Acta Chemica Scandinavica B 37 (1983) 693–698

[2_3]Cyclophanetrienes from Wittig Reactions and Titanium-mediated Reductive Coupling

DAVID TANNER and OLOF WENNERSTRÖM

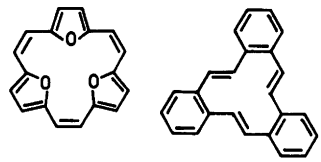
Department of Organic Chemistry, Chalmers University of Technology and University of Göteborg, S-412 96 Göteborg, Sweden

A series of new [2.2.2.]cyclophanetrienes, 4, 5, 6 and 7, has been prepared by a threefold Wittig reaction or by twofold Wittig reactions followed by titanium-mediated reductive couplings of dialdehydes. The combination of *cis*-selective Wittig reactions and intra-molecular reductive couplings is shown to be a simple and effective way to make large ring compounds containing different aromatic units. The ferrocenophane 7 in which the two five-membered rings are linked by a conjugated π-system was found by ^{1}H NMR spectroscopy to exist in two mirror image forms with opposite helicity.

It has previously been reported from this laboratory that *cis*-stereoselective multiple Wittig reactions provide convenient access to [2_4]cyclophanetetraenes, and the applicability of this one-pot synthesis of macrocycles has been demonstrated amply.[1] We now wish to report an example of the synthesis of a symmetrical [2_3]cyclophanetriene by this method. More recently, we have also employed low-valent titanium species in simple one-step syntheses of cyclophanes and annulenes *via* reductive coupling of readily available dialdehydes.[2,3] A combination of these two techniques, *i.e.* a *cis*-selective double Wittig reaction followed by intramolecular coupling of aldehyde groups has now proved to be a short and reasonably efficient synthesis of less symmetrical [2_3]cyclophanetrienes.

RESULTS AND DISCUSSION

Threefold Wittig reactions. Macrocycle synthesis employing "mixed" Wittig reagents analogous to *3* (Scheme 1) has been attempted previously. The [2_3](2,5)furanophanetriene *1* (considered to be a trioxo[18]annulene) was synthesised by Elix[4] *via* a threefold Wittig reaction (DMF, lithium ethoxide, 90 °C) while Brown and Sargent[5] have reported an analogous synthesis of Staab's [2_3]orthocyclophanetriene *2* (methanol, lithium ethoxide, reflux). However, the yield in both cases was less than one percent and in the latter case the major cyclic product (26 %) was 1,2:5.6-dibenzocyclooctatetraene.

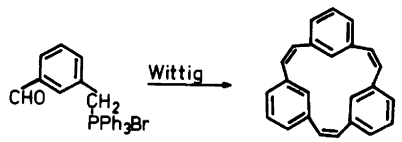


1 *2*

In our hands, the Wittig reagent *3* which is easily prepared from benzene-1,3-dicarbaldehyde (see Experimental) underwent a threefold Wittig reaction (DMF, lithium ethoxide) to yield the all-*cis*[2_3]metacyclophanetriene *4* in 28 % yield, (Scheme 1).

Cyclisation occurred smoothly at −40 °C, the various ylid-aldehyde species involved being relatively reactive due to the absence of mesomeric effects. (Wittig reagents of type *3* in which the reactive centres are in conjugation with each

0302-4369/83 $2.50

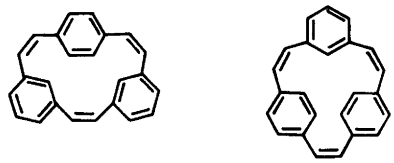


3 4

Scheme 1.

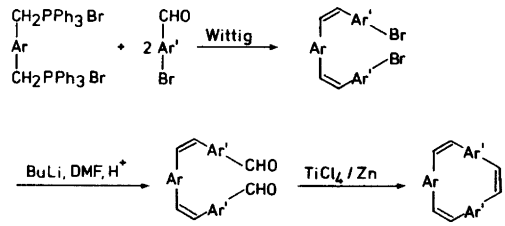
other, and thus mutually stabilised, have been observed to cyclise less readily).[6] In contrast to the reactions which gave *1* and *2*, the present reaction gave the triene *4* as the dominant ring-closed product and the yield was, in relative terms, high. As well as the enhanced reactivity of *3*, the lower reaction temperature used is undoubtedly a contributing factor, as this should have a favourable entropic effect on the ring-closure reaction. No [2.2]metacyclophanediene (or products thereof) could be detected, steric effects favouring formation of the unstrained triene *4*. However, trace amounts of two isomers of [2$_4$]metacyclophanetetraene, the all-*cis*- and the *cis,cis,cis,trans*-isomers, were observed by ^{1}H NMR spectroscopy in the crude product mixture by comparison with authentic spectra.[7]

Double Wittig reaction followed by reductive coupling. The sequence of double Wittig reaction/titanium-mediated intramolecular reductive coupling was used to synthesise cyclophanes *5*, *6* and *7* and the general method is depicted in Scheme 2.



