ELSEVIER

Journal of Organometallic Chemistry 627 (2001) 93–98

Journal of Organo metallic Chemistry

www.elsevier.nl/locate/jorganchem

Bromination of ferrocene chalcone derivatives mediated by β-cyclodextrin

Wan-yi Liu [a], Tong Xie [a], Yong-min Liang [a], Wei-min Liu [b], Yong-xiang Ma [a,*]

[a] *National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China*
[b] *Laboratory of Solid Lubrication, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, People's Republic of China*

Received 20 November 2000; received in revised form 24 January 2001; accepted 3 February 2001

Abstract

Bromination of the inclusion complex of *trans*-ferrocenylchalcone derivatives with β-cyclodextrin was studied. In the absence of β-cyclodextrin, the analogous ferrocenylchalcone does not undergo bromination at room temperature, but its inclusion complex in β-cyclodextrin brominates smoothly and gives the *erythro*-dibromide derivatives. This complexation does not induce any variation in the bromination pattern and the ferrocenyl moiety is not attacked in the reaction. These observations have been accounted for in terms of guest–host interaction patterns. The formation of complex and dibromination product has been confirmed by elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR, UV–Vis and electrochemical methods. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Ferrocenyl chalcone; β-Cyclodextrin; Bromination; Inclusion complex; *erythro*-Dibromide

---

1. Introduction

It is well known that cyclodextrin (CD) tends to form inclusion complexes with many suitable guest molecules, by the interaction of a hydrophobic or generalized lyophobic force, and acts as an enzyme model. The effects of CDs on organic reactions have received extensive attention [1]. The ability of CD to increase, stabilize or retard the availability of active substances enables it to modify the reactivity of a large variety of molecules and to improve the efficiency and selectivity of product formation [2–8]. CDs have been used extensively as reaction vessels. Thus electrophilic substitution of arenas (e.g. chlorination [9], carbonylation [10], and azo coupling [11]) can be catalyzed by CDs. Inclusion generally leads to a decrease in the amount of ortho and meta products because of shielding of these positions by the host [12]. The regio- [13] and enantio-selectivity [14] of a number of other reactions have also been influenced by the inclusion of starting materials in CDs. Recently, the asymmetric bromination of chalcone and benzylideneacetone in CD environments has been studied by Pitchumani et al. [5], but the influence of CD encapsulation on the bromination of ferrocenylchalcone derivatives has not been investigated. Furthermore, there has been no instance of the successful bromination of ferrocenylchalcone analogues by a general method so far, although the preparation of α-chloro- and α-bromoethylferrocene, as well as α,β-dibromoethyleneferrocene, was reported 30 years ago [15]. The tedious procedure, and that such compounds are highly reactive, hydrolyzable and even thermally unstable [15,16] limit their development.

Because most ferrocene derivatives fit well into the cavity of β-CD and could form real inclusion complexes [17], we are hereby reporting the use of β-CD as a reaction vessel for achieving selective reaction of organometallic molecules and the successful preparation of β-CD–α,β-dibromoethyleneferrocene analogues in water solution at ambient temperature. Our interest in utilizing the hydrophobic β-CD cavity for both increasing and decreasing the availability of an active substance and for protecting it from degradation [8] prompted us to investigate the bromination of α,β-unsaturated compounds such as ferrocenylchalcone ana-

---

* Corresponding author. Fax: +86-931-8611688.
E-mail address: mayx@lzu.edu.cn (Y.-x. Ma).

