**Asymmetric Reduction of Benzoylformic Ester to Methyl Mandelate (*S*)- or (*R*)-18. General Procedure for 20–50-mg Scale.** An ampule (2 mL) containing magnesium perchlorate ($Mg(ClO_4)_2 \cdot 1.5\ H_2O$, 1.0 equiv) sealed with a small rubber septum was evacuated and flushed with argon several times. Methyl benzoylformate (1.0 equiv) was injected via syringe, followed by a solution of the 1,4-dihydropyridine (1.0 equiv) in freshly distilled acetonitrile (1 mL). The ampule was kept in the dark and the reduction allowed to proceed for 5–10 days monitored by TLC. After this period, water (100–200 μL) was added, and the reaction mixture was concentrated in vacuo. The residue was triturated with boiling chloroform (2–3 mL) and the relative yield of methyl mandelate **18**, as a chloroform solution, was determined by using capillary GC.[17] The chloroform solution was concentrated to about 0.1 mL, and the alcohol **18** was isolated via preparative TLC using 20% ethyl acetate–hexanes as the eluent. Extraction of the silica gel bands, with ethyl acetate, gave methyl mandelate after filtration through a millipore filter, and concentration gave the crystalline alcohol **18**. After dissolving this material in 1.0 mL of methanol, the specific rotation of the sample was measured, followed by determination of the accurate concentration of **18** in the alcohol using HPLC calibration.[18]

**Pyridinium Salt 20.** Isolation of the pyridinium salt **20** was achieved during the preparative TLC by extraction of the base-line silica gel layers with ethyl acetate (5 mL). Filtration and concentration gave the orange salt **20** (40–50% recovery): $^1$H NMR ($CD_3CN$) δ 9.08 (br s, 1 H, 6-H), 8.79 (br s, 1 H, 2-H), 7.60–7.40 (m, 5 H, $C_6H_5$), 5.77 (s, 2 H, $CH_2C_6H_5$), 4.82 (d, $J$ = 5.2 Hz, 2 H, $CH_2OH$), 4.68 (br s, OH), 4.42 (q, $J$ = 7.2 Hz, 2 H, $CH_3CH_2O$), 2.66 (ns, 3 H, $CH_3$), 1.39 (t, $J$ = 7.1 Hz, 3 H, $CH_3CH_2O$).

**Determination of Enantiomeric Purity of 5b via Mosher Ester.** Verification of the ee for **5a–c** as a cross check for the HPLC determination on **14A** and **14B** was obtained in the case of **5b** by the independent method which follows: (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride[12] (44.0 mg, 0.174 mmol) was added to a solution of alcohol **5b** (10.0 mg, 0.35 mmol) in freshly distilled pyridine (2 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature over a period of 3 h and was diluted with methylene chloride (10 mL). Washing with water (2 × 5 mL) and brine (2 × 5 mL), drying ($K_2CO_3$), filtrating, and concentrating gave the crude Mosher ester: $^1$H NMR ($CDCl_3$) δ 7.85–7.05 (m, 11 H, $C_6H_5$, 6-H), 6.01 (br s, 1 H, 2-H), 4.76 (AB q, 2 H, $CH_2O$), 4.39 (s, 2 H, $CH_2C_6H_5$), 4.14 (AB m, 2 H, $CH_3CH_2O$), 3.53 (s, 3 H, OMe), 3.30 (q, $J$ = 6.1 Hz, 1 H, 4-H), 1.25 (t, 3 H, $CH_3CH_2O$), 1.04 (d, $J$ = 6.5 Hz, 3 H, $CH_3$); $^{19}$F NMR ($CDCl_3$ + $CFCl_3$, internal standard) δ −71.88, −72.05, ratio = 6:94.

