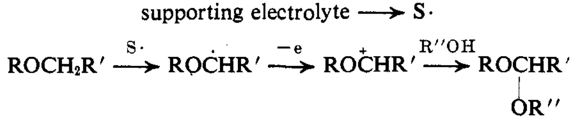
oxidation process of the radical to the cation is involved, have been reported by several workers.[5] Relative reactivities of some typical ethers in the methoxylation by Kharasch reaction and in anodic methoxylation are indicated in Table II.

Table II. Relative Reactivities (per α Hydrogen)

	Dioxane	Tetra-hydropyran	*t*-Butyl ethyl ether
Kharasch reaction	1	1.9	4.4
Anodic reaction	1	2	4

Although the establishment of the reaction mechanism in the present study seems rather premature, this anodic alkoxylation reaction may involve the abstraction of α hydrogen from ethers by anodically generated radicals and subsequent anodic oxidation of the ethereal radicals to cations. Further study on the reaction mechanism is currently in progress.



$$\text{supporting electrolyte} \xrightarrow{-e} \text{S}\cdot$$

$$\text{ROCH}_2\text{R}' \xrightarrow{\text{S}\cdot} \text{RO}\dot{\text{C}}\text{HR}' \xrightarrow{-e} \text{RO}\overset{+}{\text{C}}\text{HR}' \xrightarrow{\text{R}''\text{OH}} \text{RO}\underset{\text{OR}''}{\underset{|}{\text{C}}}\text{HR}'$$

Acknowledgment. We are extremely grateful to Professor R. Oda of Kyoto University for his kind encouragement.

[5] G. Sosnovsky and S. Lawesson, *Angew. Chem.*, 76, 218 (1964); S. Lawesson and C. Berglund, *Arkiv Kemi*, 17, 465 (1961).

Tatsuya Shono, Yoshihiro Matsumura
Department of Synthetic Chemistry, Faculty of Engineering
Kyoto University, Kyoto, Japan

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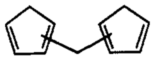
The $[1^n]$Ferrocenophanes

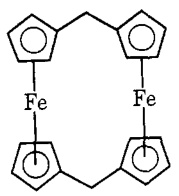
Sir:

The reaction of a transition metal halide with a hydrocarbon dianion made up of two linked cyclopentadienyl anions might be anticipated to give a polymeric metallocene in which hydrocarbon rings and metal atoms alternate,[1] a process we call polygemination.[2] Up until now only two characterized polymers have been made by this method, and both are only dimers.[1,3] We have in this way now prepared a trimer, tetramer, and pentamer, the first well-characterized polygeminate oligomers larger than dimers.[4]

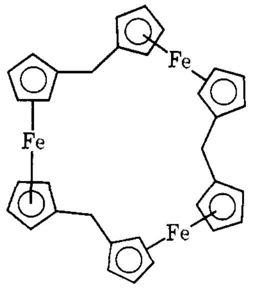
Their precursor is the easily prepared[5] bis(cyclopentadienyl)methane (I). When the hydrocarbon I is added to a tetrahydrofuran solution of *n*-butyllithium in hexane at 0° and after 10 min poured onto anhydrous ferrous chloride, a dark reaction product forms from which has been isolated thus far the dimer (II), [1.1]ferrocenophane,[6] the trimer (III), [1.1.1]ferrocenophane, the corresponding tetramer, [1.1.1.1]ferrocenophane, and the pentamer, [1.1.1.1.1]ferrocenophane.[7] The first three, which are crystalline, analyze correctly for carbon, hydrogen, and iron; the fourth, which is still amorphous, does not quite.



I



II



III

The structures of these ferrocenophanes are proven by their spectroscopic properties. The nmr spectra (Table I) of all exhibit resonances attributable to the ring and methylene protons in the required intensity ratio of 4:1. That the difference in chemical shifts of the ring protons[6,10] would decrease with increased polymerization and vanish as in 1,1′-dimethylferrocene[11] or diferrocenylmethane[12] is confirmed. The infrared spectra of the ferrocenophanes are remarkably similar. The mass spectra exhibit the required parent peaks: in the dimer at *m/e* 396, in the trimer at 594, in the tetramer at 792, and in the pentamer at 990.