PII: S0022-328X(01)00717-3

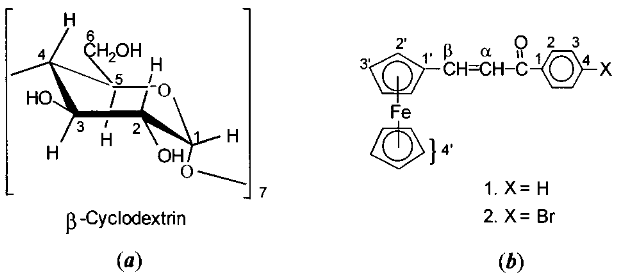


Fig. 1. Structures of (a) β-CD and (b) ferrocenylchalcone derivatives.

logues in bound form with β-CD (Fig. 1). The experiments are designed with a view to analyzing the influence of β-CD encapsulation on the bromination of these α,β-unsaturated compounds. Complex formation between the host and guest molecules has been established by various detection methods. We also report here on the electrochemical behavior of β-CD–ferrocene complexes and the related α,β-unsaturated compounds.

2. Results and discussion

Elemental analyses, IR, UV–Vis, ^{1}H-NMR, ^{13}C-NMR and cyclic voltammetry are employed to establish the complex formation and that the dibromides are 1:1 complexes. The UV spectra of complexes **1**–**6** in Me_2SO were shown in Table 1. The ^{1}H-NMR and ^{13}C-NMR spectra of β-CD in the uncomplexed and complexed forms are given in Tables 2 and 3, respectively. The cyclic voltammetric profiles of compounds **2**, **3** and **6** are shown in Figs. 2 and 3. The potential values of these compounds are listed in Table 4.

2.1. IR spectra

IR techniques were used for the detection of inclusion complexes because functional ferrocene derivatives showed characteristic IR absorption in regions where β-CD does not absorb and it is used to identify the host–guest interaction. The two bands due to the α,β-unsaturated carbonyl group in free ferrocenylchalcone analogues at 1619 and 1665 cm^{-1} were shifted to 1580 and 1650 cm^{-1}, respectively, in the inclusion complex. Similarly, the C–H bending frequencies of *trans*-alkene in ferrocenylchalcone analogues observed at 950 and 1050 cm^{-1} are shifted to 942 and 1027 cm^{-1}, respectively, in the complex. The bands of the Cp-ring in ferrocenyl at 1450 and 830 cm^{-1} apparently move to 1415 and 856 cm^{-1}, respectively. In addition, the intensities of many bands for the β-CD complexes of ferrocene derivatives are decreased compared with that of the pure compounds or a physical mixture. Such a shift of the bands for the C=C and C=O groups is not observed in a physical mixture. Finally, the bands at 1580 and 1650 cm^{-1} for the bromination product of the β-CD complexes disappeared, and that of the C=O at about 1637 cm^{-1} appeared.

2.2. UV–Vis spectra

Comparison of the UV spectrum patterns of β-CD–chalcone complexes with that of the chalcone reveals marked differences. The strongest absorption bands at 258–270 nm can be assigned to the B bands of the Cp-ring [18], and the bands at 332–396 nm can be assigned to the π → π* transition of the α,β-unsubstituted ketone conjugated with the ferrocene nucleus, or

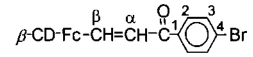
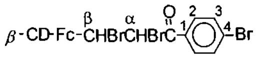
Table 1
Electronic absorption bands (nm, in Me_2SO)

No.	Compounds	Conc. (× 10^{-5} M)	1 (B band of Cp)	2 (π → π*)	3 (d → π*)
1	$FcCH{=}CHCOC_6H_5$	4.6	264(s)	372(s0	
2	$FcCH{=}CHCOC_6H_4Br$-*p*	8.1	270(s)	332(s)	510(br,w)
3	β-CD–$FcCH{=}CHCOC_6H_5$ (1:1)	1.2	262(s)	388(s)	
4	β-CD–$FcCH{=}CHCOC_6H_4Br$-*p* (1:1)	1.0	270(s)	332(s)	510(br,w)
5	β-CD–$FcCHBrCHBrCOC_6H_5$ (1:1)	1.0	260(s)	396(br, s)	
6	β-CD–$FcCHBrCHBrCOC_6H_4Br$-*p* (1:1)	0.8	258(s)	386(br, s)	

