Medium-sized Cyclophanes. Part 44.[1] Synthesis and Stereochemical Assignments of 9-Substituted 2,11-Dithia[3.3]metacyclophanes

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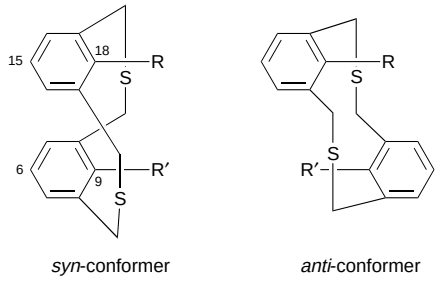
Various *syn*- and *anti*-9-substituted 2,11-dithia[3.3]metacyclophanes are obtained by the coupling reaction of the corresponding 2,6-bis(bromomethyl)benzenes and 1-substituted 2,6-bis(sulfanylmethyl)-4-*tert*-butylbenzenes under highly diluted conditions in 10% ethanolic KOH in the presence of a small amount of $NaBH_4$.

For many years various research groups have been attracted by the structures of the [3.3]MCP ([3.3]MCP = [3.3]metacyclophane) skeleton.[2,3c] When both internal substituents of a [3.3]phane are H, the molecule may be mobile. Mitchell and his co-workers demonstrated in 1970 that 9,18-dimethyl-2,11-dithia[3.3]MCP exists in *syn*- and *anti*-conformers (see Fig. 1), which do not interconvert below 200 °C.[4a] Vögtle and Schunder[5] have made extensive studies of *syn*–*anti* conversions in other dithia[3.3]MCPs, especially in relation to the size of the substituents. When electron-withdrawing groups such as halo, nitro and cyano are present, the yields of the *syn* isomers increase substantially. Very bulky groups, such as *tert*-butyl, decrease the yields of *syn* isomers. Although the effect on the ratio of *syn* and *anti* conformers of dithia[3.3]MCPs was reported, it is still not clear what the effects are, not only with respect to the properties of the internal substituents, but also of having unsymmetrically substituted benzene rings arising from charge-transfer-type interactions between the two benzene rings as well as from the steric effects of the substituents at the 6- and 15-positions.



syn-conformer *anti*-conformer

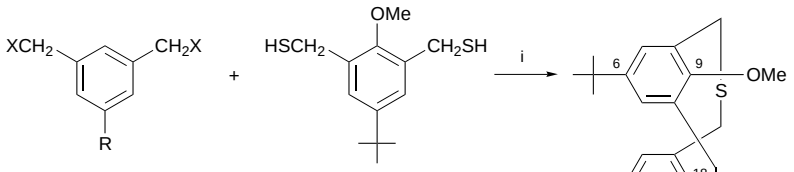
Fig. 1 *Syn*- and *anti*-conformers of dithia[3.3]metacyclophanes

All the previously studied compounds have been internally unsubstituted or methyl-substituted dithia[3.3]MCPs and it is surprising that there are very few reports on the preparation of 9-methoxy analogues. We report here the synthesis and stereochemical assignments of 9-methoxy-2,11-dithia[3.3]-MCPs. The substituent effects on the *syn* and *anti* conformations are also discussed.

The cyclizations of 5-substituted 1,3-bis(halomethyl)benzenes **3a–e** with 4-*tert*-butyl-2,6-bis(sulfanylmethyl)anisole **4a**[6,7a,b,e] were carried out at high dilution in 10% ethanolic KOH and in the presence of a small amount of $NaBH_4$, giving *syn*-9-methoxy-2,11-dithia[3.3]MCPs **5a–e** in 41–67% yields, respectively (Scheme 1).

In contrast, when the cyclizations of 5-substituted 1,3-bis(halomethyl)benzenes **3a–e** with 4-*tert*-butyl-2,6-bis(sulfanylmethyl)toluene **4b** were carried out under similar conditions, **3a–c** and **3e** gave exclusively the *anti*-9-methyl-2,11-dithia[3.3]MCPs **6a–c** and **6e** in 60–71% yields, respectively whereas **3d** gave only *syn*-9-methyl-15-nitro-2,11-dithia[3.3]MCP *syn*-**6d**. Depending on the OMe and Me substitution, different yields (inversion of selectivity) of *anti*- and *syn*-conformers were formed. Thus 9-methoxy analogues are exclusively formed as *syn*-conformers, but 9-methyl analogues are formed as *anti*-conformers.

