

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, (n), in a chain is related to the total number of units, N, by the following expression:17

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

where $c = k_{DD}/(k_{DH})(C_{2D4}/(k_{DH})(C_{2H4}))$ and $\alpha = k_{DD}/k_{DH}$, $k_c$ = 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 (n) 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 $k_{DH}/k_{DD}$ of 1.04 ± 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 a-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.


(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

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

Then (n) is given by

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

(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) polymerization pure ethylene-d4, and -d8 resulted in no detectable alkenes (capillary GC, authentic standards); (b) from the polymerization of ethylene-d4 only those oligomers of formula C4D8H2 were produced. None of the H1 or H2 isomers were observed by GC-MS.