Table 2
The proton chemical shifts of β-CD and its inclusion complex, and α,β-situations of the guest molecule of complexes in 400 MHz ^{1}H-NMR (δ, ppm)

Compound	H-1	H-2	H-3	H-4	H-5	H-6	α-H	β-H
β-CD	4.82	3.27	3.57	3.34	3.47	3.52	–	–
β-CD–$FcCH{=}CHCOC_6H_4Br$-*p*	4.85	3.30	3.65	3.38	3.55	3.61	6.56	7.61
							($J_{\alpha\beta}$ = 15.3–15.4)	
β-CD–$FcCHBrCHBrCOC_6H_4Br$-*p*	4.83	3.31	3.63	3.37	3.56	3.63	5.03	5.27
							($J_{\alpha\beta}$ = 8.7)	

Table 3
^{13}C-NMR chemical shifts (Hz) of β-CD, β-CD–chalcone–ferrocene analogues and its α,β-dibromide complexes

β-CD		 $\beta\text{-CD-Fc-}\overset{\beta}{\text{C}}\text{H=}\overset{\alpha}{\text{C}}\text{H-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-C}_6\text{H}_4\text{-Br}$				 $\beta\text{-CD-Fc-}\overset{\beta}{\text{C}}\text{HBr}\overset{\alpha}{\text{C}}\text{HBr}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-C}_6\text{H}_4\text{-Br}$			
C [a]	δ (ppm)	C[b]	δ	C[a]	δ	C[b]	δ	C[a]	δ
1	101.94	α	130.323	1	101.966	α	55.180	1	101.950
2	73.099	β	136.978	2	73.077	β	56.598	2	73.065
3	72.546	1′	86.745	3	72.427	1′	100.826	3	72.419
4	81.745	2′	68.434	4	81.573	2′	80.672	4	81.560
5	72.124	3′	68.525	5	72.064	3′	69.912	5	72.051
6	60.170	4′	69.674	6	59.963	4′	70.218	6	59.940
		1	135.493			1	135.867		
		2	132.227			2	132.459		
		3	131.603			3	131.958		
		4	133.397			4	134.691		

[a] Carbon atom of β-CD.

[b] Carbon atom of ferrocenyl and chalcone.

the corresponding bromination complexes. For the π → π* transition of bands 5 and 6, such a large bathochromic shift may indicate that the interaction of the non-bonding d-orbitals of the metal in the ferrocene nucleus with a bulky electron-donating group of the side chain on the Cp-ring. These observations reinforce the evidence from IR spectroscopy, that the β-CDs have been used successfully as reaction vessels to control bromination of ferrocenylchalcone analogues as well as having stabilized the dibromides of the corresponding chalcone.

2.3. ^{1}H-NMR spectra

Additional evidence for complex formation is provided by the ^{1}H-NMR spectra of β-CD–ferrocenylchalcone analogues and β-CD–α,β-dibromide analogues in Me$_2$SO-d_6. The protons on the CD and α,β-situations of the chalcone are identified by their specific coupling patterns [19,20]. The chemical shifts of β-CD protons in the uncomplexed and complexed forms indicate that H-1, H-2 and H-4 protons are nearly unaffected as a result of complexation. The proton signals of H-3 and H-5 in the complexes, which are oriented towards the interior of the β-CD cavity [21], are somewhat shifted downfield. In the complexes of chalcone and its α,β-dibromide with β-CD, H-6 protons move downfield. Evidence for the complex being brominated comes from the disappearance of the α,β-unsaturated hydrogen from ^{1}H-NMR spectra. These facts establish clearly that the ferrocenyl moiety is positioned within the CD cavity.