On treatment of 4-substituted 2,6-bis(bromomethyl)anisoles **8a–d** with **4a**, mixtures of *anti*- and *syn*-2,11-dithia[3.3]MCPs **5h–k** were obtained, except for 6,15-di-*tert*-butyl-2,11-dithia[3.3]MCP **5l**. By careful column chromatography (silica gel, Wako C-300), two conformers, *anti* (*anti*-**5**) and *syn*-2,11-dithia[3.3]MCP (*syn*-**5**), were easily



3a R = H, X = Br
b R = Me, X = Br
c R = Br, X = Cl
d R = NO_2, X = Br
e R = Bu^t, X = Br

4a

syn-**5**

a	R = H	(67%)
b	R = Me	(61%)
c	R = Br	(41%)
d	R = NO_2	(67%)
e	R = Bu^t	(60%)

Scheme 1 *Reagents and conditions:* i, KOH, EtOH, $NaBH_4$, high dilution

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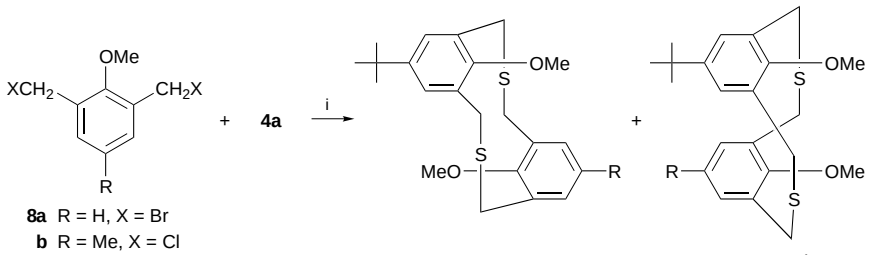
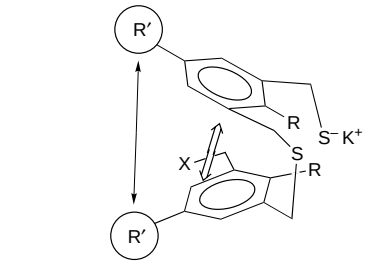


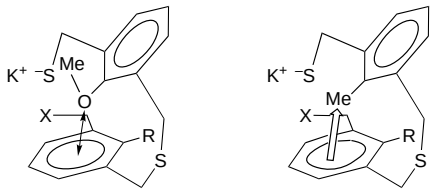
8a R = H, X = Br
b R = Me, X = Cl
c R = Cl, X = Cl
d R = Br, X = Br
e R = Bu^t, X = Cl

		anti-**5**	*syn*-**5**	*anti* : *syn*
h	R = H	(17%)	(74%)	19 : 81
i	R = Me	(31%)	(40%)	44 : 56
j	R = Cl	(12%)	(27%)	30 : 70
k	R = Br	(25%)	(13%)	66 : 34
l	R = Bu^t	(56%)	(0%)	100 : 0

Scheme 4 *Reagents and conditions:* i, KOH, EtOH, $NaBH_4$, high dilution



Steric interaction and π–π stacking interaction



Through-space interaction CH–π interaction

Fig. 3 Reaction intermediate for the cyclization to form [3.3]MCPs

separated. The ^{1}H NMR spectrum of **5l** shows this product to exist exclusively as the *anti* conformer. This result might be attributed to the bulkiness of the *tert*-butyl groups which would inhibit formation of *syn*-**5l**. Accordingly, the proportion of *syn* conformer is observed to increase with decreasing bulkiness of the substituents at the 15-position.

These findings suggest that in the case of the 9-methoxy analogues the through-space interaction between the non-bonding electron pairs of the oxygen atom of the methoxy group and the opposite aromatic π-electrons of the *anti*-conformer may disfavour the formation of this conformer.

In contrast, in the case of a 9-methyl analogue the aromatic π–π interaction between the two opposite benzene rings and the steric crowding at the internal positions 9 and 18 may inhibit the formation of the *syn*-conformer in the [3.3]MCP system, while in turn the CH–π interaction[9] between the methyl and the opposite aromatic π-electrons may favour the formation of an *anti*-conformer during the cyclization process. CH–π interactions involving aliphatic CH moieties are well documented[9] as being either conformation-controlling intramolecular processes or involving crystal-structure-controlling intermolecular forces, especially for inclusion complexes of calixarene derivatives.[10g]

In conclusion, we have demonstrated for the first time a through-space interaction between the non-bonding electron pairs of the oxygen atom of the methoxy group and the opposite aromatic π-electrons which may disfavour the formation of the *anti*-conformer during the coupling reaction of the corresponding 2,6-bis(bromomethyl)benzenes and 4-*tert*-butyl-2,6-bis(sulfanylmethyl)anisole **4a** to afford *syn*-9-methoxy-2,11-dithia[3.3]MCPs **5** exclusively.

Techniques used: ^{1}H NMR, IR, mass. spec.

References: 10

Schemes: 5

Fig. 2: Steric effect on the reaction intermediate for the cyclization to form *syn*-2,11-dithia[3.3]MCPs

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