Substituted [2$_4$]paracyclophanes

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Synthesis, characterization and stereochemistry of new derivatives of [2$_4$]paracyclophane, containing carboxylic acid ester groups, are described.

Cyclophanes in which the aromatic units are linked at the 1,4 positions by unsaturated bridges have been studied extensively.[1] It has been previously reported that *cis*-stereoselective multiple Wittig reactions provide convenient access to [2$_4$]cyclophanetetraene (**1**), and the application of this one-pot synthesis of macrocycles has been demonstrated amply by Wennerström *et al*.[2]

Inspection of molecular models (CPK) of the cyclophanes indicates that in certain conformations, the central cavities may be large enough to allow host–guest inclusion complexes with small substrates. Small-size cyclophanes have the aromatic rings in a perpendicular conformation to the large ring. Due to the rigidity of the framework, such a cavity is stable and would not collapse in the absence of a guest molecule. Therefore, substituted cyclophanes may function as multidentate ligands or as organic matrices for tightening or inclusion of the desired guest. Functional groups linked to the aromatic rings can be used to direct generated semiconductor particles in solution to the cavity of the molecule. The availability of such well defined and monodispersed particles can open up new avenues in the understanding and the application of semiconducting nanomaterials.

The geometry of the cyclophanes is determined by the balance between the resonance energy available due to delocalization of the π-electrons and the steric interaction which avoids planarity. The X-ray structure of the unsubstituted cyclophane **1** shows that the molecule has an essentially planar arrangement in which the individual phenyl rings are tilted towards the main molecular plane at an angle in the range of 27–40°.[3] The steric interaction between the inner hydrogen atoms prevents the compound from attaining a completely planar conformation, despite the more efficient delocalization of the π-electrons in the planar conformation. The conformation in solution is unknown. However, it has been shown[4] that the benzene rings rotate rapidly in the NMR time-scale exchanging inner and outer protons even at −60 °C. Thus, the energy needed to overcome the steric interaction and to compensate for the decrease in resonance energy in the unsubstituted cyclophane is rather low (<20 kJ mol^{-1}).

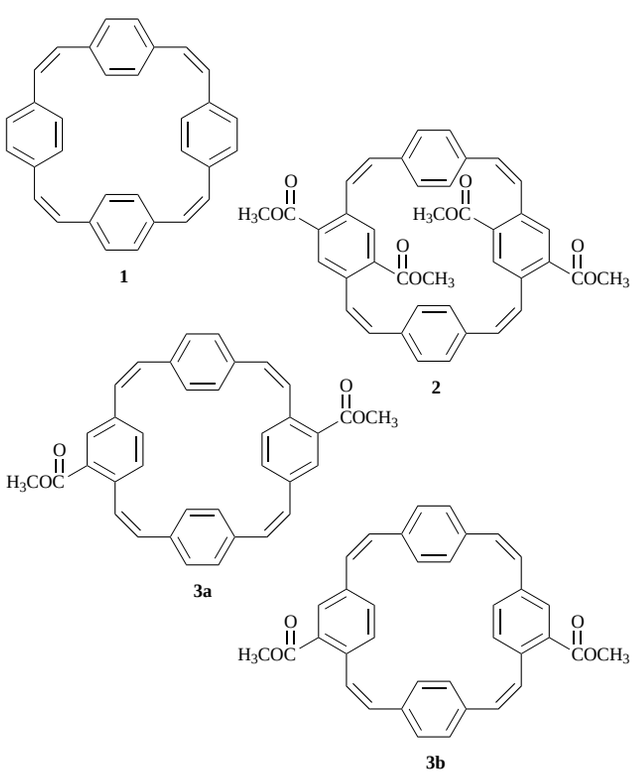
Stability of substituted cyclophanes is greatly affected by the steric compression within the molecule. A bulky substituent can therefore decrease the resonance energy. The key question is, how crucial is the influence of a functional group on the equilibrium between the steric hindrance and tendency to form a planar structure in order to enhance delocalization? Herein we report the synthesis and characterization of the substituted [2.2.2.2]paracyclophanes **2** and **3**, which are derivatives of **1** containing carboxylic acid ester groups, as well as the influence of the substituents on the system's stereochemistry.

Results and discussion

Cyclophane **2** was synthesized by the reaction of an equivalent amount of terephthalaldehyde and the bistriphenylphosphonium salt prepared in a modified procedure from dimethyl 2,5-bis(bromomethyl)terephthalate. It has been characterized by the typical chemical shifts of its aromatic and olefinic protons. As expected from the 24 π-electrons around its perimeter, there is no strong evidence for additional anisotropic shielding effects other than those due to the local aromatic and olefinic subunits and the inductive effect of the ester groups.