Table I. Proton Nmr Spectra of the $[1^n]$Ferrocenophanes[a]

n	Ring proton chemical shifts	Methylene proton chemical shifts	Measured intensities
2	5.77 (t), 5.96 (t)[b]	6.53 (s)[b]	2.0:2.0:1.0
3	5.99 (t), 6.06 (t)[b]	6.42 (s)[b]	3.93:1.07
4	5.97 (s)[c]	6.30 (s)[c]	3.99:1.01
5	6.12 (s)[b]	6.76 (s)[b]	4.05:0.95

[a] s = singlet; t = approximately a distorted triplet. [b] In CS_2 (room temperature). [c] In toluene-d_8 at 100°

The dimer, recrystallized from acetone, melts (evacuated capillary) at 245–248°,[13] and the trimer, from carbon disulfide, at 278.5–280.5°; the tetramer, from toluene, darkens at *ca.* 265° and partially melts at *ca.*

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[1] (a) T. J. Katz, V. Balogh, and J. Schulman, *J. Am. Chem. Soc.*, 90, 734 (1968); (b) T. J. Katz and J. Schulman, *ibid.*, 86, 3169 (1964).

[2] Latin *geminus*, twin.

[3] A. Lüttringhaus and W. Kullick, *Makromol. Chem.*, 44–46, 669 (1961).

[4] A polymeric material, not characterized, but believed to be larger than a dimer was described by Lüttringhaus and Kullick.[9]

[5] It is made in a few related ways, such as by the reaction of sodium cyclopentadienide with methylene chloride: H. Schaltegger, M. Neuenschwander, and D. Meuche, *Helv. Chim. Acta*, 48, 955 (1965).

[6] Previously made from ferrocene itself: W. E. Watts, *J. Organometal. Chem.*, 10, 191 (1967).

[7] The notation[8] becomes cumbersome for large oligomers, and a simple variant would be to use the notation $[1^n]$ferrocenophane, where the superscript denotes the degree of polymerization. The next member would thus be $[1^6]$ferrocenophane, read as sexiferrocenophane. An alternative notation for the quinqueferrocenophane is, of course, [𝍸]-ferrocenophane.[9]

[8] (a) B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, N. Y., 1964; (b) W. E. Watts, *Organometal. Chem. Rev.*, 2, 231 (1967).

[9] Tally marks, used by primitive man: "World Book Encyclopedia," Vol. 14; Field Enterprises Educational Corp., Chicago, Ill., 1968, p 452.

[10] (a) J. S. McKechnie, B. Bersted, I. C. Paul, and W. E. Watts, *J. Organometal. Chem.*, 8, P29 (1967); (b) W. E. Watts, *J. Am. Chem. Soc.*, 88, 855 (1966); (c) T. H. Barr and W. E. Watts, *Tetrahedron*, 24, 6111 (1968).

[11] K. L. Rinehart, Jr., D. E. Bublitz, and D. H. Gustafson, *J. Am. Chem. Soc.*, 85, 970 (1963).

[12] E. W. Neuse and K. Koda, *Bull. Chem. Soc. Jap.*, 39, 1502 (1966).

[13] Lit.[6] mp 254–256°

300°. All are yellow. The pentamer softens at about 90°. The properties of these substances will be described in greater detail in a full publication.

These oligomers were separated by dry column chromatography[14] on an inactive grade of silica gel[15] using carbon disulfide as the developer, the R_f decreasing with increasing polymerization. They were isolated from the sectioned chromatography column by Soxhlet extraction, the dimer, trimer, and tetramer with carbon disulfide, the pentamer with toluene.

The total yield of purified material was about 18%, of which approximately 10% was the di-, 20% the ter-, 30% the quater-, and 40% the quinqueferrocenophane.

This work demonstrates that the first four $[1^n]$ferrocenophanes can be made by a polygemination reaction, and it seems reasonable to suppose that other and larger polymers might be made in this way.

Acknowledgments. We are grateful to the National Institutes of Health and the National Science Foundation for support.

[14] B. Loev and M. M. Goodman, *Chem. Ind.* (London), 2026 (1967).

[15] Activity II silica gel[14] (Baker No. 3405) plus 84 g of water/lb.

Thomas J. Katz, Nancy Acton, Geoffrey Martin
Department of Chemistry, Columbia University
New York, New York 10027

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Stereochemistry of Estrogen Biosynthesis

Sir:

The loss of the angular methyl group at C-10 and of one hydrogen each from C-1 and C-2 represents the structural changes involved in the biosynthesis of estradiol from neutral C-19 precursors. Studies of this transformation have so far failed to reveal the exact nature and sequence of these events but have established that hydroxylation of the methyl group precedes its expulsion and that the hydrogen lost from C-1 is stereospecifically β.[1] In an effort to throw further light on this most significant androgen to estrogen biotransformation we have investigated the stereochemistry of the hydrogen loss from C-2 and report our results in this communication.

