Synthesis and Conformational Analysis of Spirocyclopropane- and Spirooxirane-annelated Dinaphthobicyclo [4.4.1] undecanes

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https://doi.org/10.15017/7900

出版情報：九州大学機能物質科学研究所報告. 12 (2), pp.131-135, 1998-12-25. 九州大学機能物質科学研究所
バージョン：
権利関係：

Synthesis and Conformational Analysis of Spirocyclopropane- and Spirooxirane-annelated Dinaphthobicyclo[4.4.1]undecanes

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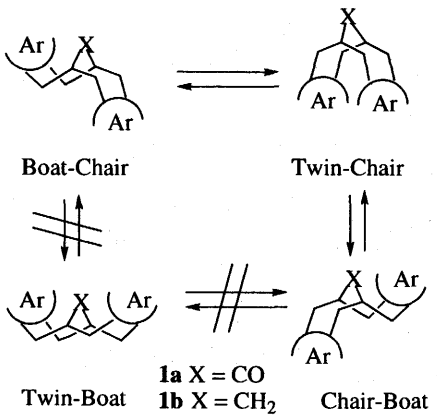
The preparation and conformational analysis of spirocyclopropane- and spirooxirane-annelated dinaphtho[*c,h*]bicyclo[4.4.1]undecane derivatives **9**, **10**, and **11** are reported. Compounds **9**, **10**, and **11** exist in equilibrium of two nonequivalent chair-boat conformers, of which the predominant conformer in the solution was studied. ^{1}H-NMR spectroscopic analysis at -60° C and the calculation of the dipole moment of the conformer revealed that the ratio of the conformers of **9**, **10**, and **11** is dependent on the polarity of the solvent.

Introduction

The development of dynamic NMR spectroscopy techniques enables us to investigate conformational equilibria.[1] In cyclophane chemistry, conformational analysis has been studied extensively,[2] especially in the field of [3.3]meta- and orthocyclophanes.[3,4] For bicyclo-[4.4.1]undecane, there are several possible conformations. The main conformers are the chair-boat, boat-chair, twin-chair, and twin-boat. Of the four conformers, the twin-boat type usually is the least stable and the twin-chair the most stable.[5]



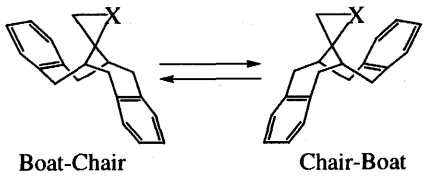
1a X = CO
1b X = CH_2

Ar = benzo, 2,3-naphtho

Scheme 1

Previously, it was reported that in the case of the benzo- and naphto-annelated bicyclo[4.4.1]undecandiene-11-ones **1a**, which possess a [3.3]orthocyclophane framework, the twin-chair conformer could not be detected, due to electronic repulsion between the π-electrons of the two layered benzo-units[6] (Scheme 1).

Introducing a bulky substituent onto the methylene bridge of the bicyclo[4.4.1]undecane fixes the compound in its twin-chair conformation, as is exemplified by the corresponding acetal or tertiary alcohol.[7] Recently, we have reported on the conformational analysis of spirocyclopropane-annelated dibenzobicyclo[4.4.1]undecanes **2-4**, which exist in an equilibrium of two nonequivalent chair-boat conformers (Scheme 2).[8]



2 X = O
3 X = CCl_2
4 X = CBr_2

Scheme 2

In the course of our continuous investigation on the conformation of bicyclo[4.4.1]undecanes, we report on the conformational behavior of spirocyclopropane- and spirooxirane-annelated dinaphtho[*c,h*]bicyclo[4.4.1]undecanes.