The ^{1}H NMR spectrum of compound **2** in $CDCl_3$ at room temperature showed two singlets at 6.77 and 7.88 ppm, assigned to the unsubstituted benzene ring and the substituted ring respectively. The two doublets at 7.00 and 6.54 ppm are due to the double bonds while the higher field singlet at 3.80 ppm is assigned to the methyl ester.

One singlet for the unsubstituted benzene ring indicates a fast rotation in the NMR time-scale. Compared to **1** we assumed



that **2** would show a larger deviation from planarity. Two conformers can be expected in compound **2** due to the hindered rotation of the benzene rings with the bulky ester substituent. These two conformers can interconvert only by the passage of one ester group through the cavity in the centre of the molecule. That there is only one singlet for the substituted ring and for the methyl ester is due to either a fast rotation of the ring or

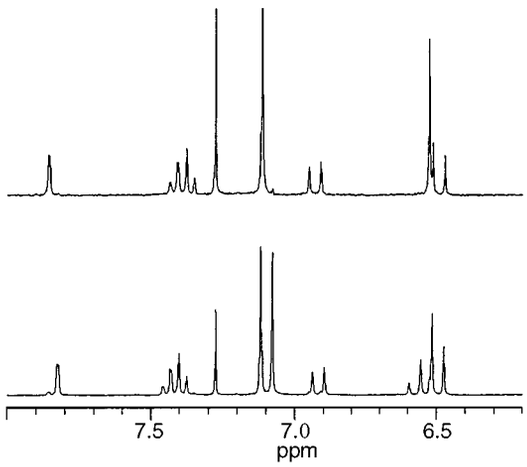


Fig. 1 Expanded ^{1}H NMR spectrum of **3a** (top) and **3b** (bottom)

to the existence of only one stable isomer. It has been pointed out earlier[5] that there is a strong influence of the substituent (R) size on the stability of the two conformers. Changing R = CH_3 to R = CH_2CH_3 changes the ratio between the conformers at room temperature from 2:1 to 9:1, respectively.[5] Therefore, it is reasonable that in this case, due to a steric effect, only one isomer is stable enough to exist. According to the spectroscopic analysis of the compounds with the methyl and ethyl substituents, the stable isomer is the one with the C_2 symmetry.[5] The two bulky groups in the *para* position of the phenyl ring may force the phenyl ring to an almost perpendicular position relative to the plane of the molecule in order to minimize the strong steric interaction. The distortion of the π-system leads to a blue shift (λ_{max} = 286 nm) compared to **1** (λ_{max} = 305 nm) despite the extension of the π-system due to the carbonyl groups. The ring strain in compound **2** seems to be so high that even the formed isomer is unstable and it decomposes in the solid state within a few days at room temperature.

A four-fold Wittig reaction between terephthalaldehyde and the bistriphenylphosphonium salt obtained from methyl 2,5-bis(bromomethyl)benzoate yields two isomers, **3a** and **3b**.

Unlike **2**, where there are two groups on each of the two parallel benzene rings, only one substituent is located on each ring in **3**. Despite their bulkiness, the substituents do not cause the molecule conformation to change drastically from the parent compound. Directing of the substituents away from the central cavity minimizes the influence of the substituent on the stability of the molecule. Thus, two quite stable isomers were formed simultaneously in almost equal amounts.

The UV–VIS absorption (λ_{max} = 296 nm) is somewhere between the unsubstituted compound **1** (λ_{max} = 305 nm) and the tetrasubstituted compound **2** (λ_{max} = 286 nm). As with compound **2**, despite the increased number of electrons in the π-system, there is a blue shift which can be attributed to the distortion from planarity of the molecule. By maintaining the conformation of the skeleton as in **1**, two isomers are available; one has a twofold axis of symmetry, while the other has a mirror plane. Using an achiral solvent, the two isomers which have C_2 and C_s symmetries exhibit very similar ^{1}H NMR spectra at room temperature (Fig. 1).