**Determination of Enantiomeric Purity of Methyl Mandelate (+)-18 via Mosher Ester.** Independent verification of the enantiomeric purity of **18**, obtained via the asymmetric reductions with **5** and **19** was obtained by the following: A solution of (+)-methyl mandelate **18** (91% ee via specific rotation, 30.8 mg, 0.185 mmol) in pyridine–carbon tetrachloride (5 mL, 1:1) was treated with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (70.2 mg, 0.278 mmol) and stirred at room temperature for 1 h. The reaction mixture was washed with water (3.5 mL), and the separated organic phase was dried ($MgSO_4$) and concentrated, leaving a pale-yellow oil: 67.3 mg, 95%; $^{19}$F NMR ($CDCl_3$–$CFCl_3$) δ −72.20 (s), −72.52 ns), ratio of the peaks = 94:6 (88% ee); $^1$H NMR n$CDCl_3$, 270 MHz) δ 6.13 (s), 6.11 (s), ratio of methoxyl peaks = 94.4:5.6 (89% ee). This is in good agreement with the optical purity obtained via polarimetric determination (91% ee) when **5b** was employed.

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(17) Capillary gas chromatography calibration was determined for methyl benzoylformate and racemic methyl mandelate using 1,4-dimethoxybenzene as the internal standard. The calibration factors, $f_i$ = 0.85 ± 0.03 and $f_i$ = 0.93 ± 0.08, were determined using column, injector, and detector temperatures of 110, 210, and 250 °C, respectively, and a carrier gas flow ($N_2$) of 10 psi.

(18) HPLC calibration to determine the concentration of **18** in methanol was performed using (±)-**18** and 1,4-dimethoxybenzene as an internal standard, giving a calibration factor, $f_i$ = 0.843 ± 0.017, on a normal phase column (4.6 mm × 25 cm), Zorbax Sil, Du Pont Instruments, with 10% THF–hexanes as the eluent.

# A Novel Cyclophane. Host–Guest Complexation and Selective Inclusion of Aromatic Guests from Nonaqueous Solution

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**Abstract:** A novel cyclophane, 2,2,20,20-tetramethyl-11,29-dinitro-7,15,25,33-tetraoxaheptacyclo-[32.2.2.2$^{3,6}$.2$^{16,19}$.2$^{21,24}$.1$^{9,13}$.1$^{27,31}$]hexatetraconta-3,5,9(44),10,12,16,18,21,23,27(39),28,30,34,36,37,40,42,45-octadecaene (**1**), was synthesized by the reaction of 3,5-bis(bromomethyl)nitrobenzene (**2**) with bisphenol A (**3**). Both stepwise 2:2 cyclization of **2** and **3** via U-shaped precursor **4** and direct 2:2 cyclization of **2** and **3** were performed under several reaction conditions. With the coexistence of benzene in the reaction solvent, relatively high yield of **1** was achieved even without operation under high dilution conditions. This can be explained in term of a "template" effect of benzene in the cyclization step. The cyclophane **1** formed a "column-type" cave and included aromatic guests in this cave. This was confirmed by X-ray crystal structure analysis of the complex with benzene. The stoichiometry and the stability of the various inclusion complexes at high temperatures and under reduced pressure were examined. The remarkable discrimination selectivity in the inclusion complex formation from mixtures of guests is reasonably explained by the "packing-size relationship".

Incipient studies of the chemistry of cyclophanes by Cram and others were largely concerned with the chemical and physical properties of the small-membered cyclophanes.[1] However, during the past decade, great effort was devoted to the synthesis of large-membered cyclophanes, and consequently a number of novel and interesting cyclophanes were prepared. It was observed that some of these cyclophanes formed inclusion complexes with various neutral molecules.[2] Selective inclusion complex formation with organic guests is of great significance in many respects. One of the fundamental problems is to design cyclophanes which show

**Table I.** Comparison of the Yield of **1** by Stepwise and Direct Methods

| stepwise 2:2 condensation via U-type precursor **4** | direct 2:2 condensation | | |
|---|---|---|---|
| without $C_6H_6$ H.D.[a] | without $C_6H_6$ H.D.[a] | with $C_6H_6$ H.D.[a] | |
| 28% | 4% | 23% | 21% |

[a] H.D. = high dilution method.