Received November 20, 1998
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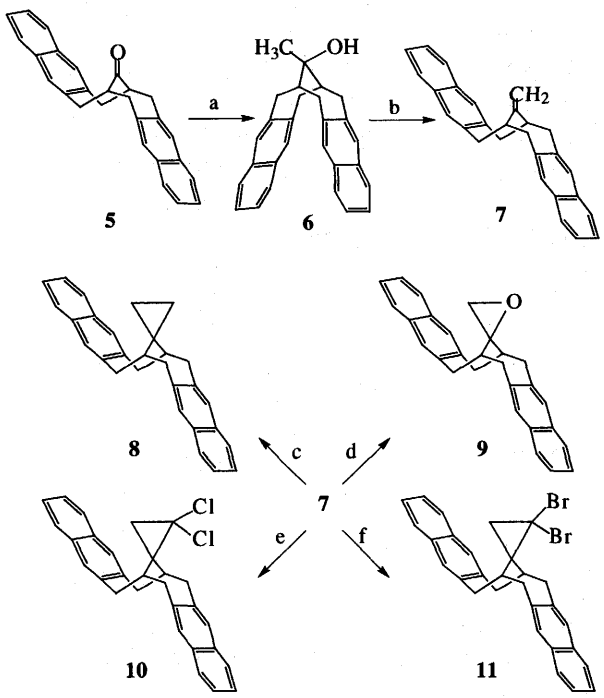
Results and Discussion

Preparation of dinaphtho[c,h]bicyclo[4.4.1]undecanes

The framework of dinaphtho[*c,h*]bicyclo[4.4.1]undecane was prepared by the base-catalyzed reaction of dimethyl 3-oxoglutarate and 2,3-bis(bromomethyl)naphthalene under phase-transfer conditions, as has been reported previously.[9] The reaction of **5** with methylmagnesium iodide gave the tertiary alcohol **6** in a good yield.[9] The alcohol **6** was dehydrated with 20% sulfuric acid in ethanol under reflux, to afford olefin **7** in 73% yield.

Spirocyclopropane-annelated dinaphthobicyclo[4.4.1]undecanes were synthesized from olefin **7**. The cyclopropane **8** was prepared by Simmons-Smith reaction of the olefin **7** in 19% yield. Although the dihalo-substituted spirocyclopropane could be constructed by [2+1]cycloaddition of **7** with dihalocarbenes under phase-transfer conditions, yields of **10** and **11** were very low. It was reported previously that, in the case of the dibenzobicyclo[4.4.1]undecane, introduction of a spirocyclopropane proceeds in fairly good yields.[8] In the dinaphtho-analogs the introduction of the cyclopropane does not proceed easily, owing to the steric hinderance of the naphtho rings. Contrary to these results, oxirane **9** was easily obtainable in 84 % yield by epoxidation of **7** with *m*-CPBA.



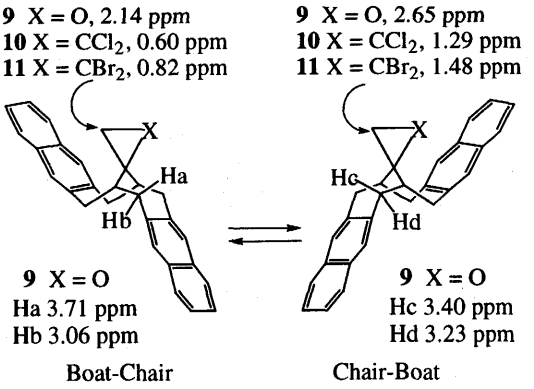
a: CH_3I-Mg / Et_2O-CH_2Cl_2 (65%),
b: 20% H_2SO_4-EtOH (73%),
c: CH_2I_2-Zn-CuCl / Et_2O (19%)
d: *m*-CPBA / CH_2Cl_2 (84%)
e: 50%NaOH aq. / $CHCl_3$ / 15-crown-5 (12%)
f: 50%NaOH aq. / $CHBr_3$ / 15-crown-5 /Benzene (10%)

Scheme 3

Conformational analysis by ^{1}H-NMR spectroscopy and calculation of the dipole moment

Introduction of the cyclopropane ring onto the methylene bridge does not freeze the conformation of the dinaphtho-[*c,h*]bicyclo[4.4.1]undecanes. Compounds **9**, **10**, and **11** are flexible and exist as an equilibrium of a mixture of two distinguishable chair-boat (C-B) and boat-chair (B-C) conformers (Scheme 4), as evidenced by broad peaks in the ^{1}H NMR spectrum at room temperature. These peaks resolve to sharp signals at a lower temperature.