5 6

Thus, a double Wittig reaction was carried out under *cis*-selective conditions between an aromatic bisphosphonium salt and two equivalents of an aromatic aldehyde substituted with bromine in the appropriate position. This yielded *cis,cis,*-dienes as the major products which were routinely converted to the corresponding dialdehydes. Intramolecular coupling of the carbonyl groups using the low-valent titanium species obtained by reduction of titanium tetrachloride with zinc then yielded the [2$_3$]cyclophanetrienes in reasonably good yield. In principle, aromatic dialdehydes could be used directly in the first step (this was actually done in the synthesis of *7*) but the present method avoids production of the corresponding [2$_4$]cyclophanetetraenes which are known to form easily under the conditions used.[1] The *cis,cis*-dienes isomerised partly, albeit quite slowly, upon work-up and subsequent handling and the dialdehydes were used without delay after isolation. The yields in the various steps were acceptable and the overall ease of operation and work-up makes the sequence shown in Scheme 2 an attractive one.



Scheme 2.

The presence of two *cis* double bonds in the dialdehydes used in the final step favours the desired intramolecular coupling reaction over intermolecular processes and high dilution techniques are unnecessary, a THF solution of the dialdehyde being added slowly to the pre-formed titanium reagent (THF, reflux). The desired all-*cis* trienes were the sole isolable products. This type of reductive coupling has been used previously by Kasahara *et al.*[8] in the final ring closure of the *trans,cis,trans* isomer of *7*. These workers employed a low-valent titanium species prepared from titanium trichloride and lithium aluminium hydride, which in our hands proved generally less satisfactory then the titanium tetrachloride/zinc reagent.

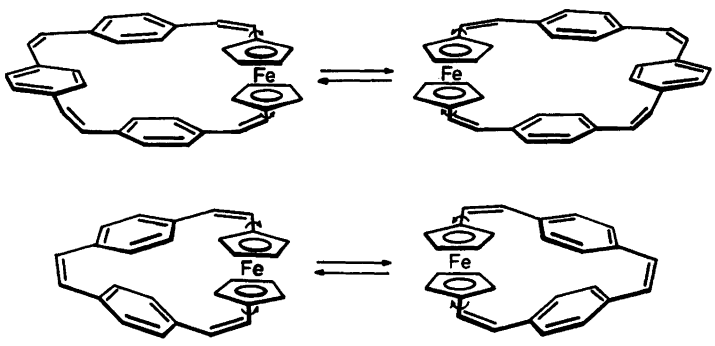
Stereochemistry. The gross structures of the cyclic products are apparent from the spectral data given in the Experimental section. From inspection of CPK models, it is immediately clear that for cyclophanes *6* and *7* the double bond formed in the final step must have the *cis* configuration, while for *5* this double bond may be either *cis* or *trans*. However, the *trans* isomer should be more strained and most of the sterically feasible conformations force the isolated protons on the metasubstituted benzene rings over the face of the parasubstituted ring. This would be

expected to result in a strong shielding of these protons in the ^{1}H NMR spectrum, but no such effects are obtained. The IR spectrum also shows the absence of *trans* double bonds. Since the NMR data are consistent with a single isomer, the all-*cis* configuration can be assigned with confidence to cyclophane *5*.

