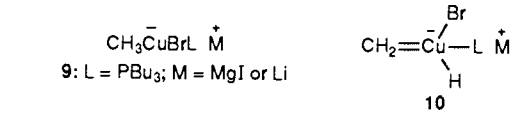
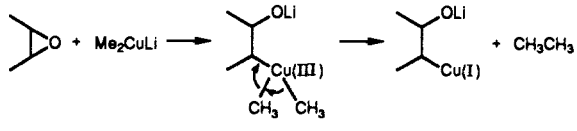
thylcopper-phosphine complex has been reported not to react with oxiranes,[1a,b] and in fact, the reaction of methyllithium with 1,2-epoxybutane in the presence of cuprous iodide instead of cuprous bromide in our reaction system did not give any product including butanol, which probably would be attributed to the intervention of the methylcopper-phosphine complex. Thus, a pathway through an intemediary methylcopper-phosphine complex might be less possible. Although a dimethylcopper(I) complex might be next postulated as the working species in our reactions, its possibility might be also less likely[6] since the treatment of an alkyllithium such as methyllithium or *n*-butyllithium with the CuI-phosphine complex has been reported to afford not the dialkylcopper(I) complex but the alkylcopper-phosphine complex,[7] and the dimethylcopper complex, even if generated, would afford the methyl addition products with oxiranes.[1] Thus, although the mechanism cannot be clearly defined at this stage, we supposed that the "ate" complex **9** holding a bromine atom might have a definite lifetime under our reaction conditions because of the poorer leaving ability of bromine compared to iodine and be a key species for the reduction of oxiranes. For the reduction of oxiranes by **9**, in turn, three pathways might be assumed as possible candidates. They are (1) electron transfer from **9** to the epoxy ring followed by a hydrogen abstraction,[8] (2) generation of the methylenecopper hydride-phosphine complex **10** by α-elimination from **9**,[9,10] and (3) hydrogen transfer from **9** to the epoxy ring. The possibility of pathway 1 would be diminished[11] because the more negative



reduction potential of the oxirane compared to the ketone[12] is inconsistent with the explanation by the electron transfer pathway of this reaction to bring about the preferential reduction of the epoxy ring over the carbonyl functionality, and one-electron transfer from the low-valent transition-metal compounds to oxiranes cleaves the ring bond between the oxygen and the more substituted carbon[13] while the products due to the cleavage of the ring bond between the oxygen and the less substituted carbon are obtained in our reaction system. When electron-rich olefins such as *n*-butyl vinyl ether and 1-phenyl-1-(trimethylsiloxy)ethylene were subjected to the reaction with methylmagnesium iodide in the presence of $CuBr(PBu_3)_2$, the corresponding cyclopropane derivatives, were formed, although in minor amounts, suggesting the intervention of **10**. Detailed mechanistic investigations are in progress.

(6) This possibility, however, might not be entirely excluded because a pathway via a metalated intermediate of Cu(I) arising from a Cu(III) precursor as shown below has been suggested by a referee; cf.: Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1989**, *30*, 2391.



(7) (a) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128. (b) Whitesides, G. M.; Stedronsky, E. R.; Casey, C. P.; Filippo, J. S., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 1426.

(8) In the addition reaction of the cuprates to allylic epoxides or α,β-unsaturated carbonyl compounds, the electron-transfer pathways has been postulated. See ref 7a. Also see: (a) Wieland, D. M.; Johnson, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 3047. (b) Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141.

(9) Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978; pp 285-288.

(10) For a recent investigation on the copper hydride-phosphine complex, see: Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

(11) In the case of α-epoxy ketones such as isophorone oxide and carvone oxide, however, the possibility that α,β-unsaturated ketones as the reduction products were formed through the electron-transfer pathway may not be excluded because lithium dimethylcuprate has been reported to perform the reduction of the epoxy group of steroidal α-epoxy ketones via electron transfer to the carbonyl group, giving β-hydroxy ketones along with α,β-unsaturated ketones and β-methyl ketones as consecutive derivatives; cf.: Bull, J. R.; Lachmann, H. H. *Tetrahedron Lett.* **1973**, 3055.

(12) Willits, C. O.; Ricciuti, C.; Knight, H. B.; Swern, D. *Anal. Chem.* **1952**, *24*, 785.

(13) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561.