In the ^{1}H NMR spectra of **9**, **10** and **11** at -60 ℃, one of the two methylene groups of the spirocyclopropane moiety appears at a higher magnetic field than the other, since the methylene protons take their position above the naphthalene ring and are shielded by the ring current (δ 2.14 ppm for **9**B-C, 2.65 ppm for **9**C-B; 0.60 ppm for **10**B-C, 1.29 ppm for **10**C-B; 0.82 ppm for **11**B-C, 1.48 ppm for **11**C-B; in $CDCl_3$ at -60 ℃). The ratio of B-C to C-B conformers for **10** and **11** was determined from these peaks. It was difficult to estimate the ratio of the conformers of **9** by these peaks, because of an overlapping of the signals. Fortunately, the benzylic protons show two types of double-doublet pattern, and these resolved sharp peaks could be used to determine the ratio of the conformer of **9** (δ 3.71 and 3.06 ppm for **9**B-C, 3.40 and 3.23 ppm for **9**C-B; in $CDCl_3$ at -60 ℃) (Scheme 4).



Scheme 4

The conformers of **9**, **10**, and **11** were assigned and the ratios of the conformers were determined by ^{1}H NMR spectra at -60 ℃. These results are summarized together with the dipole moment of the B-C and C-B conformers of **9**, **10**, and **11**, calculated by PM3[10] (Table 1).

Table 1 Conformer ratios[a] and calculated dipole moment

Compd.	Dipole moment[b] (B-C/C-B)	⊿D (C-B - B-C)	Ratio of B-C/C-B conformers
2	1.38 D/2.06 D	0.68	68/32
3	1.07 D/1.61 D	0.54	31/69
4	1.21 D/1.78 D	0.57	37/63
9	1.31 D/2.19 D	0.88	87/13
10	1.03 D/1.67 D	0.64	64/36
11	1.16 D/1.87 D	0.71	76/24

[a] In $CDCl_3$, at -60 °C, [b]PM 3 calculation

Dinaphthobicyclo[4.4.1]undecanes **10** and **11** exist predominantely in the B-C conformation. This is in contrast to dibenzobicyclo[4.4.1]undecanes **3** and **4** which prefer the C-B conformation. Temperature dependence on the conformer ratios is clear in **3** and **4**, and the B-C conformers are estimated to be present in more than 50% in $CDCl_3$ at 25℃.[7] In our former research, we have concluded that the conformer ratios of **2**, **3**, and **4** are controlled by $\Delta S°$.[7] In order to determine the parameters $\Delta H°$, $\Delta S°$, and $\Delta G°$ of **9**, **10**, and **11** by van't Hoff plot, dynamic ^{1}H NMR spectroscopy in $CDCl_3$ over a temperature range of -60 ℃ to 0 ℃ was carried out. Unfortunately, all efforts failed owing to the fact that the values of the temperature dependence of the conformer ratio was not observed clearly, and the parameters could not be established accurately.

The oxiranes **2** and **9** prefer the B-C conformation in order to avoid the electronic repulsion between the lone-pair electrons of the oxygen atom and the π-electrons of the benzo ring.

There is some correlation between the ratio of the B-C conformer and the calculated dipole moment. Interestingly and unexpectedly, the ratio of the B-C conformer increases, as the difference of the calculated dipole moment of the respective conformers increases. Especially, in the case of the dinaphthobicyclo[4.4.1]-undecanes **9**, **10**, and **11**, a good correlation was observed.