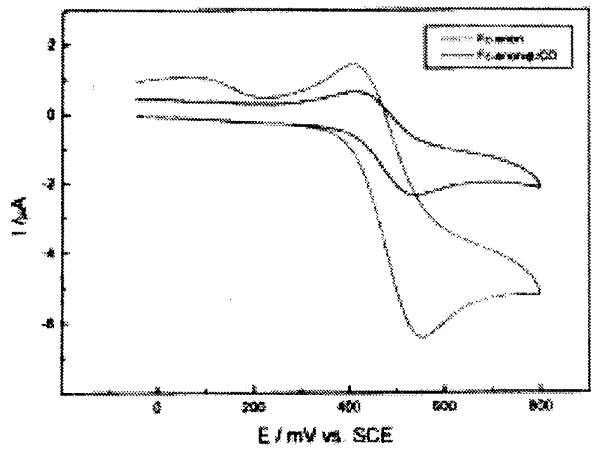


Fig. 2. The cyclic voltammetric profile of compounds **2** and **3** (in Me$_2$SO).

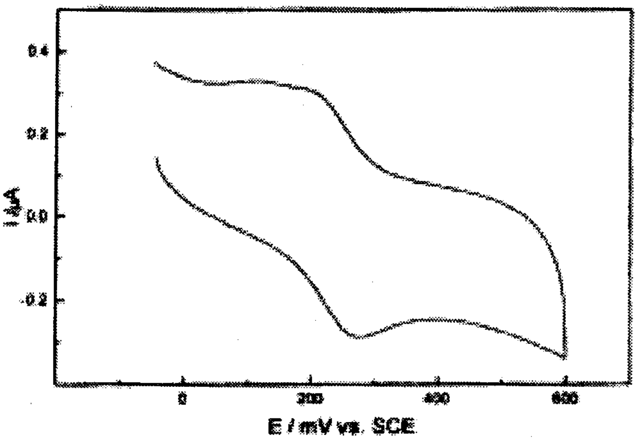


Fig. 3. The cyclic voltammetric profile of compound **6** (in Me$_2$SO).

Table 4
Electrode potentials (versus Ag | AgCl) and peak-to-peak separation for the one-electron oxidation of the series β-CD complexes (measured at 0.1 V s^{-1})

No.	Compound	E_{pa} (V)	E_{pc} (V)	$\bar{E}_p$ (V)	$\Delta\bar{E}_p$(mV)	Conc. 10^{-4} M
1	FcCH=CHCOC$_6$H$_5$	0.462	0.315	0.388	153	4.6
2	FcCH=CHCOC$_6$H$_4$Br-p	0.554	0.416	0.485	139	6.3
3	β-CD–FcCH=CHCOC$_6$H$_5$	0.457	0.315	0.386	142	1.4
4	β-CD–FcCH=CHCOC$_6$H$_4$Br-*p*	0.539	0.410	0.475	129	0.9
5	β-CD–FcCHBrCHBrCOC$_6$H$_5$	0.304	0.206	0.255	99	0.9
6	β-CD–FcCHBrCHBrCOC$_6$H$_4$Br-*p*	0.287	0.132	0.209	155	1.0

2.4. ^{13}C-NMR spectra

The ^{13}C-NMR chemical shifts for the carbon atoms of β-CD, β-CD–ferrocenylchalcone analogues and the brominated complex are significant. The most marked difference of ^{13}C-NMR chemical shifts is on the α- and β-carbon atoms. A comparison of the ^{13}C-NMR spectra of the β-CD–ferrocenylchalcone analogue and its brominated complex reinforces the evidence for formation of an inclusion complex between β-CD and the substrate, and clearly indicates that the β-CD acts as a reaction vessel to control the bromination of ferrocenylchalcone analogues as well as stabilizing the corresponding dibromide products.

2.5. Electrochemistry

Figs. 2 and 3 compare the responses of the ferrocenyl enone and β-CD–ferrocenyl enone complex, which bears one strong electron-withdrawing group, with that of β-CD–ferrocenyl dibromide complex, which bears one strong electron-donating group. The voltammetric profiles possess features of electrochemical reversibility and their redox potential separations are changed noticeably. The oxidation of ferrocene derivatives depends on the electronic character of the substituents, as revealed in the early years of ferrocene chemistry [22]. An analysis of the results of cyclic voltammetric measurements showed that the oxidation potentials of ferrocene derivatives were sensitive to structure and conformation effects as well. For example, the correlation between the changes of substituents and redox potentials in 1-aryl-3-ferrocenyl-2-propene-1-one derivatives has already been noted [23].