The required aromatization substrates stereoselectively labeled with tritium in the 2β and 2α positions were prepared by the following sequences. Treatment of 3β-tosyloxy-5α,6α-epoxyandrostan-17-one (I) with Li_2CO_3 in dimethylacetamide gave 5α,6α-epoxyandrost-2-en-17-one (II). Reduction of II with lithium aluminum hydride afforded androst-2-ene-5α,17β-diol (III) which on oxidation with *m*-chloroperbenzoic acid gave 2α,3α-epoxyandrostane-5α,17β-diol (IV). Reduction of IV with [^{3}H]-$LiAlH_4$ yielded [2β-^{3}H]3α,5α,17β-triol V; acetylation and subsequent dehydration with thionyl chloride in pyridine provided [2β-^{3}H]androst-4-ene-3α,17β-diol diacetate (VI). Mild alkaline hydrolysis of VI followed by oxidation with the Jones reagent[2] at 0° gave one of the required precursors, [2β-^{3}H]androst-4-ene-3,17-dione (VII). The same compound with the isotope in the epimeric 2α orientation was prepared by a route in which the olefin II also served as the starting material. Hydroboration of II with tritiated diborane[3] and subsequent oxidation gave a mixture of products from which, after careful separation, pure [2α-^{3}H]3α-hydroxy-5α,6α-epoxyandrostan-17-one (VIII) was obtained. The conversion of VIII to the other substrate, [2α-^{3}H]androst-4-en-3,17-dione (IX), proceeded analogously to that described above for the 2β-labeled material VII. The well-documented *trans* mechanism of lithium aluminum hydride reduction of epoxides[4] and the *cis* nature of hydroboration[5] allowed confidence in the stereochemical assignment of the isotope in each instance.[6] It should be emphasized that the above syntheses were so designed that the introduction of the 3-ketone and hence labilization of the α-methylene at C-2 was the last step in each sequence. This limited the exposure of the introduced tritium to enolization and served to preserve the integrity of the label as confirmed by the constancy of the specific activity prior to and after the oxidation in both instances.[7] Substrates VII and IX were shown to be homogeneous by reverse isotope dilution analysis and were devoid of radioactivity following alkali treatment. To permit ready determination of tritium loss upon incubation both VII and IX were mixed with an appropriate amount of [^{14}C]androsten-4-ene-3,17-dione to obtain substrates with a specific tritium to carbon-14 ratio.

The incubations were carried out with human placental microsomes prepared according to Ryan.[8] The incubation mixture contained, in addition to the microsomes and 100–150 μg of steroid substrate, a NADPH-generating system consisting of 10 μM NADPH, 120 μM glucose 6-phosphate, and 9.6 units of glucose 6-phosphate dehydrogenase. The incubations were carried out at pH 7.2 at 37° for 1 hr and terminated by the addition of acetone. Products and recovered starting material were isolated by dilution with carrier, separation by quantitative thin layer chromatography, and recrystallization to constant isotope ratio.

The results of the incubations are listed in Table I. The estrone obtained from the substrate VII with the isotope in the 2β orientation exhibited an 83% loss of

Table I. Stereochemistry of C-2 Hydrogen Loss in Placental Aromatization

	Substrate	
	2β-^{3}H (VII)	2α-^{3}H (IX)
Substrate ^{3}H/^{14}C^a	11.1	5.8
Estrone ^{3}H/^{14}C	1.9	5.4
% ^{3}H lost	83	7
Recovered substrate ^{3}H/^{14}C	12.0	7.3

^{a} Expressed as ratio of counts per minute.

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[1] P. Talalay, *Ann. Rev. Biochem.*, **34**, 347 (1965), and references cited therein.

[2] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

[3] Prepared *in situ* from sodium borotritiide and boron trifluoride etherate.

[4] L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949); M. Mousseron, R. Jacquier, M. Mousseron-Canet, and R. Zagdoun, *Bull. Soc. Chim. France*, 1042 (1952); G. M. Helmkamp and B. F. Rickborn, *J. Org. Chem.* **22**, 479 (1957).

[5] H. C. Brown, and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 247 (1959).

[6] The stereochemical assignments were confirmed by *Bacillus sphaericus* dehydrogenations, the results of which will be presented in the full paper.

[7] Oxidations with the Jones reagent in other similar situations also proceeded without loss of isotope by enolization: J. Fishman, *J. Am. Chem. Soc.*, **87**, 3455 (1965); J. Ramseyer and H. Hirschmann, *J. Org. Chem.* **32**, 1850 (1967).

[8] K. J. Ryan, *J. Biol. Chem.*, **234**, 268 (1959).