The authors suggest that this effect is due to different arrangements of the solvent sphere in the B-C- and the C-B conformers. It can be expected that a polar solvent shows the highest ordering near the largest charge separation within the solvated molecule, *i.e.* near the functionality of highest electronegativity. In the molecules under discussion the functionalities with the highest electronegativity rest within the bridge of the [4.4.1]undecane subunit. In the C-B conformers of the dinaphtho derivatives one of the naphtho units effectively dissects the region a potentially perfectly structured solvent sphere would occupy. The impairment means a destabilization of the C-B conformer in favor of the B-C conformer, in which solvation is unimpaired. This destabilization in favor of the B-C conformer increases with an increase of enthalpy gained by the solvent sphere, that is with an increase of the dipole moment of the solvated molecule. On the other hand, in the benzo-derivatives the benzo-unit in the C-B conformer affects the solvent sphere to a much lesser degree, so that the ratio of conformers is determined by the dipole moment of the molecules and their effective enthalpy differences ($\Delta \Delta H_f°$), which have been calculated to be less than 1.2 kcal/mol for all the conformer pairs discussed.

Experimental

General - All mps were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Nippon Bunko IR-700 spectrometer as KBr pellets. ^{1}H NMR spectra (internal Me_4Si) were measured on a JEOL EX270 NMR spectrometer unless stated otherwise. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS 700 instrument. Mass spectral analyses were performed under 70 eV electron-impact (EI) conditions. Column chromatography was carried out on silica gel (Wako gel, C300). Recycle preparative HPLC was carried out on a Japan Analytical Industry LC 908.

15-Methylidene-5,6,7,12,13,14-hexahydro-6,13-methanodinaphtho[a,f]cyclodecene (7). - An ethanolic solution (80 mL) of 11-hydroxy-11-methyl-dinaphtho[2,3-*c*;2',3'-*h*]bicyclo[4,4,1]undeca-3,8-diene **6** (1.78 g, 5.42 mmol) and sulfuric acid (20%, 150 mL) was heated under reflux for 6 h. After being cooled, the reaction mixture was extracted with dichloromethane, washed with aqueous $NaHCO_3$ solution and water, dried over $MgSO_4$, and evaporated *in vacuo* to leave a residue, which was recrystallized from benzene to give **7** (1.83 g, 73%). **7**: colorless prisms; mp 223-224.5 ℃ (benzene); IR(KBr) 1639, 1498, 895, 876, 767, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$ at r.t.) δ 2.40-3.66 (10H, m), 4.43 (2H, s), 7.22-7.95 (12H, m); ($CDCl_3$ at -60 ℃.) δ 2.50-3.66 (4H, m), 3.02-3.18 (4H, m), 3.18-3.38 (4H, m), 4.45 (2H, s), 7.32-7.44 (2H, m), 7.22-7.52 (4H, m), 7.70-7.82 (4H, m), 7.82-7.90 (2H, m); MS.(m/z) 360(M^+); HRMS (M^+) Calcd for $C_{28}H_{24}$ 360.1878, Found 360.1880; E.A. Found: C, 93.13; H, 6.67. Calcd. for $C_{28}H_{24}$, 93.29; H,6.71.

Spiro[cyclopropane-1,15'-{5,6,7,12,13,14-hexa-hydro-6,13-methanodinaphtho[a,f]cyclodecene}] (8). - Under an inert atmosphere, a mixture of zinc powder (0.73 g, 11.1 mmol) and cuprous chloride (1.10 g, 11.1 mmol) in dry ether (50 mL) was heated under reflux for 30 min. To its mixture, a dry ether solution (100 mL) of **7** (400 mg,

11.1 mmol) and diiodomethane (1.49 g, 5.55 mmol) was added dropwise for 20 min. The whole mixture was heated under reflux for 4 days, poured into 10% sulfuric acid, extracted with dichloromethane, washed with aqueous $NaHCO_3$ solution and water, dried over $MgSO_4$, and evaporated *in vacuo* to leave a residue.