For the sake of simplicity we shall discuss the protons and carbons of half the molecule, which is symmetrical to the other half. The protons 7(8)H and 21(22)H appear as two singlets (7.07 and 7.12 ppm, respectively) in isomer **3b** and as single line in **3a** (7.11 ppm). Similarly, the two doublets due to 19H and 18H (6.50 and 6.57 ppm) in **3b** appear as a narrow AB-system (6.52 ppm) in **3a** (Fig.1). It is reasonable to assume that in the isomer of C_s symmetry, the difference in chemical shifts between 7(8)H and 21(22)H or 19H and 18H, is more pronounced than in the isomer of C_2 symmetry. However, based on the ^{1}H NMR spectra, an unambiguous assignment cannot be made due to small differences in chemical shifts. An absolute proof can be achieved by the assignment of the interaction between protons or carbon atoms at positions 7 and 6, where an interaction is expected only in the case of the isomer of C_2 symmetry.

Table 1 Crystallographic data for compounds **1** and **3b**

Compound	**1**[3]	**3b**
Formula	$C_{32}H_{24}$	$C_{36}H_{28}O_4$
M_r	408.6	524.6
Space group	*Pcab*	$P2_1$
a/Å	8.251(1)	9.903(1)
b/Å	22.370(4)	21.196(3)
c/Å	25.131(5)	6.646(1)
β/°		95.15(1)
V/Å^3	4638.6	1389.4
Z	8	2
D_c/g cm^{-3}	1.17	1.25
μ(Cu-Kα)/cm^{-1}	5.23	6.07

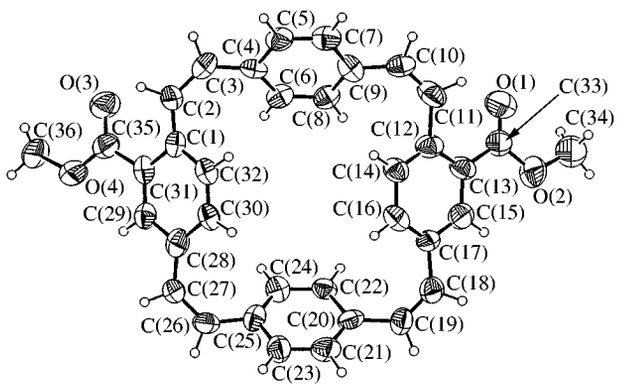


Fig. 2 Molecular structure of **3b**

The ^{1}H NMR spectra of **3a** and **3b** show only one singlet resulting from both interior and exterior aromatic protons of the unsubstituted benzene ring. Therefore the rotation or flipping of the benzene rings must be fast in the NMR time-scale. However, decreasing the temperature to 220 K led to some interesting results. While the spectrum of **3a** did not change, except for a small deviation in chemical shifts, the spectrum of **3b** showed a broadening of the signal at 7.12 ppm. Broadening of only one of the singlets is possible when the two singlets are due to protons on two different benzene rings as in the system with C_s symmetry. In such a system, one of the benzene rings should exhibit a more hindered rotation. Increasing the temperature to 320 K reveals a better resolved spectrum of **3a** that shows very clearly that the signal at 7.11 ppm is in fact a classical AB-system with a J_{HH} value of 8.1 Hz. On this basis the compounds **3a** and **3b** have been identified as those of C_2 and C_s symmetry, respectively.

The X-ray structure of **3b** supports our preliminary assumptions. The two ester groups in **3b** are pointing out of the internal cavity in a C_s symmetry (Fig. 2), while the basic skeleton stays as in the unsubstituted cyclophane (**1**). Relative to the structure of **1**, we find very small differences in bond lengths and bond angles in the cyclophane backbone of **3b**. This result was expected as only one substituent is attached to each benzene ring. That the molecule can direct the substituent out from the internal cavity minimizes the influence of the substituent on the backbone structure.

The two main differences between **3b** and **1** are the angles between the phenyl rings and the molecular plane and the molecular packing. It was expected from the blue shift of the UV spectrum of **3b** that delocalization of the π-electrons over the entire molecule is less efficient. The structure of **3b** shows a larger deviation of the phenyl rings (35.9, 39.7, 40.7, 44.6°) relative to the phenyls in **1** (27.0, 31.1, 35.3, 40.0°).