(1) (a) Smith, B. H. "Bridged Aromatic Compounds"; Academic Press: New York, 1964. (b) Cram, D.J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, *73*, 5691. (c) Cram, D. J. *Acc. Chem. Res.* **1971**, *4*, 204.

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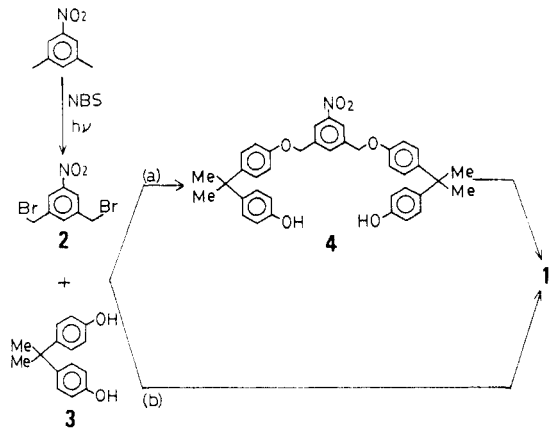
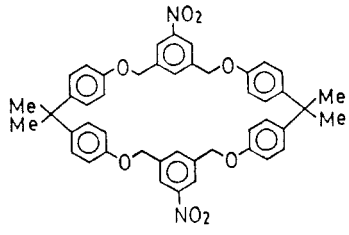
**Scheme I**




guest selectivity in the formation of inclusion complexes. From this viewpoint, we are interested in the construction of molecules, which (1) are nonaqueous soluble, (2) possess hydrophobic cavities of well-defined dimensions, and (3) have high inclusion selectivity for organic guests.

Recently we reported briefly the synthesis of a novel cyclophane, 2,2,20,20-tetramethyl-11,29-dinitro-7,15,25,33-tetraoxaheptacyclo[32.2.2.2$^{3,6}$.2$^{16,19}$.2$^{21,24}$.1$^{9,13}$.1$^{27,31}$]hexatetraconta-3,5,9-(44),10,12,16,18,21,23,27(39),28,30,34,36,37,40,42,45-octadecaene (**1**), from 3,5-bis(bromomethyl)nitrobenzene (**2**) and bisphenol A (**3**), which forms a 1:1 inclusion complex with benzene.[3]




**1**

In this paper, we present in detail (1) the synthesis of **1** by stepwise 2:2 cyclization of **2** and **3** via the U-shaped precursor **4** under high dilution conditions or by direct 2:2 cyclization of **2** and **3** in the presence of benzene as a template, (2) the formation of inclusion complexes of **1** with several aromatics determined on the basis of $^1$H NMR study and thermogravimetric and differential scanning calorimetric (TG-DSC) measurement, (3) the molecular structure determination of the benzene complex by X-ray crystallography, and (4) discrimination selectivity in complex formation from a mixture of guests.

## Results and Discussion

**Synthesis of 1.** For the synthesis of **1**, routes a and b outlined in Scheme I were tried.

(2) (a) Odashima, K.; Koga, K. "Cyclophane"; Keehn, P. M., Rosenfield, S. M., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 11. (b) Tabushi, I.; Yamamura, K. "Topics in Current Chemistry"; Vögtle, F.; Ed.; Springer: Berlin, 1983; Vol. 113, p 145. (c) Murakami, Y. "Topics in Current Chemistry"; Vögtle, F., Ed.; Springer: Berlin, 1983; Vol. 115, p 107. (d) Murakami, Y.; Sunamoto, J.; Okamoto H.; Kawanami, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1537. (e) Tabushi, I.; Sasaki, H.; Kuroda, Y. *Tetrahedron Lett.* **1976**, 3327. (f) Tabushi, I.; Sasaki, H.; Kuroda, Y. *J. Am. Chem. Soc.* **1976**, *98*, 5727. (g) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005. (h) Odashima, K.; Itai, A.; Iitaka, Y.; Koga, K. *J. Am. Chem. Soc.* **1980**, *102*, 2504. (i) Odashima, K.; Itai, A.; Arata, Y.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 4347. (j) Soga, T.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 4351. (5) Vögtle, F.; Puff, H.; Friendrichs, E.; Müller, W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 1389. (l) Diederich, F.; Dick, K. *Tetrahedron Lett.* **1982**, *23*, 3167. (m) Toda, F.; Tanaka, K.; Ulibarri, Daumas, G.; Sanchez, Ma. C. *Chem. Lett.* **1983**, 1521. (n) Toda, F.; Tanaka, K.; Mak, C. W. *Tetrahedron Lett.* **1984**, *25*, 1359. (o) Miller, S. P.; Whitelock, H. W. *J. Am. Chem. Soc.* **1984**, *106*, 1492. (p) Tabushi, I.; Yamamura, K.; Nonoguchi, H.; Hirotsu, K.; Higuchi, T. *J. Am. Chem. Soc.* **1984**, *106*, 2621. (q) Canceill, J.; Gabard, J.; Lacombe, L.; Collet, A. Paper presented at the 3rd International Symposium on Calthrate Compounds and Molecular Inclusion Phenomena, Tokyo, Japan, 1984, Abstract 1010.