In electrochemistry studies, all the complexes exhibit quite similar anodic processes (at the potential values shown in Table 4) that are not significantly affected by the presence of β-CD. However, Fig. 2 shows that the cyclic voltammetric profiles of the complexes varied greatly in terms of peak current when in the presence of β-CD. Because the β-CD is not directly substituted to the ferrocenyl moiety it did not affect the oxidation potential significantly, but its bulkiness should decrease the oxidation peak current.

We can comment on the redox properties of this ferrocenyl complex, in comparison with those of the corresponding parent ferrocene derivatives **1** and **2**.

(1) The fact that the ferrocenyl subunits give rise to single separate, electrochemically reversible, one-electron oxidations suggests that the iron(II) subunit is in electronic communication with its substituent.

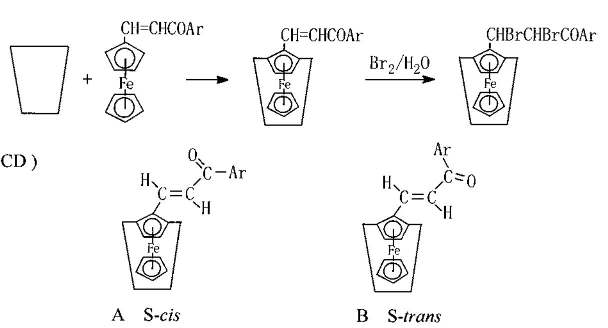
(2) The fact that β-CD–chalcone complex **4** occurs at a potential of 0.475 V, which is greater than that of the β-CD–Fc-dibromoethylene analogue **6** at 0.209 V, indicates that the α,β-dibromoethylene moiety has been obtained and that it is a stronger electron-donating group.

(3) Finally, that the β-CD–Fc-α,β-dibromoethylene analogous complex occurs at a lower potential suggests it should be a more oxidizable moiety, which provides evidence that the present framework correlates with electronic effects of the substituents in the series of title compounds. As far as the β-CD–ferrocenyl α,β-dihalogenated analogue is concerned, if it is assumed that electronic effects essentially govern the localization of the redox potentials of the electron removals (neglecting for instance steric effects), we can tentatively propose that there is a predominance of inductive effects over resonance effects.

2.6. Bromination

The stereospecific addition of bromine to the carbon–carbon double bond of α,β-unsaturated ketones is well documented by several examples [20] and using CD as an organic medium for the addition of bromine to a chalcone has been reported recently by Pitchumani et al. [5]. These results offer great tools for the systematic investigation of bromine addition to the complexes of CD–ferrocenylchalcone analogues. Our results indicate that β-CD–ferrocenylchalcone analogues can be brominated to yield exclusively *erythro*-dibromides as in the case of conventional bromination of chalcone. We also studied the isolation of brominated products of the above enones from their β-CD complexed forms, but the attempts to prepare such pure compounds have been unsuccessful. These compounds are highly reactive, readily hydrolytic and also thermally unstable. It is worth noting that the formation of CD complexes is essential for these bromination reactions, since the α,β-dihalides are difficult to obtain by conventional halogenation methods [15]. The reaction proceeds by electrophilic attack of the halogen to the double bond to form an intermediate cyclic brominium ion followed by attack of halide ion to the cyclic intermediate. The overall result shows an anti-addition of the two-halogen atoms to the double bond. The ferrocenyl moiety was not attacked by halogen. In general, the halogen will oxidize the iron(II) of the ferrocenyl framework. This difference in the bromination reactivity of the β-CD enone complexes may be explained on the basis of the specific complexing mode of the substrate into the CD cavity. The ferrocenyl moiety penetrates the cavity of β-CD tightly and entirely by the axial inclusion mode. The side chain locates away from the wall to permit an interaction between the double bonds and the active bromine. Meanwhile, the formation of an inclusion complex of dibromide with β-CD leads to an increase in its thermostability.