The epoxidation of unreacted starting material **7** was carried out to remove **7**. A solution of *m*-CPBA (70%, 550 mg, 2.22 mmol) in dichloromethane (20 mL) was added dropwise at 0 ℃ to a solution of mixture of **7** and **8** in dichloromethane (20 mL). The reaction mixture was stirred for 1h at 0 ℃ and for 2h at room temperature. Then it was washed with aqueous 10% NaOH solution and water, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to leave a residue. And the residue was column chromatographed with chloroform-hexane(1:1) to give **8** (78 mg, 19%) and **9** (205 mg, 49%). **8**: colorless prisms; mp 226-227.5 ℃ (cyclohexane); IR(KBr) 1498, 1461, 1016, 874, 740 cm^{-1}; ^1H NMR ($CDCl_3$ at r.t.) δ -0.45- -0.02 (2H, m), 0.02-0.45 (2H, m), 1.35-1.50 (2H, m), 2.55-2.88 (2H, m), 2.88-3.20 (2H, m), 3.35-3.72 (2H, m), 3.35-3.72 (2H, m), 7.30-7.52 (6H, m), 7.52-7.88 (6H, m); ($CDCl_3$ at -60 ℃.) δ -0.24 (2H, t, J = 7.1 Hz), 0.29 (2H, t, J = 7.1 Hz), 1.36-1.54 (2H, m), 2.72 (4H, d, J = 6.9 Hz). 3.07 (2H, dd, J = 13.9, 5.3 Hz), 3.53 (2H, d, J = 13.9 Hz), 7.36-7.56 (4H, m), 7.68-7.92 (4H, m); MS.(m/z) 374(M^+); HRMS (M^+) Calcd for $C_{29}H_{26}$ 374.2035, Found 374.2033. **9**: yellow needles; mp 265-267 ℃ (benzene); IR(KBr) 1469, 1233, 954, 894, 877, 741, 649 cm^{-1}; ^1H NMR ($CDCl_3$ at r.t.) δ 1.90-2.00 (2H, m), 2.02-2.16 (2H, m), 2.42-2.84 (4H, m), 2.92-3.24 (2H, m), 3.30-3.82 (2H, m), 7.30-7.50 (6H, m), 7.62-7.82 (6H, m); ($CDCl_3$ at -60 ℃.) δ 1.86-2.20 (B-C conformer) and 2.02-2.16 (C-B conformer) (total 2H, each m), 2.14 (C-B conformer) and 2.65 (B-C conformer) (total 2H, each s), 3.06 (C-B conformer) and 3.23 (B-C conformer) (total 2H, each dd, J = 5.6, 14.2 Hz), 3.40 (B-C conformer) and 3.71 (C-B conformer) (total 2H, each d, J = 14.2 Hz), 7.36-7.60 (6H, m), 7.72-7.92 (6H, m); MS.(m/z) 376(M^+); HRMS (M^+) Calcd for $C_{28}H_{24}O$ 376.1827, Found 376.1830; E.A. Found: C, 89.16; H, 6.43. Calcd. for $C_{28}H_{24}O$, 89.33; H, 6.43.

*Spiro{5,6,7,12,13,14-hexahydro-6,13-methanodinaphtho[a,f]cyclodecene-15,2'-oxirane} (**9**).* - A solution of *m*-CPBA (70%, 273 mg, 1.11 mmol) in dichloromethane (10 mL) was added dropwise at 0 ℃ to a solution of **7** (200 mg, 0.56 mmol) in dichloromethane (10 mL). The reaction mixture was stirred for 2h at 0 ℃ and for 2h at room temperature. Then it was washed with aqueous 10% NaOH solution and water, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to leave a residue, which was recrystallized from benzene to give **9** (175 mg, 84%).

