Synthesis of annularly functionalised BINOL-based chiral cyclophanes

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Chiral cyclophanes with annular functionality were synthesised by coupling carbonyl dibromides with (*S*)-BINOL. Semi-empirical calculations by MOPAC (PM3) were also performed on the cyclophanes prepared to view their cavity sizes.

Keywords: chiral cyclophanes, annular functionality

The wide applications of macrocycles emphasise their efficacy in various fields such as molecular recognition,[1] metal extraction and separation,[2] medical diagnostics[3] and drug delivery systems,[4] chemical synthesis,[5] polymer chemistry[6] and in food science.[7] The macrocycles also play a vital role in molecular architecture and topology[8] and more recently in the field of nano-chemistry.[9] Chiral cyclophanes[1,10] have substantial significance in host–guest complexation since they show stereoselective binding with chiral guest molecules. Thus, synthesis of chiral macrocycles with varied functionality is becoming more important. In particular, BINOL-based cyclophanes[11] are gaining significance since they act as a stationary phase together with chromatographic silica in chiral columns.[12] Hence, the synthesis of BINOL-based chiral cyclophanes with various functionalities is particularly important in order to analyse their utility in this context. In our earlier reports,[11c-f,13] we demonstrated the synthesis of BINOL-based chiral cyclophanes with intra-annular functionality. Herein, we report the synthesis of BINOL-based chiral cyclophanes incorporating mono-, di- and polycarbonyl groups in the annulus ring of the cyclophanes. Semi-empirical calculations were also performed on the prepared cyclophanes to view their cavity sizes for accommodating guest molecules.

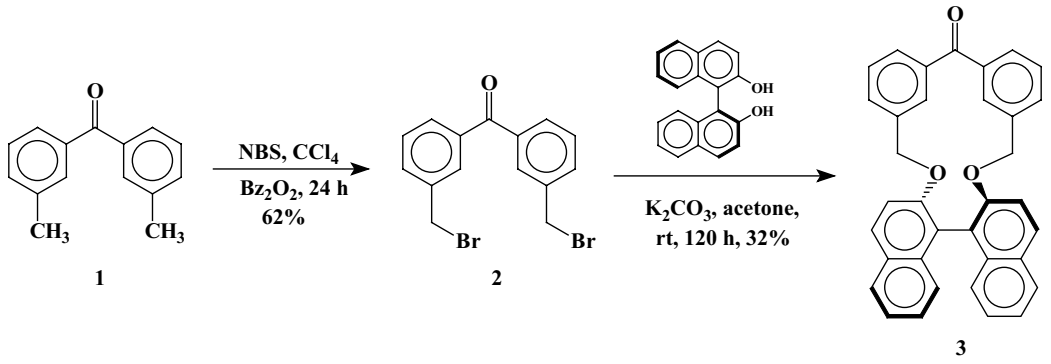
Results and discussion

The strategy for the synthesis of BINOL-based chiral cyclophanes is to prepare dibromides with a carbonyl moiety and couple them with (*S*)-BINOL to furnish the chiral cyclophanes incorporating a carbonyl moiety in the annulus ring of the cyclophanes. We were particularly interested in the use of various benzophenone dibromides** as a core moiety for this purpose. Preparation of 3,3'-dimethyl- and 4,4'-dimethylbenzophenones is straightforward using literature procedures.[14] Reaction of 3,3'-dimethylbenzophenone (**1**) with 2.2 equivalents of NBS in the presence of benzoyl peroxide in CCl_4 for 24 h afforded dibromide **2**[15**] in 62% yield. Reaction of equimolar amounts of dibromide **2** with (*S*)-BINOL in the presence of K_2CO_3 in acetone at room temperature for 120 h gave a crude product, which was purified using column chromatography to furnish the cyclophane **3** in 32% yield (Scheme 1).

The optical rotation of the cyclophane **3**, which gave satisfactory elemental analysis, was found to be $[\alpha]_D^{25}$ –90.0 (*ca* 0.2, $CHCl_3$). The ^{1}H NMR of carbonyl cyclophane **3** showed doublets at δ 4.85 and 5.01 (J = 13.7 Hz) for methylene protons along with a multiplet at δ 7.05-7.91 for aromatic protons. In ^{13}C NMR, the cyclophane **3** showed 17 carbons in the aromatic region in addition to the signal at δ 69.1 for methylene carbons. The monomeric structure of the cyclophane **3** was shown by the mass spectrum of **3**, which showed the molecular ion peak at *m/z* 492. Semi-empirical calculations[16] using MOPAC (PM3) on the cyclophane **3** showed a small C_2 symmetric cavity of the size 4.56 × 4.56 Å. The cyclophane **3**, being C_2 symmetric in nature exhibits a C_2 symmetric cavity (Fig. 1).