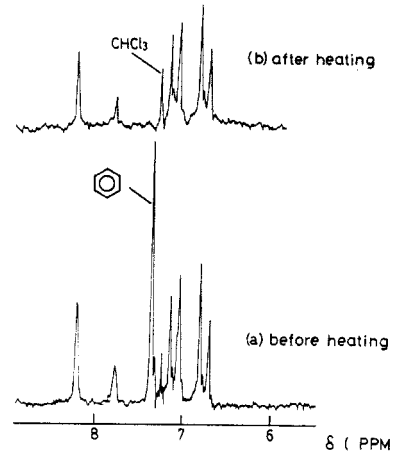



**Figure 1.** NMR spectral change.

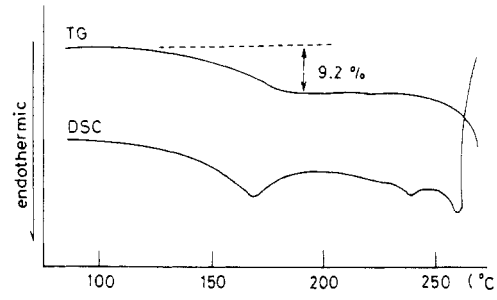



**Figure 2.** TG-DSC curves of the **1**–benzene complex.

Route a consists of a stepwise 2:2 cyclization via the U-shaped precursor **4**, the 1:2 condensate of **2** and **3**. By 1:1 cyclization between **2** and **4** in the presence of a base under high dilution conditions, **1** was obtained in moderate yield. To determine the factors which influence the yield of **1**, several experiments were carried out under conditions of different concentration, reaction time, and solvent. It was observed that the yield was influenced in greater or smaller degree by all these reaction conditions. One-pot direct 2:2 cyclization between **2** and **3** (route b) under high dilution conditions gave **1** in only 4% yield. But, a remarkable improvement was achieved for this direct 2:2 cyclization when the condensation reaction was carried out in the presence of benzene. With the coexistence of benzene in the reaction solvent, the yield of **1** under high dilution conditions was improved 5–6 times to give **1** in 23% yield. Moreover, with the coexistence of benzene in the reaction solvent, slow addition of the reactants was found not to be essential for the condensation. Namely, **1** was obtained in 21% yield on stirring a solution which contained all reactants and the base. The yields of the product prepared by different routes are summarized in Table I.

The data indicate that a satisfactory yield of **1** is achieved by a simple operation in the coexistence of benzene. In the condensation, benzene presumably acts as a template by forming a stable complex with **1**. But, the presence of benzene had no influence on the yield of **1** in the condensation between **2** and **4**. Consequently, benzene is not effective as a template in the condensation of **2** with **4**, whereas it is effective in the direct condensation of **2** with **3**. This phenomenon suggests that benzene acts as a template by suppressing the extension of the **2–3–2** condensate and organizing the condensate in a conformation close enough to the ring being formed.