Cyclophanes *4*, *5* and *6* are expected to be relatively unstrained, conformationally mobile species and it is difficult to predict which conformations are of lowest energy. This expectation is borne out by the room-temperature ^{1}H NMR spectra which show the patterns expected for rapid equilibration between the possible conformers in each case, with low barriers to the flipping of the para- and meta-substituted benzene rings. The compounds thus resemble more closely the anlogous all-*cis*[2₄]cyclophanetetraenes [1,7] than the more strained and compact [2₂]para- and metacyclophanedienes.[9,10] The chemical shifts of the aromatic and olefinic protons are unremarkable, and no unusually strong shielding or deshielding effects are apparent. In cyclophane *6*, however, the singlet from the olefinic protons is shifted to slightly lower field than the signals from the adjacent parasubstituted benzene ring. This type of deshielding effect has been observed in other [2₃]cyclophanetrienes, particularly those incorporating parasubstituted *cis*-stilbene subunits.[11]

Stereochemically, the ferrocenophane *7* is of greater interest. We have previously synthesised the "homologous" all-*cis* [2₄] (1,1′)ferrocenophanetetraene *8* which, from the study of models and on the basis of UV and ^{1}H NMR spectroscopy was suggested to adopt a helix-like conformation which allowed extensive conjugation between the "top" and "bottom" halves of the molecule.[12] Further, DNMR studies showed that the interconversion of the two helical mirror-image conformers *via* rotation of the entire ferrocene unit through the central cavity of the cyclophane takes place over a barrier of 40 kJ mol^{-1} (see Scheme 3). In the fast exchange spectra of *8*, the ferrocene protons appear as an AA′XX′-pattern which changes to an ABCD-pattern in the "frozen" conformational mixture.

Inspection of a CPK model of the ferrocenophane *7* suggests that this molecule must also be constrained to a helix-like geometry, the helix being much "tighter" than that of *8*. The effect of the shortened bridge between the cyclopentadienyl rings in *7* should be to force the benzene rings out of conjugation with the adjacent double bonds and also to raise the barrier to the interconversion of the enantiomeric helical conformers. The former effect is apparent from comparison of the UV spectra of *7* and *8*. While *8* has an intense absorption band around 312 nm, the ferrocenophane *7* has no strong band above 230 nm. The observed difference between *7* and *8* supports our earlier conclusion that the ferrocenophane *8* does indeed possess unbroken conjugation between its two five-membered rings. This point has been discussed more recently by Katz and Pesti [13] who, in claiming the first example of this type of structure, made the observation that in *8* "adjacent double bonds are not constrained parallel". While this statement is obviously accurate, a rigidly clamped π-system is hardly a necessary condition for π-electron conjugation.



7 *8*

Scheme 3.

Concerning the dynamic stereochemistry of *7*, the room-temperature ^1H NMR spectrum is consistent with a species of C_2-symmetry in which the rotation or flipping of the benzene rings is still rapid on the NMR time-scale (as in *8*) while rotation of the ferrocene unit through the central cavity of the cyclophane is already "frozen". The protons on the benzene rings thus give rise to the expected AA'BB'-pattern centred on δ 7.08 while the cyclopentadienyl protons constitute an ABCD spin system appearing as four sharp, well-resolved, multiplets at δ 4.36, 3.99, 3.81 and 3.56. No significant broadening of the NMR signals due to rapid rotation of the ferrocene unit was observed at elevated temperatures. However, a distinct broadening and shift of the signals due to decomposition of the sample to give paramagnetic ferrocenium ions was apparent at temperatures above 100 °C in dideuterotetrachloroethane.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were obtained on a Bruker WH 270 instrument, IR spectra on a Beckman IR9, UV spectra on a Varian Cary 210 and mass spectra on an AEI MS 902 instrument.

The apparatus, reaction conditions and work-up for the Wittig reactions have been described earlier.[1]

[2$_3$]Metacyclophanetriene, 4. Benzene-1,3-dialdehyde (10 g) and sodium borohydride (750 mg) were dissolved in ethanol (200 ml) and stirred for 1 h. The solvent was removed by evaporation and the residue dissolved in hot water and then cooled. Unreacted dialdehyde (2.1 g) was collected. The aqueous solution was extracted several times with diethyl-ether. The ethereal solution was dried over $MgSO_4$ and the solvent removed to give *3-hydroxymethylbenzaldehyde* (5.7 g, 57 %, colourless oil). The crude product was treated with hydrobromic acid in acetic acid (33 %, 25 ml) and stirred for 1 h at room temperature. The mixture was poured onto ice-water and the white precipitate of *3-bromomethylbenzaldehyde* was collected and dried (6.6 g, 82 %, m.p. 36–37 °C).