The participation of β-CD in this bromination reaction is shown schematically in Fig. 4. Harada and Takahashi [23] previously reported that ferrocene and its derivatives could form 1:1 stoichiometric inclusion complexes with β-CD that are thermostable. In the structures of **A** and **B**, the ferrocenyl group with the carbon–carbon double bond resides inside the cavity, whereas the benzoyl group is outside. These structures do not experience any hindrance to anti-addition of bromine due to the free rotation of the carbon–carbon single bond between the olefinic and the carbonyl groups. These results offer hints that CD may be a useful protecting framework for ferrocene moieties to allow for the reactions of reactive molecules with the ferrocene-attached functional groups. Thus a perusal of the structure of the complexes reveals that bromination of structures **A** and **B** results in anti-addition to obtain *erythro*-dibromide.



A S-*cis* B S-*trans*

Fig. 4. Conformation of β-CD–ferrocene–chalcone analogous complex.

3. Experimental

3.1. Materials

β-CD was made in China, recrystallized twice with double-distilled water. Bromine (AR) was used directly. Ferrocenylchalcone compounds were synthesized by reported procedures [24,25].

3.2. Preparation of β-CD complexes

The cyclodextrin complex was prepared according to the literature [26]. To 40 ml of warm water were added 2.5 mmol of β-CD, then an equimolar amount of the guest molecule solution in ether. An orange suspension was obtained after stirring for 2 h. Then the inclusion complex was filtered, washed with water, ether–acetone (5:1) and then ether, and dried in an air oven at 60°C for about 3 h. An orange–red or pale-red solid was obtained (yield 90%).

3.3. Bromination of β-CD–enone complexes

The bromination of enone was carried out following the general procedure. 1.5 g of β-CD–enone complex was dissolved in 20 ml of water at room temperature (r.t.) and a mild excess of bromine was added dropwise into it for a few minutes, then stirred for 10–15 min. After completion of the reaction, the excess bromine was removed and the complex was filtered, washed with water, ether–acetone (5:1), and then ether, and dried in an air oven at 60°C for about 3 h. An orange or yellowish solid was obtained. The dibromide was recrystallized from water to give a yellow microcrystalline product (yield 84%). Anal. Found: C, 45.96; H, 6.09. Calc. for $C_{40}H_{70}O_{35}$–$C_{19}H_{16}OBr_2Fe$ (β-CD–$FcCHBrCHBrCOC_6H_5$): C, 45.42; H, 5.37%. Anal. Found: C, 43.86; H, 5.58. Calc. for $C_{40}H_{70}O_{35}$–$C_{19}H_{15}Br_3FeO$ (β-CD–$FcCHBrCHBrCOC_6H_4Br$-*p*): C, 43.33; H, 5.14%.

3.4. Equipment and procedures

The elemental analyses were recorded using a Carblo-Erba 1106 elemental analyzer. The IR spectra were measured in the region 200–4000 cm^{-1} on an FT-170SX spectrometer using KBr discs. The ^1H- and ^{13}C-NMR spectra were recorded using a 400 MHz NMR spectrometer (in Me_2SO-d_6) with Me_4Si as the internal reference standard. A UV–Vis HP-8452A spectrometer was employed (concentration of β-CD complex varied from 8.1×10^{-5} to 0.8×10^{-5} M) to measure the region of 200–800 nm, using Me_2SO as the solvent at r.t. Cyclic voltammetric experiments were performed on a BAS-100B electrochemical analyzer equipped with a three-electrode assembly with 0.03 M

Bu_4NBr as support electrolyte and Me_2SO as solvent. The working electrode was a 200 μm diameter Pt disk embedded in a Co glass seal and was polished consecutively with polishing Al_2O_3 and a diamond suspension between runs. Ag | AgCl was the reference electrode. A Pt filament was used as an auxiliary electrode. The measurements were made at a scan rate of 100 mV s^{-1}.