**Inclusion Complex Formation and Thermal Stability.** When the crude yellowish oil, which was obtained on concentration of the reaction mixture of route a, was treated with benzene, a white crystalline powder was formed. On the basis of $^1$H NMR integration, this was identified as a complex of **1** containing benzene in strict 1:1 stoichiometry (Figure 1a). Furthermore, from TG-DSC curves shown in Figure 2, the crystal morphology of the complex seemed to change on heating. Between 135 and 170 °C, the weight of the sample decreased about 9.2% endothermically.

**Table II.** Inclusion Complexes of **1**: Stoichiometry and Thermal Stability

| complex | guest compd | host:guest molar ratio[a] | thermal dec, °C[b] | $\Delta H$,[c] kcal mol$^{-1}$ |
|---|---|---|---|---|
| **1** | benzene | 1:1 | 135.5 (+54.9) | 9.52 (+1.97) |
| **2** | toluene | 1:1 | 125.5 (+14.9) | 9.18 (+1.20) |
| **3** | *o*-xylene | 1:1 | 121.2 (−22.8) | 9.60 (+0.84) |
| **4** | *m*-xylene | 1:1 | 110.0 (−29.1) | 9.44 (+0.73) |
| **5** | *p*-xylene | 1:1 | 101.0 (−36.0) | 9.29 (+0.66) |
| **6** | mesitylene | *d* | | |
| **7** | methyl benzoate | *d* | | |

[a] Determined by $^1$H NMR ($CDCl_3$) after vacuum (0.1 torr) drying for 6 h at room temperature for each complex. [b] The beginning temperature of the evolution of the gaseous guest component on TG-DSC measurement. The values in parentheses are the relative thermal stabilities (difference between the decomposition point of the inclusion complex and the boiling point of the guest molecule at ordinary pressure). [c] The enthalpy change resulting from the evolution of the gaseous guest component. The values in the parentheses are the relative thermal stabilities (difference between the enthalpy change of the inclusion complex and the enthalpy of evaporation of the respective neat guest molecule at ordinary pressure). [d] None of these can be included by **1**.

In the $^1$H NMR spectrum of the sample heated up to 180 °C, the peak of benzene (δ 7.36) disappeared completely (Figure 1b). Therefore, the decrease of the weight should correspond to the evolution of benzene from the complex (theoretical weight loss: 9.4%). From these observations and its stability under vacuum drying (0.1 torr at room temperature), we concluded that **1** strongly includes benzene.

Other kinds of aromatics such as toluene and xylene isomers revealed analogous complexation, but mesitylene and methyl benzoate did not act as guests for **1**. A list of the inclusion complexes with their thermal stabilities is given in Table II.

The complexes were fairly stable under vacuum drying at room temperature. But, heating resulted in not only weight decrease with guest evolution but also endothermic change within a specific temperature range for each compound (Table II). In the cases of the benzene and toluene inclusion complexes, these temperature ranges lie above the boiling point of the corresponding guest molecule. This indicates a particularly strong complexation.[4] The others, however, showed the evolution of guest at the temperature below the boiling point of the corresponding pure guest component. The difference between the beginning temperature of the thermal decomposition of the complex and the boiling point of the guest at ordinary pressure is given in parentheses in Table II. The enthalpy change of each inclusion complex was calculated on the basis of peak area in the DSC curve. The result is also shown in Table II.

**X-ray Structure of the Benzene-Included Complex of 1.** The ORTEP crystal packing diagram of the **1**–benzene inclusion complex solved by UNICS III[5] is shown in Figure 3. The complexed host molecules adopt a "dished chairlike" conformation. The column-type cave is created not only from the channels between the host molecules packed up one above the other but also from the cavities of the host molecules themselves. In the channels, the guests, benzene molecules, are located. From the interatomic distances in the crystal, the channel seems to be slightly larger than the space necessary to tightly hold the benzene molecules. But the benzene molecule is found to be situated closely to the edge of **1**. This structural arrangement is similar to that observed for the complexation of 1,4-dioxane with tetraazaparacyclophane.[6]

Other kinds of aromatics such as toluene and xylene isomers are considered to form analogous complexes. But there is no direct evidence since the single crystals of these complexes suitable for crystallographic study could not be obtained.