The crude product above, 3-bromomethylbenzaldehyde (5.97 g) and triphenylphosphine (7.86 g) were dissolved in dry DMF (50 ml) and heated to 130 °C. The solution was cooled and a few crystals of the phosphonium salt, prepared by addition of diethyl ether to a small sample of the solution, were added. The white precipitate of the *phosphonium salt from 3-bromomethylbenzaldehyde* was collected and carefully dried (7.6 g, 55 %, m.p. 301–303 °C).

The triphenylphosphonium salt from 3-bromomethylbenzaldehyde (4 g) was dissolved in dry DMF (100 ml) and the mixture cooled under nitogen to −40 °C. Freshly prepared lithium ethoxide in ethanol was added dropwise to the stirred solution which slowly changed colour from orange to yellow. The addition was complete within a few hours when no further colour change was observed on addition of base. The mixture was warmed to room temperature and water (100 ml) was added followed by extraction with diethyl ether. The combined ethereal solutions were washed with water, dried over $MgSO_4$ and solvent removed. The white semi-solid residue was separated from triphenylphosphine oxide by column chromatography to give crude *[2$_3$]metacyclophanetriene, 4* (265 mg, 48 %). The crude product was purified by distillation at $6 \cdot 10^{-2}$ mm Hg, 160 °C, to give pure *4* (113 mg, 20 %, white solid m.p. 72–75 °C). UV (ethanol): 253 nm, ε 13 400. ^1H NMR (270 MHz, $CDCl_3$): δ 7 · 18 (3 H, t, *J* 8 Hz), 6.94 (6 H, dd, *J* 2 Hz), 6.69 (3 H, m) aromatic protons, 6.57 (6 H, s) olefinic protons. MS (70 eV): *m/e* 306 (100 %, M^+). Abs. mass 306.142±0.003; calc. for $C_{24}H_{18}$ 306.141. The distillation residue was purified by preparative TLC to give another 8 % of the cyclophane *4* and *ca.* 8 % (42 mg) of a mixture of all *cis* and *cis,cis,cis,trans* [2$_4$]metacyclophanetetraene, identified by comparison of the ^1H NMR spectrum with that from authentic material.[7]

General procedure for intramolecular reductive coupling of dialdehydes. A three-necked round-bottomed flask (250 ml) fitted with N_2 inlet, reflux condenser and Schlenk-type dropping funnel is charged with dry THF (100 ml, distilled from Na–benzophenone) and cooled to −78 °C. Titanium tetrachloride (30 mmol) is then added carefully, with stirring, followed by zinc powder (60 mg-atom) and dry pyridine (0.5 ml). The resulting black mixture is first refluxed under nitrogen for 1 h and then a solution of the dialdehyde (3 mmol) in dry THF (100 ml) is added *slowly via* the Schlenk funnel over a period of *ca* 12 h. The reaction is followed by TLC (disappearance of the dialdehyde) and finally cooled to 0 °C (ice bath) and quenched by addition of 10 % aqueous K_2CO_3. The resulting grey precipitate is filtered off and both filtercake and filtrate extracted with dichloromethane. The combined organic phases are dried ($MgSO_4$) and the solvent removed to yield a residue which is chromatographed on a short column of silica gel with dichloromethane as eluent. The products

can be recrystallised from a mixture of dichloromethane and methanol.

[2$_3$]Metametaparacyclophanetriene, 5. 3-Bromobenzaldehyde (7.4 g) and the bistriphenylphosphonium salt from 1,4-bis-(bromomethyl) benzene (15.76 g) were dissolved in dry DMF (200 ml) and cooled to −40 °C under nitrogen. Freshly prepared lithium ethoxide (40 mmol) was added slowly during 3 h to the stirred solution. The mixture was then warmed to room temperature and diluted with water (200 ml). The aqueous phase was extracted with diethyl ether two or three times. The combined ethereal fractions were washed with water, dried ($MgSO_4$) and concentrated to allow triphenyl phosphineoxide to precipitate. The remaining solution contained three isomers, the *cis,cis-*, the *cis,trans-* and the *trans,trans-*isomer of *1,4-bis-(bromostyryl)benzene* (5.7 g, 65 %).