Likewise, radical bromination of 4,4'-dimethylbenzophenone (**4**) using NBS in CCl_4 gave 4,4'-bis(bromomethyl)benzophenone (**5**)[17**] in good yield, which was reacted with (*S*)-BINOL in the presence of K_2CO_3 in acetone at room temperature for 120 h to give the cyclophane **6** in 43% yield (Scheme 2).

The ^{1}H NMR of **6** displayed doublets at δ 5.01 and 5.18 (J = 13.7 Hz) for the methylene protons displayed the aromatic protons. The ^{13}C NMR of the cyclophane **6** showed 14 signals for aromatic carbons and a signal for carbonyl at δ 194.2 and one signal for methylene carbon at δ 70.0. The dimeric structure of the cyclophane **6** was corroborated by the FAB-MS spectrum, which shows the molecular ion



Scheme 1

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** See Safety Caution in Experimental.

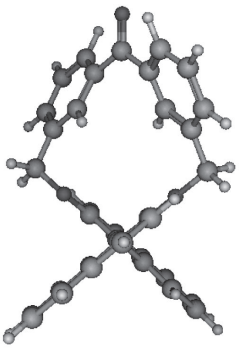


Fig. 1 Energy minimised structure of cyclophane **3**

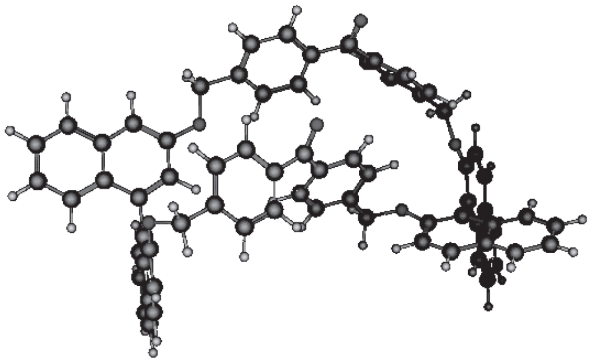


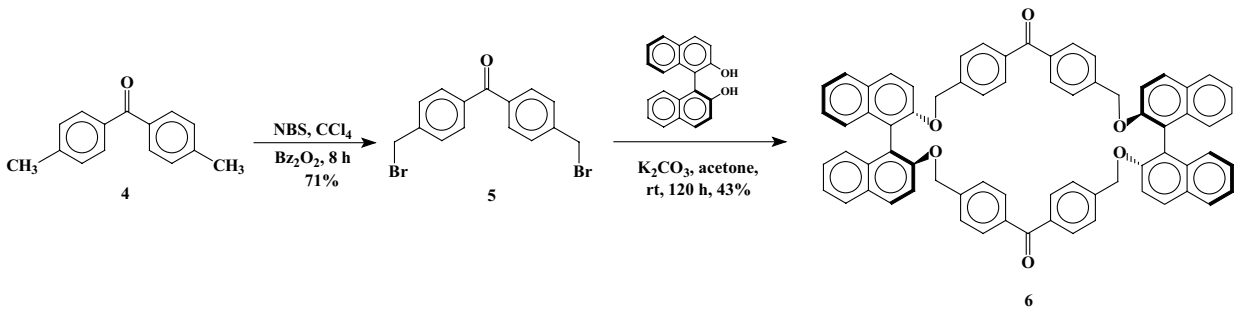
Fig. 2 Energy minimised structure of cyclophane **6**.

peak at *m/z* 984. The cyclophane **6** showed the optical rotation $[\alpha]_D^{25}$ –200 (*c* 0.16, $CHCl_3$) and gave satisfactory elemental analysis. The semi-empirical calculations by MOPAC (PM3) showed a medium-sized cavity within the cyclophane **6** of the size 11.56 Å × 8.24 Å (Fig. 2).