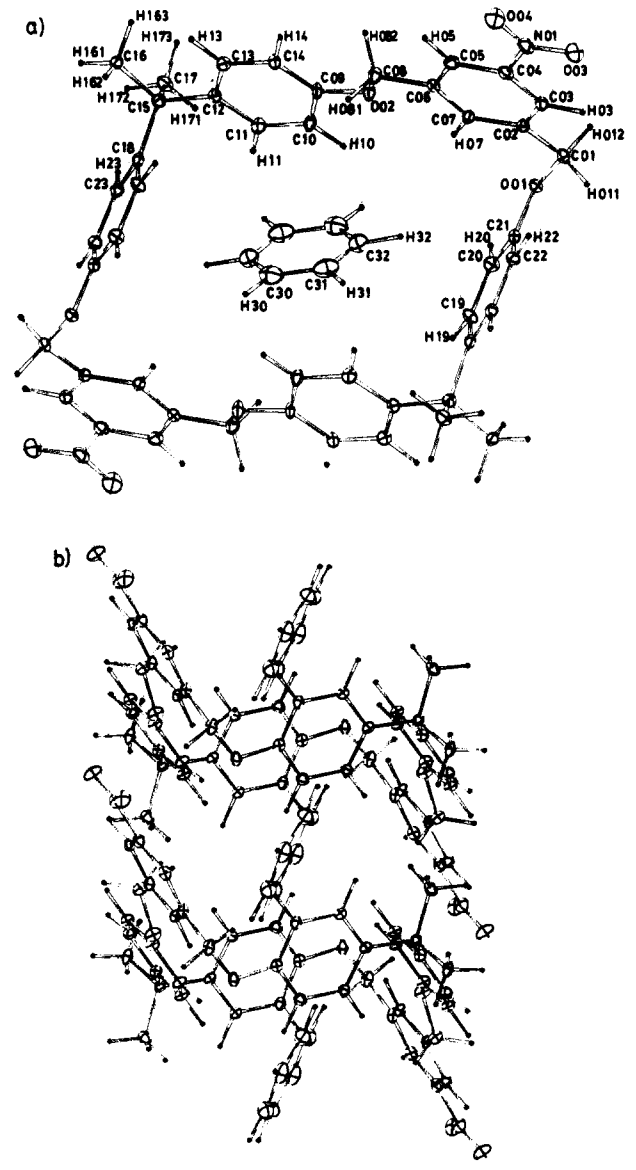



**Figure 3.** Perspective ORTEP[5] crystal packing diagram of the **1**–benzene complex as viewed along (a) the *z* axis and (b) the *x* axis.

The hydrophobic interaction contribution to complex stability would be functions of the packing of **1** and of the depth of penetration of the guest molecule into **1**. Then, a simplified "packing-size relationshp", which is realized for the cyclodextrin inclusion complexes,[7] can be made to explain the fact that the aromatic inclusion complexes were thermally stable to a different extent (Table II). On the assumption of similar crystal packing of these aromatic complexes, the inclusion of small guests results in a short distance contact between host molecules to introduce strong hydrophobic interaction. To accommodate the larger guests (*o*-, *m*-, and *p*-xylene) in the hydrophobic region, a somewhat larger channel is necessary, resulting in a somewhat looser packing. The strength of the hydrophobic interaction would be reflected in the thermal stability of those adducts.

**Inclusion Selectivity and Guest Discrimination.** The host **1** underwent the competitive inclusion of aromatic guest molecules. In some instances, high discrimination of one guest species was achieved from a mixture of the guests. For example, the competitive inclusion of benzene/*p*-xylene with **1** yielded the benzene complex in a relative guest excess of 97%. The results for the

(3) Saigo, K.; Kubo, M.; Lin, R.-J.; Youda, A.; Hasegawa, M. *Tetrahedron Lett.* **1985**, *26*, 1325.
(4) Baker, W.; Gilbert, B.; Ollis, W. D. *J. Chem. Soc.* **1952**, 1443.
(5) Sakurai, T.; Kobayashi, K. *Rep. Inst. Phys. Chem. Res.* **1979**, *55*, 69–77.
(6) Abbott, S. J.; Bannett, A. G. M.; Godfrey, C. R. A.; Kalindjian, S. B.; Simpson, G. W.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1982**, 796.
(7) Tabushi, I.;Kiyosuke, Y.; Sugimoto, T.; Yamamura, K. *J. Am. Chem. Soc.* **1978**, *100*, 916.