References

[1] K. Takahashi, Chem. Rev. 98 (1998) 2013 and references cited therein.
[2] Y.-M. Li, X.-J. Yao, X. Feng, X.-M. Wang, J.-T. Wang, J. Organomet. Chem. 509 (1996) 221 and references cited therein.
[3] V. Ramaurthy, D.F. Eaton, Acc. Chem. Res. 21 (1988) 300.
[4] (a) V. Ramaurthy, Tetrahedron 42 (1986) 5753. (b) K. Pitchumani, M.C. Durai Manickam, C. Sprinivasan, Tetrahedron Lett. 35 (1991) 2975.
[5] K. Pitchumani, P. Velusamy, S. Sabithamala, C. Srinivasan, Tetrahedron 50 (1994) 7903.
[6] (a) H.S. Banu, K. Pitchumani, C. Srinivasan, Tetrahedron 55 (1999) 9601. (b) K. Takahashi, Chem. Rev. 98 (1998) 2013.
[7] A. Uneo, Supramol. Sci. 3 (1996) 31.
[8] G. Wenz, Angew. Chem. Int. Ed. Engl. 33 (1994) 803.
[9] R. Breslow, P. Campbell, J. Am.Chem. Soc. 91 (1969) 3085.
[10] M. Komiyama, H. Hirai, J. Am. Chem. Soc. 106 (1984) 174.
[11] H. Rong, D. Ye, V.T. D'Souza, Tetrahdron Lett. 32 (1991) 5231.
[12] M. Komiyama, J. Chem. Soc. Perkin Trans. I (1989) 2031.
[13] (a) M.S. Syamala, V. Ramamurthy, Tetrahedron 44 (1988) 7232. (b) M.S. Syamala, B.N. Rao, V. Ramamurthy, Tetrahedron 44 (1988) 7234. (c) J.-T. Lee, H. Alper, J. Org. Chem. 55 (1990) 1854.
[14] (a) M. Barra, R.H. Rossi, J. Org. Chem. 54 (1989) 5020. (b) S. Colonna, A. Manfredi, R. Annunziata, N. Gaggero, L. Casella, J. Org. Chem. 55 (1990) 5862. (c) H. Sakuraba, Y. Tananaka, F. Toda, J. Incl. Phenom. Mol. Recognit. Chem. 11 (1991) 195.
[15] A. Robert, P.B. Walter, Jr. Fitzgerald, J. Org. Chem. 26 (1961) 4179.
[16] G.R. Buell, E. McEwen, J. Kleinberg, Tetrahedron Lett. 5 (1959) 16.
[17] S.I. Goldberg, D.W. Wayo, J.A. Afalford, J. Org. Chem. 28 (1963) 1708.
[18] (a) T. Kuwana, D. Bublitz, G. Hoh, J. Am. Chem. Soc. 82 (1960) 5811. (b) J.G. Masson, M. Rosenblum, J. Am. Chem. Soc. 82 (1960) 4206.
[19] A.G. Nagy, S. Toma, J. Organomet. Chem. 266 (1984) 2571.
[20] J. March, Advanced Organic Chemistry, Third ed., McGraw-Hill, New York, 1987, p. 659.
[21] S. Toma, Chem. Zvesti 119 (1965) 703.
[22] J.M. Osgerby, P.L. Pauson, J. Chem. Soc. (1957) 656
[23] A. Harada, S. Takahashi, J. Incl. Phenom. 2 (1984) 791.
[24] K. Vekama, F. Hivagana, N. Matsuo, H. Koinuma, Chem. Lett. (1978) 703
[25] E. Solcaniora, S. Toma, A. Fiedlerova, Org. Magn. Reson. 14 (1980) 181.
[26] O.L. Alves, S.F. Fanseca, J. Incl. Phenom. 7 (1989) 589.