The crude oil above was dissolved in dry ether (100 ml) under N_2 and cooled to 0 °C. Butyllithium (25 ml, 1.6 M in hexane, Merck) was added *via* syringe and the mixture was stirred for 3 h. Dry DMF (5 ml) was added and stirring continued for another hour. Finally, hydrochloric acid (100 ml, 3 M) was added and the mixture stirred for 30 min more. The ethereal solution was separated, washed with water, dried ($MgSO_4$), concentrated and cooled. A light yellow precipitate of *cis,cis-1,4-bis(3-formylstyryl)benzene* was collected (1.83 g, 42 %, m.p. 64–68 °C). ^{1}H NMR (270 MHz, $CDCl_3$): δ 9.93 (2 H, s) aldehyde protons, 7.74 (2 H, m), 7.70 (2 H, dt), 7.49 (2 H, dt), 7.37 (2 H, t) metasubstituted ring protons, 7.07 (4 H, s) parasubstituted ring protons, 6.64–6.61 (4 H, AB-pattern, *J* 12 Hz) olefinic protons. MS (70 eV): *m/e* 338 (100 %, M^+), 310 (18), 203 (13), 202 (10), 178 (10). Abs. mass 338.131; calc. for $C_{24}H_{18}O_2$ 338.131.

The reductive coupling of *cis,cis*-1,4-bis(3-formylstyryl)-benzene as described by the general procedure above gave *[2$_3$]metametaparacyclophanetriene, 5,* as white crystals (477 mg, 52 %, m.p. 127–129 °C). UV (ethanol): 274 nm, ε 25 500. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.43 (2 H, m), 7.23 (2 H, t), 7.17 (2 H, dt), 7.05 (2 H, dt) metasubstituted ring protons, 7.20 (4 H, s) parasubstituted ring protons, 6.70, 6.55 (4 H, AB-pattern, *J* 12.5 Hz), 6.48 (2 H, s) olefinic protons. MS (70 eV): *m/e* 306 (100 %, M^+), 290 (6), 289 (11), 276 (8). Abs. mass 306.140; calc. for $C_{24}H_{18}$ 306.141.

[2$_3$]Metaparaparacyclophanetriene, 6. 4-Bromobenzaldehyde (7.4 g) and the bistriphenylphosphonium salt from 1,3-bis-(chloromethyl) benzene (13.98 g) were dissolved in dry DMF (200 ml) under N_2 and the mixture was cooled to −40 °C. Freshly prepared lithium ethoxide (40 mmol) was then added dropwise under 3 h to the stirred solution. The resulting mixture was warmed to room temperature and diluted with water (200 ml). The aqueous solution was then extracted with two or three portions of diethyl ether. The combined ether fractions were washed with water, dried ($MgSO_4$), and the solution concentrated. The precipitated triphenylphosphine oxide was filtered off and the rest of the solvent evaporated. The crude product (5 g) was used in the subsequent reaction.

The combined products from two of the reactions above (10 g) were dissolved in dry diethyl ether (100 ml) under N_2 and cooled to 0 °C. Butyl-lithium (30 ml, 1.6 M, Merck) was added *via* syringe and the mixture was stirred for 3 h. Dry DMF (10 ml) was added and stirring was continued for another hour. Finally, hydrochloric acid (150 ml, 2 M) was added followed by stirring for 30 min more. The ethereal solution was washed with water, dried ($MgSO_4$), and the solvent evaporated. The residual oil was carefully chromatographed on silica gel with dichloromethane as eluent. The first fractions contained unreacted starting material followed by monoaldehydes. Subsequent fractions contained the desired *cis,cis 1,3-bis(4-formylstyryl)benzene* (1.20 g, 16 %, colourless oil). ^{1}H NMR (270 MHz, $CDCl_3$): δ 9.93 (2 H, s) aldehyde protons, 7.67, 7.31 (8 H, AA'BB'-pattern, *J* 8 Hz) parasubstituted ring protons, 7.11–7.03 (4 H, m) metasubstituted ring protons, 6.61, 6.54 (4 H, AB-pattern, *J* 12 Hz) olefinic protons.

The crude oil from the reaction above was used in an intramolecular reductive coupling as described above to give [2$_3$]metaparaparacyclophanetriene, *6* (275 mg, 30 %. m.p. 75–77 °C). UV (ethanol): 227 (sh), ε 23 500. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.30 (1 H, t), 7.10 (2 H, d) 6.99 (1 H, broad s) metasubstituted ring protons, 6.86, 6.62 (8 H, AA'BB'-pattern, *J* 8 Hz) parasubstituted ring protons, 7.01 (2 H, s), 6.61, 6.50 (4 H, AB-pattern, *J* 13 Hz) olefinic protons. MS (70 eV): *m/e* 306 (100 %, M^+), 305 (9), 303 (6), 291 (6), 290 (8), 289 (13), 277 (8), 276 (15), 138 (8). Abs. mass 306.141; calc. for $C_{24}H_{18}$306.141.