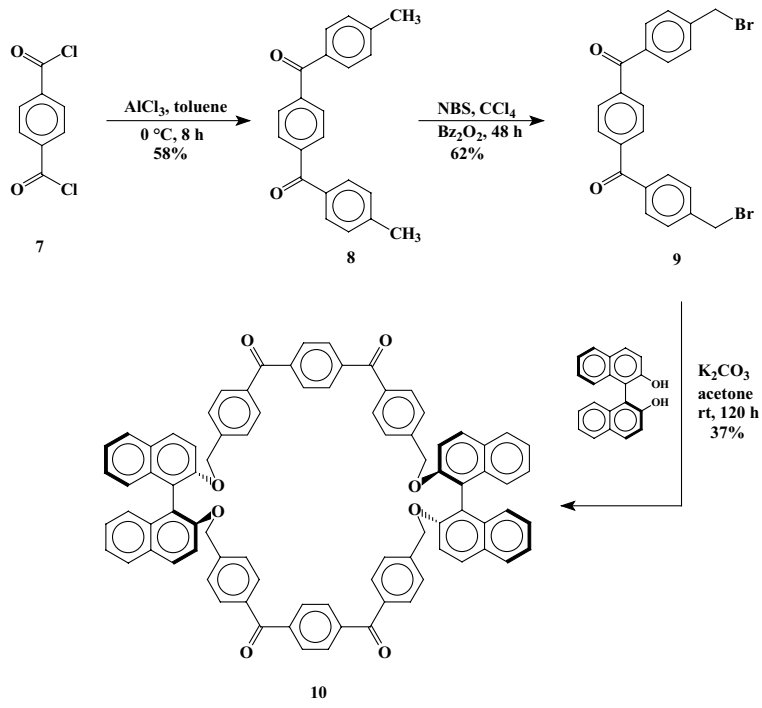
The carbonyl carbons were placed at a distance of 8.24 Å from each other. The oxygen atom of one BINOL moiety is placed 11.56 Å from the diagonal oxygen atom of the other BINOL moiety of the cyclophane **6** in the minimal energy configuration.

Interestingly, when the *p*-isomer of the dibromide **9**[13**] derived from terephthalyl chloride (**7**) was subjected to similar conditions with one equiv. of (*S*)-BINOL, the resultant cyclophane **10** was obtained found to be dimeric (Scheme 3).

The cyclophane **10** was characterised by IR, ^1H and ^{13}C NMR, mass spectrometric and optical rotation data. The dimeric structure was revealed by the FAB-MS data, which showed the molecular ion peak at *m/z* 1192. The cyclophane **10** also possesses a linear cavity as revealed by the semi-empirical calculations by MOPAC (PM3). The



Scheme 2



Scheme 3

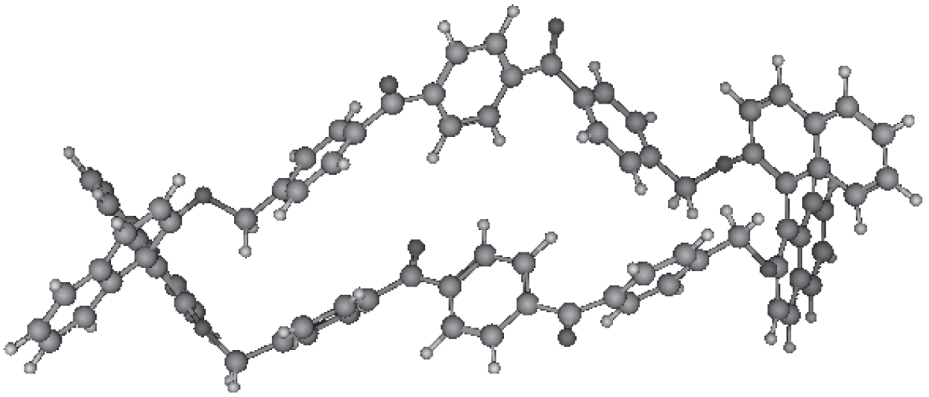


Fig. 3 Energy minimised structure of cyclophane 10.

distance between a carbonyl carbon of one of the bridging moieties and the nearest carbonyl carbon of the other bridging moiety is 5.86Å. (Fig. 3).

Reduction of these chiral cyclophanes to respective chiral alcohols and the uses of them as catalysts for organic transformations are under investigation.

Experimental

Safety caution: All of the bromomethyl compounds mentioned in this paper are severe irritants.