Synthesis of a Membrane-Insertable, Sodium Cation Conducting Channel: Kinetic Analysis by Dynamic ^{23}Na NMR

Akio Nakano,† Qingshan Xie, Jesus V. Mallen, Luis Echegoyen,* and George W. Gokel*

Department of Chemistry, University of Miami Coral Gables, Florida 33124

Received October 16, 1989

We report herein the synthesis and characterization of a rationally designed, completely synthetic compound that inserts in phosphatidylcholine (pc) vesicles. Using the dynamic (equilibrium) NMR method presented initially by Riddell and Hayer,[1] recently extended by Hinton et al.,[2] we demonstrate that this molecule significantly enhances the rate at which Na^+ is transported compared to a closely related carrier model. We believe this enhanced rate to be due to formation of a channel-like structure.

Cation transport in nature generally occurs by either the carrier or channel mechanism. The former has been studied extensively while few attempts of the latter approach have been reported.[3-8] In recognition of nature's ability to set the structural stage using covalent bonds and then to permit flexible systems to adapt to the functional requirements, we prepared (see below) a tris(macrocyclic) system. It was thought that the three macrorings would provide donor relays at the two membrane surfaces and a third, internal relay point. The macrorings would be held together by two spacers, and the channel would be completed by two side arms. Spacer and side-arm length was estimated from distances known for gramicidin channels.[9-11] Relay distances in gramicidin channels are obviously much closer than in the present case but represent only one of many possibilities.

Two compounds were prepared for the present study. We have previously reported[12] *N,N'*-didodecyl-4,13-diaza-18-crown-6 (**1**), which was chosen as the carrier. The tris(macrocyclic) system *N,N'*-bis{12-[*N*-(*N'*-dodecyl-4,13-diaza-18-crown-6)]dodecyl}-4,13-diaza-18-crown-6 (**2**), the synthesis of which is shown in Scheme I, has three diaza-18-crown-6 residues linked and terminated by dodecyl chains. It was anticipated that the inner

* Address correspondence concerning design and synthesis to G.W.G. and concerning NMR and kinetics to L.E.

† On leave from Toa University, Shimonoseki, Japan.

(1) Riddell, F. G.; Hayer, M. K. *Biochem. Biophys. Acta* **1985**, *817*, 313-317.

(2) Buster, D. C.; Hinton, J. F.; Millett, F. S.; Shungu, D. C. *Biophys. J.* **1988**, *53*, 145-152.

(3) (a) Behr, J. P.; Lehn, J. M.; Dock, A. C.; Moras, D. *Nature* **1982**, 295. (b) Julien, L.; Lehn, J.-M. *Tetrahedron Lett.* **1988**, 3803-3806.

(4) Tabushi, I.; Kuroda, Y.; Yokoto, K. *Tetrahedron Lett.* **1982**, 4601-4604.

(5) (a) Neevel, J. G.; Nolte, R. J. M. *Tetrahedron Lett.* **1984**, 2263-2266. (b) Kragton, U. F.; Roks, M. F. M.; Nolte, R. J. M. *J. Chem. Soc., Chem. Commun.* **1985**, 1275-1276.

(6) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 960-961.

(7) Führhop, J.-H.; Liman, U.; David, H. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 339-340.

(8) Carmichael, V. E.; Dutton, P. J.; Fyles, T. M.; James, T. D.; Swan, J. A.; Zojaji, M. *J. Am. Chem. Soc.* **1989**, *111*, 767-769.

(9) See: Urry, D. W.; Trapane, T. L.; Venkatachalam, C. M. *J. Membr. Biol.* **1986**, *89*, 107 and references therein.