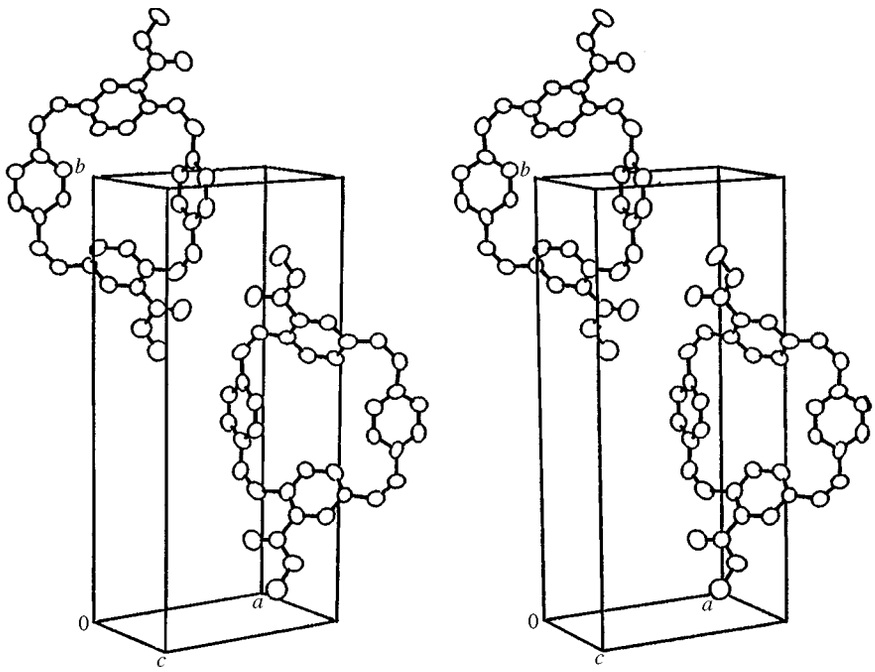


Fig. 3 Stereoscopic view of the molecular packing of **3b**

Due to the bulky substituents and their orientation, the unique molecular packing found in the crystal structure of **1** becomes totally different in **3b** (Table 1). Unlike the four pairs of molecules in **1**,[3] we find in **3b** two molecules in a smaller cell unit and the space group changes to $P2_1$ (Fig. 3).

The skeleton of **1** is unexpectedly planar. Its relatively planar structure requires a considerable increase in the ethylene bond angles (carbons 2, 3, 10, 11, 18, 19, 16 and 27) to an average of 131.9°. It has been suggested[3] that the driving force for the flattening of the molecule would be either to increase resonance or decrease steric interaction within the molecule. As there are 24 π-electrons in the perimeter, it is assumed that the deformation of the bond angles is due mainly to steric interaction.

As its planar structure exists in the solid phase, the unique crystal order in **1**, where every two molecules are facing each other, is a possible explanation for its unexpected planar conformation. However, the X-ray structure of **3b** indicates that this has only a small effect on the crystal order of the molecular structure. The bulky ester groups in **3b** distort the 'stack packing' of the molecules, but the strained planar conformation is still obtained.

Due to a decrease in symmetry in **3b** (relative to **1**) a non bonded interaction between the internal protons on the adjacent phenyl rings can be detected by a NOESY experiment. The spectrum clearly shows NOE interactions between protons 7(8)H and 14H as well as 16H and 21(22)H,[6] despite the large deviation of the phenyl rings relative to the molecular plane in **3b**.

In conclusion, the unexpected planar conformation of the skeleton is probably due to the internal steric interaction. The unique structure of [2.2.2.2]paracyclophane allows the introduction of only one bulky substituent attached to each parallel benzene ring. The ring strain due to the two functional groups in the *para* position on the same benzene ring is influenced drastically by the size of the substituent.

Experimental

NMR Spectroscopy

All NMR analyses were perform on Bruker AMX-400 pulsed FT spectrometer in $CDCl_3$ (internal reference: δ_H 7.27, δ_C 77.0), at 400.13 MHz (^1H) and 100.61 MHz (^{13}C) at 295 K. Coupling constants (J) are given in Hz.

X-Ray crystal structure analyses

Intensity data were measured with RNRAF-NONIUS CAD-4 computer controlled diffractometer, using graphite crystal-monochromated Cu-Kα radiation (λ = 1.541 78 Å).†

Synthesis of cyclophane 2

Dimethyl 2,5-dimethylterephthalate was prepared by chloromethylation of *p*-xylene[7] followed by oxidation with nitric acid (78%),[8] the acyl chloride was esterified (methanol) in toluene[9] (75%, mp 114–115 °C, lit.,[10] 114–116 °C) then brominated[11] with *N*-bromosuccinimide (NBS) in carbon tetrachloride (colorless crystals, 45%, mp 169–170 °C, lit.,[11] 169–171 °C). To a solution of triphenylphosphine (3.1 g, 12 mmol) in toluene (45 ml) at 70 °C, was added dimethyl 2,5-bis(bromomethyl)-terephthalate (2.1 g, 5.5 mmol) in small portions over a period of 1 h. The temperature was gradually raised to 110 °C and gentle reflux was continued for 3 h, the hot mixture was then filtered giving a white solid which was washed several times with toluene and diethyl ether (90%, mp >350 °C).