*2,2-Dichlorospiro[cyclopropane-1,15'-{5,6,7,12,-13,14-hexahydro-6,13-methanodinaphtho-[a,f]-cyclodecene}] (**10**).* - To a vigorously stirred aqueous NaOH solution (50%, 25 mL) was added a solution of **7** (200 mg, 0.56 mmol) and 15-crown-5 (61 mg, 0.28 mmol) in chloroform (15 mL) for 10 min at room temperature. The reaction mixture was heated under reflux in an oil bath at 60 ℃ for 84 h. Afterwards the mixture was cooled and poured into ice-water. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layer and extract were combined, washed with aqueous $NaHCO_3$ solution and water, dried over $MgSO_4$, and evaporated *in vacuo* to leave a residue. The residue was subjected to recycle preparative HPLC with chloroform as a solvent, giving **10** (29 mg, 21%) and unchanged **7** (82 mg, 41%). **10**: colorless prisms; mp 262-267 ℃ (benzene); IR(KBr) 1497, 1463, 878, 764, 479 cm^{-1}; ^1H NMR ($CDCl_3$ at r.t.) δ 0.58-0.70 (B-C conformer) and 1.20-1.36 (C-B conformer) (total 2H, each bs), 2.25-2.52 (2H, m), 2.64-2.90 (2H, m), 3.00-3.20 (2H, m), 3.28-3.48 (C-B conformer) and 3.70-3.86 (B-C conformer) (total 2H, each m), 7.28-7.90 (12H, m); ($CDCl_3$ at -60 ℃.) δ 0.60 (B-C conformer) and 1.29 (C-B conformer) (total 2H, each s), 2.22-2.36 (B-C conformer) and 2.36-2.50 (C-B conformer) (total 2H, each m), 2.50-2.82 (4H, m), 3.06-3.16 (B-C conformer) and 3.18-3.30 (C-B conformer) (total 2H, each m), 3.32 (C-B conformer) and 3.72 (B-C conformer) (total 2H, each d, J = 15.0), 7.30-7.56 (6H, m), 7.64-7.88 (6H, m); MS.(m/z) (M^+) 446 (7), 444(35), 442(38): (M^+-Cl_2) 372(9); HRMS (M^+) Calcd for $C_{29}H_{24}Cl_2$, 446.1220(14), 444.1233(69), 442.1255(100). Found, 446.1209(12), 444.1230(63), 442.1242(100).

*2,2-Dibromospiro[cyclopropane-1,15'-{5,6,7,12,-13,14-hexahydro-6,13-methanodinaphtho[a,f]cyclodecene}] (**11**).* - To a vigorously stirred aqueous NaOH solution (50%, 25 mL) was added a solution of **7** (200 mg, 0.56 mmol), 15-crown-5 (61 mg, 0.28 mmol), and bromoform (1g, 2.8 mmol) in benzene (15 mL) for 10 min at room temperature. The reaction mixture was heated under reflux in an oil bath at 80 ℃ for 84 h. Afterwards the mixture was cooled and poured into ice-water. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layer and extract were combined, washed with aqueous $NaHCO_3$ solution and water, dried over $MgSO_4$, and evaporated *in vacuo* to leave a residue. The residue was subjected to recycle preparative HPLC with chloroform as a solvent, giving **11** (30 mg, 10%) and unchanged **7** (57 mg, 28%). **11**: colorless

prisms; mp 283-286 ℃ (benzene); IR(KBr) 1498, 1461, 1428, 1388, 1059, 876, 742 cm^{-1}; ^1H NMR ($CDCl_3$ at r.t.) δ 0.80-0.95 (B-C conformer) and 1.50-1.60 (C-B conformer) (total 2H, each bs), 2.32-2.65 (2H, m), 2.70-2.92 (2H, m), 3.08-3.30 (2H, m), 3.66-3.78 (C-B conformer) and 3.83-3.95 (B-C conformer) (total 2H, each m), 7.28-7.92 (12H, m); ($CDCl_3$ at -60 ℃.) δ 0.82 (B-C conformer) and 1.48 (C-B conformer) (total 2H, each s), 2.28-2.46 (B-C conformer) and 2.50-2.60 (C-B conformer) (total 2H, each m), 2.60-2.90 (4H, m), 3.00-3.30 (2H, m), 3.32-3.40 (C-B conformer) and 3.72-3.82 (B-C conformer) (total 2H, each m), 7.34-7.56 (6H, m), 7.62-7.92 (6H, m); MS.(m/z) (M^+) 534(9), 532(16), 530(8): (M^+-Br) 453(14), 451(14): (M^+-Br_2) 372(16); HRMS (M^+) Calcd for $C_{29}H_{24}Br_2$, 534.0212(52), 532.0277(100), 530.0245(50) Found , 534.0263(12), 532.0260(22), 530.0251(15).

We are grateful to Yasuko Tanaka for the high-resolution mass spectra measurements.

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