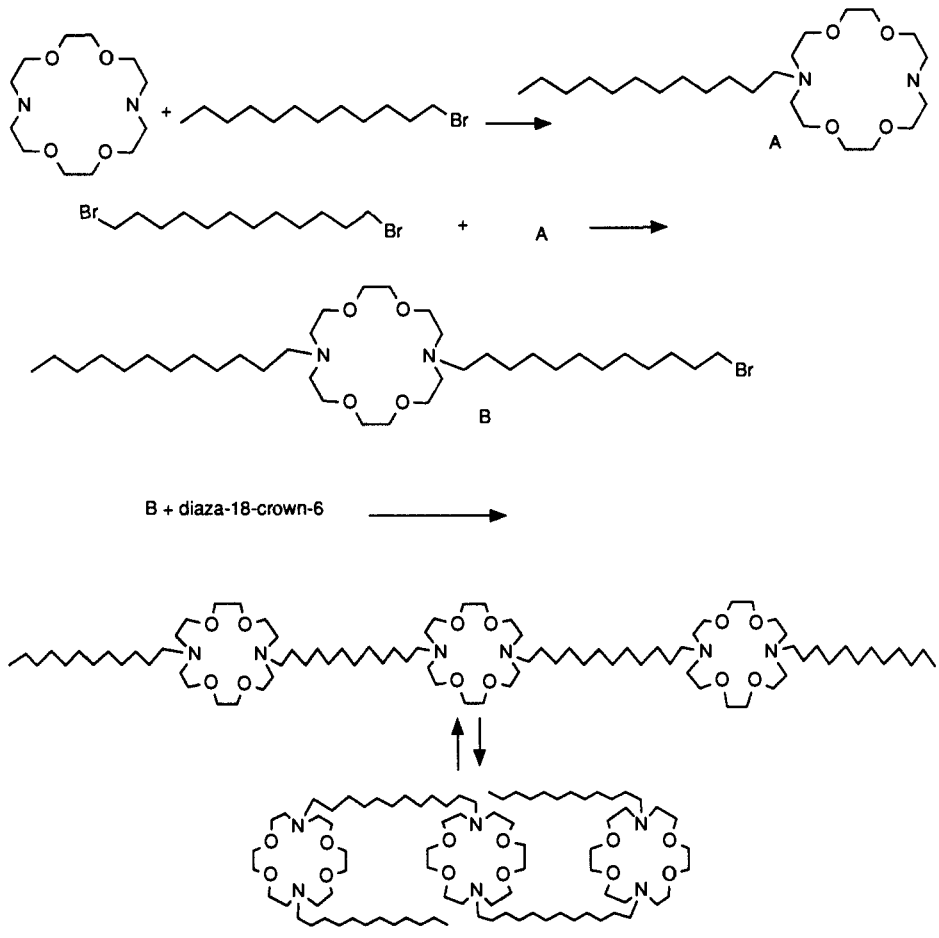
(10) Wallace, B. A.; Ravikumar, K. *Science* **1989**, *241*, 182.

(11) Langs, D. A. *Science* **1989**, *241*, 188.

(12) Gatto, V. J.; Arnold, K. A.; Viscariello, A. M.; Miller, S. R.; Morgan, C. R.; Gokel, G. W. *J. Org. Chem.* **1986**, *51*, 5373-5384.

0002-7863/90/1512-1287$02.50/0

Scheme I



macroring would embed in the membrane and the two terminal rings would be near the bilayer surfaces. These notions are in keeping with recent findings of amphiphilic behavior by crowns noted by the groups of Okahara[13] and Kuwamura[14] and by our group.[15]

Two approaches may be used to assess cation flux: steady-state methods and unidirectional flow techniques. The latter are plagued by difficulties: liposome breakage that may be confused with transport, the existence of a trans-membrane potential, etc. Lecithin large unilamellar (LUV) vesicles were prepared by the dialytic detergent removal method of Reynolds[16] (30 mM pc, 20% volume entrapment, 220-nm diameter determined by laser scattering, $[Na^+] = 120$ mM). Dysprosium (external solution, 5 mM, tripolyphosphate)[17] was added to distinguish $^{23}Na_{inside}$ from $^{23}Na_{outside}$ ($[^{23}Na]_{in}/[^{23}Na]_{out} = 1{:}4.5$). Incorporation of **1**, **2**, or gramicidin D was accomplished by microliter injection of the appropriate stock solution (1 mM) followed by a 30- or 60-min incubation at 50 °C.[2] Final concentrations were typically 20–140 μM. As previously shown,[2] incubation was critical for insertion, equilibrium, and stable, maximal spectral line widths (internal ^{23}Na). Kinetic order was probed by using several concentrations of ionophore in each case. (See Table I.)