**Table III.** Selectivity in the Complexation of **1** for a Mixture of Guests

| entry | guest | respective percentages | |
|---|---|---|---|
| 1 | benzene/toluene | 78.7 | 21.3 |
| 2 | benzene/*o*-xylene | 88.0 | 12.0 |
| 3 | benzene/*m*-xylene | 95.0 | 5.0 |
| 4 | benzene/*p*-xylene | 98.5 | 1.5 |
| 5 | toluene/*o*-xylene | 70.3 | 29.7 |
| 6 | toluene/*m*-xylene | 92.7 | 7.3 |
| 7 | toluene/*p*-xylene | 93.3 | 6.7 |
| 8 | *o*-xylene/*m*-xylene | 88.3 | 11.7 |
| 9 | *o*-xylene/*p*-xylene | 89.1 | 10.9 |
| 10 | *m*-xylene/*p*-xylene | 92.5 | 7.5 |

competitive complexation are summarized in Table III. The sequence of inclusion selectivity of **1** toward aromatics is as follows: benzene > toluene > *o*-xylene > *m*-xylene > *p*-xylene > chloroform ≫ mesitylene, methyl benzoate. It is noteworthy that this sequence of selectivity is the same as that of the $\Delta T$ values in Table II. This means that the higher the thermal stability the complex possesses, the more the cyclophanes pack closely in the inclusion process and the more easily the complex is formed.

The thermodynamic stability of the inclusion complexes can be usually explained by the free-energy change in the complexation. Namely, complexation features depend on enthalpy and conformational changes. As shown in Table II, the sequence of the enthalpy change $\Delta\Delta H$ is the same as that of selectivity in the competitive complexation. This means that the enthalpy change plays a particularly definitive role in the stability of the complexes and in selectivity of the complexation. This result supports our assumption that **1** in the inclusion complexes packes in a similar conformation.

## Experimental Section

Melting points were measured by a Laboratory Devices MEL-TEMP and are uncorrected. $^1$H NMR spectra were recored with a Hitachi R-40 or a JEOL GX-400 spectrometer in the solvent indicated. Chemical shifts are reported in parts per million downfield from $SiMe_4$ as an internal standard. IR spectra were determined on a JASCO IR-810 spectrometer and reported in inverse centimeters. TG-DSC curves were recorded with a Rigaku Denki Thermoflex TG-DSC instrument with the heating rate of 5 °C/min under a nitrogen stream. All commercially available solvents and organic materials were purified by standard procedures.

3,5-Bis(bromomethyl)nitrobenzene (**2**) was prepared according to the method reported in the literature:[8] mp 102–105 °C [Lit. 105–106.5 °C]; IR (KBr) 1540, 1360, and 1220; $^1$H NMR ($CDCl_3$) $\delta$ 8.14 (s, 2 H), 7.71 (s, 1 H), 4.50 (s, 4 H).