Cyclophane **2** was prepared by the multiple Wittig reaction[12] of terephthalaldehyde and the above mentioned salt in dry freshly distilled DMF, extracted with diethyl ether (yellowish oil) and purified by column chromatography (silica gel, 1:3 acetone–light petroleum). The upper fractions were combined and chromatographed (silica gel, 25:1 chloroform–acetone). The first fraction was identified as the expected product (1–2%). δ_H 7.88 [4H, s, 14(15)H], 7.00 [4H, d, J_{HH} 12.1, 11(18)H], 6.77 [8H, s, 7(21)H], 6.54 [4H, d, J_{HH} 12.1, 10(19)H], 3.80 (12H, s, CH_3); δ_C 135.2 [C9(20)], 129.5 [C7(21)], 129.7 [C10(19)], 130.3 [C11(18)], 139.8 [C12(17)], 133.8 [C15(14)], 132.4 [C13(16)], 166.4 (CO), 52.7 (CH_3); *m/z* (EI) 640 (M^+, 80%); λ_{max}/nm 286.

Synthesis of cyclophanes 3a and 3b

2,5-Dimethylbenzoic acid (Aldrich) was esterified by methanol and distillated under vacuum (colorless product, 90%, bp 87 °C at mmHg). Methyl 2,5-dimethylbenzoate was brominated[11] with NBS and recrystallized from CCl_4 (colorless crys-

† Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/96.

tals, 40%, mp 81–82 °C). According to the same procedure as **2**, triphenylphosphine (3.9 g, 14.8 mmol) was reacted with methyl 2,5-bis(bromomethyl)benzoate (2.0 g, 6.2 mmol) to give the expected salt (90%).

Cyclophanes **3a** and **3b** were prepared by the reaction of this salt and terephthalaldehyde.[12] The reaction mixture was extracted with diethyl ether and purified by column chromatography (silica gel, methylene chloride). The first yellow fraction (2–3%) collected was composed of the two isomers. The isomers were then isolated (PTLC silica gel, 17 : 1 chloroform–acetone). Isomer **3b** was recrystallized (propan-2-ol and then dichloromethane, yellow crystals, mp 194–195 °C) while isomer **3a** was afforded as a yellowish oil. **3a** δ_H 7.85 (2H, 15H), 7.41 (2H, d, J_{HH} 8.1, 16H), 7.36 (2H, d, J_{HH} 8.1, 14H), 7.11 [8H, s (AB-system), 7(21)H], 6.93 (2H, d, J_{HH} 12.4, 11H), 6.52 [4H, s (AB-system), 19(18)H], 6.49 (2H, d, J_{HH} 12.4, 10H), 3.85 (6H, s, CH_3); δ_C 132.0 (C15), 136.7 (C17), 131.5 (C16), 130.5 (C14), 138.5 (C12), 129.5 (C13), 167.1 (CO), 52.0 (CH_3), 130.1 (C11), 128.8 (C10), 135.5 (C9), 129.3 (C7), 128.6 (C21), 135.6 (C20), 130.9 (C19), 128.7 (C18); *m*/*z* (EI) 524 (M^+, 100%); λ_{max}/nm 296. **3b** δ_H 7.83 (2H, s, 15H), 7.44 (2H, d, J_{HH} 8.0, 16H), 7.39 (2H, d, J_{HH} 8.0, 14H), 7.12 (4H, s, 21H), 7.07 (4H, s, 7H), 6.92 (2H, d, J_{HH} 12.3, 11H), 6.57 (2H, d, J_{HH} 12.3, 18H), 6.50 [4H, d, J_{HH} 12.3, 10(19)H], 3.84 (6H, s, CH_3); δ_C 131.5 (C15), 137.1 (C17), 131.7 (C16), 130.6 (C14), 138.3 (C12), 129.7 (C13), 167.1 (CO), 52.0 (CH_3), 129.6 (C11), 129.1 (C10), 135.5 (C9), 129.0 (C7), 128.9 (C21), 135.5 (C20), 130.7 (C19), 128.9 (C18); *m*/*z* (EI) 524 (M^+, 100%); λ_{max}/nm 296.

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