Table I. Intravesicular ^{23}Na Line Widths as a Function of Incubation Time and Ionophore Concentration

concn, (μM)	$\Delta\nu_{1/2}$, Hz time[a] = 0	$\Delta\nu_{1/2}$, Hz time = 60	k_{in}[b]
	Gramicidin		
0	8.9	8.9	
0.5	8.9	9.5	1.88
2.5		11.4	7.85
5.0	9.4	17.0	25.4
7.0		23.1	44.6
15.0	12.9		
40[c]			1.4×10^3
	N,N'-Didodecyl-4,13-diaza-18-crown-6 (**1**)		
0	9.0	9.0	
20	9.0	9.0	
40	9.0	9.1	0.31 ± 0.08
60	9.0	9.4	1.23 ± 0.16
100		10.3	4.08 ± 0.63
140		13.0	12.6 ± 2.98
	Tris(macrocycle) **2**		
0	9.0	9.0	
20	9.0	11.0	6.28 ± 2.73
40	9.3	13.0	12.6 ± 1.88
60	9.5	15.0	18.8 ± 2.86
80		16.0	22.0 ± 1.73

[a] In min. [b] In s^{-1}. [c] Extrapolated.

The present work confirms the elegant study reported last year by Hinton et al.[2] in which ^{23}Na flux in the gramicidin channel was shown to be second order. We compare the cation flux rates obtained for **1** and **2** at 40 μM concentrations (nonnormalized) with a value for gramicidin obtained by extrapolation. The rates are as follows: carrier (**1**), 0.31 s^{-1}; channel former (**2**), 13.5 s^{-1}; and gramicidin, 1.4×10^3 s^{-1}. Thus the synthetic channel exhibits

(13) (a) Okahara, M.; Kuo, P. L.; Yamamura, S.; Ikeda, I. *J. Chem. Soc., Chem. Commun.* **1980**, 586. (b) Kuo, P.; Tsuchiya, K.; Ikeda, I.; Okamura, M. *J. Colloid Interface Sci.* **1983**, *92*, 463.
(14) (a) Kuwamura, T.; Kawachi, T. *Yukagaku* **1979**, *28*, 195; *Chem. Abstr.* **1979**, *90*, 206248d. (b) Kuwamura, T.; Akimaru, M.; Takahashi, H.; Arai, M. *Kenkyu Hokoku—Asahi Garasu Kogyo Gijutsu Shoreikai* **1979**, *35*, 45; *Chem. Abstr.* **1981**, *95*, 61394q. (c) Kuwamura, T.; Yoshida, S. *Nippon Kagaku Kaishi* **1980**, 427; *Chem. Abstr.* **1980**, *93*, 28168e.
(15) Echegoyen, L. E.; Hernandez, J. C.; Kaifer, A.; Gokel, G. W.; Echegoyen, L. *J. Chem. Soc., Chem. Commun.* **1988**, 836–837.
(16) Mimms, L. T.; Zanpighi, G.; Nozaki, Y.; Tanford, C.; Reynolds, J. A. *Biochemistry* **1981**, *20*, 833.
(17) Ogino, T.; Shulman, G. I.; Avison, M. J.; Gullans, R. S.; den Hollander, J. A.; Shulman, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 1099–1103.
(18) LeMoigne, J.; Simon, J. *J. Phys. Chem.* **1980**, *84*, 170.

cation flux ca. 40-fold greater than the simple carrier but ca. 100-fold poorer than gramicidin at this concentration.

It should be noted that, after incubation of the vesicles with **2**, a decrease in the $[Na]_{inside}/[Na]_{outside}$ ratio from 1:4.5 to 1:9 was observed. This is not troubling since the dynamic NMR method is solely dependent on the rate of exchange between internal and external sodium ions which are at the same equilibrium concentration. The only concern would be if such vesicular rupture leads to increased ionophore concentration in the vesicles. Although this seems unlikely to us, the maximum effect would only be a factor of 2.

Tentative confirmation that sodium transport is mediated differently by **1** and **2** can be found in the respective kinetic orders. Carrier-mediated transport (**1**) exhibits second-order kinetics, but the tris(macrocycle) **2** shows first-order kinetics. As noted above, gramicidin is second order, due to the fact that the channel is dimeric. We think **1** exhibits second-order kinetics due to the requirement of a flip-flop mechanism for transport utilizing this ionophore. Monensin, also a carrier, shows first-order kinetics but is capable of simple diffusion of a kind that seems unlikely with **1**.[1]

Finally, it should be noted that the structure of gramicidin channels makes one associate a tunnel shape with the term "channel". The gramicidin channel is an excellent channel, but it is not the only one and should be regarded as an example rather than a definition. The present channel may be flatter and more like, as the dictionary says, a "groove" or a "trench". Relay from ring to ring, although obviously involving distances longer than known for gramicidin, does not disqualify this system from the designation channel.