[2$_3$](1,1')Ferrocenoparaparacyclophanetriene, 7. The bistriphenylphosphonium salt from 1,1'-bis(chloromethyl)-ferrocene [12] (6.1 g, 7.5 mmol) was reacted with benzene-1,2-dicarbaldehyde (2.0 g, 15 mmol) under the standard conditions for the Wittig reactions (−20 °C) described above and in Ref. 12 to give *1,1'-bis(4-formylstyryl)ferrocene* as a dark red oil (*ca.* 1.3 g, 3 mmol, 35–40 %) consisting of the *cis,cis*-isomer after purification by column chromatography

(silica gel, dichloromethane). ^{1}H NMR (270 MHz, $CDCl_3$): δ 9.99 (2 H, s) aldehyde protons, 7.78 7.46 (8 H, AA'BB'-pattern J 8 Hz) parasubstituted ring protons, 6.47, 6.33 (4 H, AB-pattern, J 12 Hz) olefinic protons, 4.89, 4.83 (8 H, m) ferrocene protons. The *cis,trans-* and *trans,trans*-isomers were also formed in the Wittig reaction but in minor amounts.

The crude *cis,cis*-1,1'-bis(4-formylstyryl)ferrocene above was used without further purification in the intramolecular reductive coupling as described above to give cis,cis,cis-*[2$_3$](1,1')ferrocenoparaparacyclophanetriene, 7,* as bright red needles (250 mg, 20 %, m.p. 189–191 °C). UV (ethanol): 475 nm (ε 500), 285 (sh), 230 (ε 36 000). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.08 (8 H, m) parasubstituted ring protons, 6.97 (2 H, s), 6.55 and 6.07 (4 H, AB-pattern, J 12 Hz) olefinic protons, 4,36 (2 H, m), 3.99 (2 H, m), 3.81 (2 H, m), 3.56 (2 H, m) ferrocene protons. MS (70 eV): *m/e* 414 (100 %, M^+) no other peaks >5 %. Abs. mass 414.107; calc. for $C_{28}H_{22}Fe$ 414.107.

Acknowledgements. We are indebted to Mrs. I. Raston for skillful technical assistance and to the Swedish Natural Science Reseach Council for financial support.

REFERENCES

1. a. Thulin, B., Wennerström, O., Somfai, I. and Chmielarz, B. *Acta Chem. Scand. B 31* (1977) 135; b. Tanner, D., Thulin, B. and Wennerström, O. *Acta Chem. Scand. B 33* (1979) 443.
2. Tanner, D. and Wennerström, O. *Tetrahedron Lett.* (1981) 2313.
3. Tanner, D., Wennerström, O. and Vogel, E. *Tetrahedron Lett.* (1982) 1221.
4. Elix, J. A. *Aust. J. Chem. 22* (1969) 1951.
5. Brown, C. and Sargent, M. V. *J. Chem. Soc. C* (1969) 1818.
6. Tanner, D. and Wennerström, O. *Unpublished results.*
7. Thulin, B., Wennerström, O. and Somfai, I. *Acta Chem. Scand. B 32* (1978) 109.
8. Kasahara, A., Izumi, T. and Shimizu, T. *Chem. Lett.* (1979) 1119.
9. Dewhirst, K. C. and Cram, D. J. *J. Am. Chem. Soc. 80* (1958) 3115; Coulter, C. L. and Trueblood, K. N. *Acta Crystallogr. 16* (1963) 667.
10. Mitchell, R. H. and Boekelheide, V. *J. Am. Chem. Soc. 92* (1970) 3510; Hanson, A. W. and Röhrl, M. *Acta Crystallogr. B 28* (1972) 2032.
11. Cram, D. J. and Dewhirst, K. C. *J. Am. Chem. Soc. 81* (1959) 3963; Trueblood, K., Mirsky, K., Maverick, E., Knobler, C. and Grossenbacker, L. *Acta Crystallogr. B 38* (1982) 2428.
12. Tanner, D. and Wennerström, O. *Acta Chem. Scand. B 34* (1980) 529.
13. Katz, T. and Pesti, J. *J. Am. Chem. Soc. 104* (1982) 346.

Received December 6, 1982.