All the melting points are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on JEOL GSX 400 NMR spectrophotometer at 400 and 100.4 MHz respectively. The mass spectra were recorded on a JEOL JMS-DX 303 HF (EI, 70 eV) and FAB-MS on a JEOL SX 102/DA-6000 using *m*-nitrobenzyl alcohol (NBA) as the matrix. The optical rotations were recorded on an Autopol-II automatic spectropolarimeter. The organic extracts of crude products were dried over anhydrous sodium sulfate. Column chromatography was carried out with silica gel (ACME, 100–200 mesh). 3,3'- and 4,4'-dimethylbenzophenone were synthesised using the literature procedures.[15]

Preparation of 3,3'-bis(bromomethyl)benzophenone **(2)**:[15**] Freshly prepared NBS (0.779 g, 4.4 mmol) was added in portions to a solution of 3,3'-dimethylbenzophenone (0.42 g, 2.0 mmol) in the presence of benzoyl peroxide in CCl_4 (100 ml) and the reaction mixture was refluxed for 48 h, after which it was cooled and succinimide was filtered off. Evaporation of the organic layer gave the crude product which was purified by column chromatography using hexane: $CHCl_3$ (2 : 1) as eluant. Yield 62%; M.p 57°C (lit.[15] 59°C); IR (KBr, cm^{-1}) 1656 (C=O); ^{1}H NMR δ 4.47 (s, 4H), 7.23–7.56 (m, 8H).

Preparation of 4,4'-bis(bromomethyl)benzophenone **(5)**:[17**] Following the above procedure, the dibromide **5** was obtained from 4,4'-dimethylbenzophenone as a colourless solid. Yield 71%; M.p 130–131°C (lit.[17] 135–137°C); IR (KBr, cm^{-1}) 1658 (C=O); ^{1}H NMR δ 4.57 (s, 4H); 7.54 (d, 4H, *J* = 8.3 Hz); 7.83 (d, 4H, *J* = 8.3 Hz).

Synthesis of chiral cyclophane **3**: The dibromide **2** (0.368 g, 1.0 mmol, (*S*)-BINOL (0.286 g, 1.0 mmol) and K_2CO_3 (13.8 g, 0.1 mol) in acetone (400 ml) was stirred at room temperature for 120 h. The reaction mixture was then evaporated to give a residue, which was extracted using $CHCl_3$ (3 × 100 ml). The organic layer was washed with water (2 × 100 ml); NaOH (150 ml); finally brine (150 ml) and evaporated. The crude product was purified over silica gel using hexane: $CHCl_3$ (1: 1). Yield 32%; M.p 170–172°C; $[\alpha]_D^{25}$ –90.0 (*c* 0.2, $CHCl_3$); IR (KBr, cm^{-1}) 1658 (C=O); ^{1}H NMR δ 4.85 (d, 2H, *J* = 13.7 Hz); 5.01 (d, 2H, *J* = 13.7 Hz); 7.05–7.91 (m, 20H); ^{13}C NMR δ 69.1, 118.3, 120.5, 123.2, 124.3, 125.4, 126.1, 126.5, 127.1, 127.8, 128.0, 129.3, 134.1, 136.1, 138.5, 139.4, 153.1, 194.8; *m/z* (EI, 70 eV) 492 (M^+, 7), 467 (9), 439 (13), 368 (16), 302 (23), 257 (20), 217 (18), 183 (100), 155 (12), 129 (28), 97 (36); Anal. Calcd for $C_{35}H_{24}O_3$: C, 85.3; H, 4.9. Found: C, 85.3; H, 4.9.

Synthesis of chiral cyclophane **6**: Following the procedure as mentioned above, the chiral cyclophane **6** was synthesised from the dibromide **5** (0.368 g, 1.0 mmol) and (*S*)-BINOL (0.286 g, 1.0 mmol). Yield 43%; M.p 190°C; $[\alpha]_D^{25}$ –200 (*ca* 0.16, $CHCl_3$); IR (KBr, cm^{-1}) 1658 (C=O); ^{1}H NMR δ 5.01 (d, 4H, *J* = 13.7 Hz); 5.18 (d, 4H, *J* = 13.7 Hz); 6.93 (d, 8H, *J* = 7.8 Hz); 7.19–7.35 (m, 16H); 7.39 (d, 8H, *J* = 9.3 Hz); 7.85–7.97 (m, 8H); ^{13}C NMR δ 70.0, 115.3, 120.5, 123.9, 124.2 125.3, 125.4, 126.2, 126.6, 128.0, 129.5, 134.1, 136.1, 142.1, 153.1, 194.2; *m/z* (FAB-MS) 984 (M^+); Anal. Calcd. For $C_{70}H_{48}O_6$: C, 85.3; H, 4.9. Found: C, 85.3; H, 4.9.