Acknowledgment. We thank the National Institutes of Health for grants (GM-33940 to L.E. and G.W.G. and GM-36262 to G.W.G.) The synthetic effort was sponsored by the latter and characterization by the former.

Supplementary Material Available: Experimental details of the ^{23}Na NMR measurements, NMR sample preparation, materials, vesicle preparations, and the synthesis of compound **2** (4 pages). Ordering information is given on any current masthead page.

β-Agostic Interactions in $(C_5H_4Me)_2Zr(CH_2CH_2R)(PMe_3)^+$ Complexes

Richard F. Jordan,* Prudence K. Bradley,
Norman C. Baenziger,* and Robert E. LaPointe

Department of Chemistry, University of Iowa
Iowa City, Iowa 52242

Received September 5, 1989

Agostic C–H–M interactions are potentially important structural features of unsaturated metal complexes that are intermediates in olefin polymerization, C–H activation, and other metal-mediated or -catalyzed reactions.[1,2] Here we report observations that establish the presence of β-agostic interactions in $(C_5H_4Me)_2Zr(CH_2CH_2R)(PMe_3)^+$ complexes. These results suggest that similar interactions may be present in the $Cp_2M(R)^+$ and $Cp_2M(R)(olefin)^+$ ions which are believed to be key intermediates in metallocene-based Ziegler–Natta olefin polymerization catalyst systems.[3]

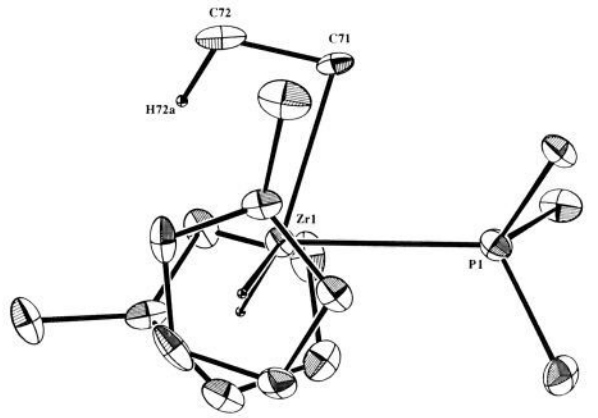
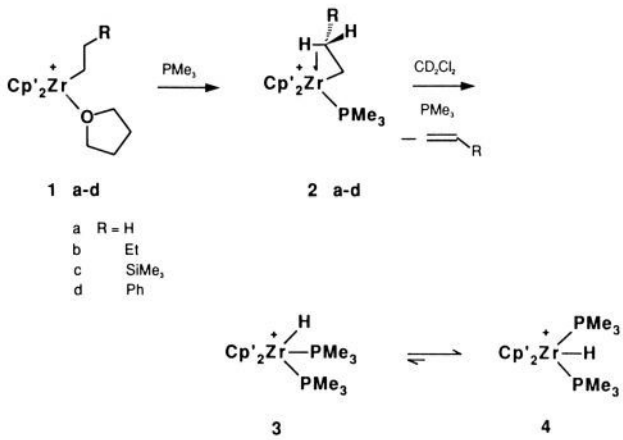


Figure 1. Structure of the cation of **2a**. Key bond distances (angstroms) and angles (degrees): Zr1–C71, 2.290 (9); Zr1–C72, 2.629 (9); Zr1–H72a, 2.16; Zr1–P1, 2.691 (3); C71–C72, 1.47 (2); Zr–C1C, 2.21; Zr–C2C, 2.21; P1–Zr1–C71, 73.6 (3); Zr1–C71–C72, 84.7 (5); C1C–Zr1–C2C, 132.3 (*Cn*C denotes centroid of Cp′ ring).

Scheme I



The cationic THF complexes $Cp'_2Zr(CH_2CH_2R)(THF)^+$ (**1a–d**, Scheme I, Cp′ = C_5H_4Me) are prepared by reaction of the cationic hydride $Cp'_2Zr(H)(THF)^+$ with the appropriate olefin.[4] Complexes **1a,b,d** have normal, undistorted alkyl ligands as established by NMR and IR spectroscopies (normal ^1H and ^{13}C shifts, $J_{C\alpha-H}$ = 115 Hz, $J_{C\beta-H}$ = 122–129 Hz, no low-frequency ν_{C-H}).[5] Reaction of **1a–d** with PMe_3 in CD_2Cl_2 or THF at −78

(1) Reviews: (a) Brookhart, M.; Green, M. L. H.; Wong, L. *Prog. Inorg. Chem.* **1988**, *36*, 1. (b) Crabtree, R. H.; Hamilton, D. G. *Adv. Organomet. Chem.* **1988**, *28*, 299.

(2) Leading references: (a) Bailey, N. A.; Jenkins, J. M.; Mason, R.; Shaw, B. L. *J. Chem. Soc., Chem. Commun.* **1965**, 237. (b) Cotton, F. A.; LaCour, T.; Stanislowski, A. G. *J. Am. Chem. Soc.* **1974**, *96*, 754. (c) Dawoodi, Z.; Green, M. L. H.; Mtetwa, V. S. B.; Prout, K. *J. Chem. Soc., Chem. Commun.* **1982**, 1410. (d) Brookhart, M.; Green, M. L. H. *J. Organomet. Chem.* **1983**, *250*, 395. (e) Cracknell, R. B.; Orpen, A. G.; Spencer, J. L. *J. Chem. Soc., Chem. Commun.* **1984**, 326. (f) Crabtree, R. H.; Holt, E. M.; Lavin, M.; Morehouse, S. M. *Inorg. Chem.* **1985**, *24*, 1986. (g) Schmidt, G. F.; Brookhart, M. *J. Am. Chem. Soc.* **1985**, *107*, 1443. (h) Koga, N.; Obara, S.; Kitaura, K.; Morokuma, K. *J. Am. Chem. Soc.* **1985**, *107*, 7109. (i) Kanamori, K.; Broderick, W. E.; Jordan, R. F.; Willett, R. D.; Legg, J. I. *J. Am. Chem. Soc.* **1986**, *108*, 7122. (j) Dawoodi, Z.; Green, M. L. H.; Mtetwa, V. S. B.; Prout, K.; Schultz, A. J.; Williams, J. M.; Koetzle, T. F. *J. Chem. Soc., Dalton Trans.* **1986**, 1629. (k) Cotton, F. A.; Luck, R. L. *Inorg. Chem.* **1989**, *28*, 3210.

(3) (a) Eisch, J. J.; Piotrowski, A. M.; Brownstein, S. K.; Gabe, E. J.; Lee, F. L. *J. Am. Chem. Soc.* **1985**, *107*, 7219 and references therein. (b) Jordan, R. F.; Bajgur, C. S.; Willett, R.; Scott, B. *J. Am. Chem. Soc.* **1986**, *108*, 7410. (c) Jordan, R. F.; LaPointe, R. E.; Bajgur, C. S.; Echols, S. F.; Willett, R. *J. Am. Chem. Soc.* **1987**, *109*, 4111. (d) Jordan, R. F. *J. Chem. Educ.* **1988**, *65*, 285. (e) Gassman, P. G.; Callstrom, M. R. *J. Am. Chem. Soc.* **1987**, *109*, 7875. (f) Hlatky, G. G.; Turner, H. W.; Eckman, R. R. *J. Am. Chem. Soc.* **1989**, *111*, 2728. (g) Bochmann, M.; Wilson, L. M.; Hursthouse, M. B.; Motevalli, M. *Organometallics* **1988**, *7*, 1148 and references therein. (h) Lin, Z.; LeMarechal, J.-F.; Sabat, M.; Marks, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 4127. (i) Hedden, D.; Marks, T. J. *J. Am. Chem. Soc.* **1988**, *110*, 1647. (j) Giannetti, E.; Nicoletti, G. M.; Mazzocchi, R. *J. Polym. Sci., Polym. Chem. Ed.* **1985**, *23*, 2117. (k) Dyachkovskii, F. S.; Shilova, A. K.; Shilov, A. E. *J. Polym. Sci., Part C* **1967**, *16*, 2333.

(4) Jordan, R. F.; LaPointe, R. E.; Bradley, P. K.; Baenziger, N. *Organometallics* **1989**, *8*, 2892.

(5) All complexes are studied as the BPh_4^- salts. The spectroscopic data for **1c** do not allow unambigious assignment of the structure of the alkyl ligand. Full characterization data are given as supplementary material. Mechanistic details of the β-H elimination reactions will be reported separately (P. K. Bradley and R. F. Jordan, in preparation).

0002-7863/90/1512-1289$02.50/0