Preparation of 1,4-ditoluoylbenzene **(8)**:[18] To a solution of terephthalyl chloride (2.03 g, 10 mmol) in dry toluene (200 ml) anhydrous $AlCl_3$ (6.67 g, 50 mmol) was added over a period of 1 h at 0°C. After stirring vigorously for 8 h, during which the evolution of hydrogen chloride ceased, the reaction mixture was poured over ice followed by the addition of conc. HCl (50 ml). This reaction mixture was extracted with ether (2 × 100 ml) and dried. Evaporation of the organic layer gave a residue, which was recrystallised from $CHCl_3$: hexane (1: 3). Yield 58%; M.p. 121°C –123°C; IR (KBr, cm^{-1}) 1658 (C=O); ^{1}H NMR δ 2.41 (s, 6H); 7.31 (d, 4H, *J* = 7.8 Hz); 7.73 (d, 4H, *J* = 7.8 Hz); 8.07 (s, 4H); ^{13}C NMR δ 28.7, 128.2, 129.0, 132.1, 137.2, 137.9, 143.6, 195.2; *m/z* (FAB-MS) 314 (M^+); Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.8. Found: C, 83.9; H, 5.7.

Preparation of 4,4''-bis(bromomethyl)-1,4-dibenzoylbenzene **(9)**:[13**] To a solution of 4,4'-ditoluoylbenzene (**8**) (0.618 g, 2.0 mmol) in CCl_4 (100 ml) in the presence of benzoyl peroxide was added freshly prepared NBS (0.779 g, 4.4 mmol) in portions and the reaction mixture was refluxed for 48 h. The reaction mixture was cooled and the succinimide was filtered off. Evaporation of the reaction mixture gave the crude dibromide which was recrystallised from hexane: $CHCl_3$ (2: 1). Yield 62%; M.p. 139°C (lit.[13] 138–139°C); IR (KBr, cm^{-1}) 1657 (C=O); ^{1}H NMR δ 4.65 (s, 4H); 7.52 (d, 4H, *J* = 8.3 Hz); 7.80 (d, 4H, *J* = 8.3 Hz); 8.10 (s, 4H); ^{13}C NMR δ 33.4, 128.8, 129.3, 131.5, 136.8, 137.8, 143.8, 195.7; *m/z* (FAB-MS) 474 (M^+ + 2); 473 (M^+ + 1); 472 (M^+).

Synthesis of chiral cyclophane **(10)**: The dibromide **9** (0.472 g, 1.0 mmol); (*S*)-BINOL (0.286 g, 1.0 mmol) and K_2CO_3 (13.8 g, 0.1 mol) in acetone (400 ml) were stirred at room temperature for 120 h. The reaction mixture was then evaporated to give a residue, which was extracted using $CHCl_3$ (3 × 100 ml). The organic layer was washed with water (2 × 100 ml); NaOH (150 ml); finally brine (150 ml) and evaporated. The crude product was purified over silica gel using hexane: $CHCl_3$ (1: 1); Yield 37%; M.p 163°C; $[\alpha]_D^{25}$ –83.33 (*ca* 0.9, $CHCl_3$); IR (KBr, cm^{-1}) 1656 (C=O); ^{1}H NMR δ 5.06 (d, 4H, *J* = 14.2 Hz); 5.22 (d, 4H, *J* = 13.7 Hz); 7.03 (d, 8H, *J* = 7.3 Hz); 7.23–8.01 (m, 40H); ^{13}C NMR δ 70.5, 115.5, 120.6, 123.9 125.4 126.5, 127.9, 129.5, 129.9, 130.3, 130.2 135.8, 135.9 140.9, 142.8, 143.9, 153.7, 195.7; *m/z* (FAB-MS) 1192 (M^+); Anal. Calcd for $C_{84}H_{56}O_8$: C, 84.5; H, 4.7. Found: C, 84.5; H, 4.7.

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