**Synthesis of the Cyclophane 1. Route a: Stepwise 2:2 Cyclization.** To a solution of sodium ethoxide prepared from ethanol (30 mL) and crushed sodium (0.92 g, 40 mmol) was added bisphenol A (**3**) (9.10 g, 40 mmol) at once, and the mixture was gently relfluxed for 0.5 h under stirring to give a homogeneous solution. A solution of 3,5-bis(bromomethyl)nitrobenzene (**2**) (3.09 g, 10 mmol) in tetrahydrofuran (THF) (50 mL) was added dropwise to the refluxing solution in a period of 0.5 h, and the reaction mixture was refluxed for an additional 3 h. After cooling, the solvent was evaporated and the yellowish oil remaining was dissolved in 60 mL of $CH_2Cl_2$ and washed 3–4 times with 60 mL of 0.1 N NaOH until the unreacted **3** was undetectable. The organic layer was separated and dried over anhydrous $Na_2SO_4$. After evaporation of the solvent, the residue was separated by silica gel column chromatography (eluent: $CH_2Cl_2$/hexane = 7/3) to give the U-shaped precursor **4** (4.83 g, 80%): mp 63–64 °C; IR (KBr) 3420, 1527, 1510, 1228, 1180 and 830; $^1$H NMR ($CDCl_3$) $\delta$ 1.66 (s, 12 H), 5.08 (s, 4 H), 6.6–7.2 (m, 16 H), 7.79 (s, 1 H), and 8.20 (s, 2 H).

Anal. Calcd for **4** ($C_{38}H_{37}NO_6$): C, 75.60; H, 6.18; N, 2.32. Found: C, 75.31; H, 6.12; N, 2.52.

A solution of **4** (1811 mg, 3 mmol) and *t*-BuOK (694 mg, 6 mmol) in ethanol (120 mL) and a solution of **2** (927 mg, 3 mmol) in THF (120 mL) were simultaneously added dropwise with vigorous stirring to a mixture of EtOH/THF (250/250 mL) in a period of 10 h under refluxing. After completion of the addition, the solution was refluxed for an additional hour. The resulting solution was concentrated and shaken with $CHCl_3$/0.1 M HCl (60/60 mL). The aqueous layer was extracted twice with 50-mL portions of $CHCl_3$. The organic layers were combined, dried ($Na_2SO_4$), and concentrated to dryness to give a yellowish viscous oil. The oil was treated with benzene (100 mL) under stirring for 3 h to give the **1**–benzene complex as a whitish crystalline powder (870 mg, 35%): mp 280 °C dec; IR (KBr) 1526, 1510, 1350, 1240, 1220, and 1180; $^1$H NMR ($CDCl_3$) $\delta$ 1.64 (s, 12 H), 5.14 (s, 8 H), 6.78 (d, 8 H, $J$ = 9 Hz), 7.09 (d, 8 H, $J$ = 9 Hz), 7.36 (s, 6 H), 7.76 (s, 2 H), and 8.17 (s, 4 H).

Anal. Calcd for **1**–$C_6H_6$ ($C_{52}H_{48}N_2O_8$): C, 75.34; H, 5.84; N, 3.38. Found: C, 75.07; H, 5.76; N, 3.30.

The complex was dissolved in a minimum amount of $CHCl_3$ on heating, and then MeOH (ca. one-third the volume of $CHCl_3$) was added to the solution. Yellowish needle crystals of the **1**–$CHCl_3$ complex deposited on standing for 24 h at room temperature. The crystals were collected and dried at room temperature in vacuo: mp 280 °C dec; IR (KBr) 1526, 1510, 1350, 1240, 1220, and 1180; $^1$H NMR ($CD_2Cl_2$) $\delta$ 1.64 (s, 12 H), 5.14 (s, 8 H), 6.78 (d, 8 H, $J$ = 9 Hz), 7.09 (d, 8 H, $J$ = 9 Hz), 7.32 (s, 1 H), 7.78 (s, 2 H), 8.16 (s, 4 H).

Anal. Calcd for **1**–$CHCl_3$ ($C_{47}H_{42}Cl_3N_2O_8$): C, 64.86; H, 4.98; N, 3.22; Cl, 12.22. Found: C, 64.59; H, 4.69; N, 3.30; Cl, 12.32.

The sample heated up to 180 °C was identified to be free **1**. The free cyclophane decomposed at ca. 280 °C: IR (KBr) 1526, 1510, 1350, 1240, 1220, and 1180; $^1$H NMR ($CDCl_3$) $\delta$ 1.64 (s, 12 H), 5.14 (s, 8 H), 6.78 (d, 8 H, $J$ = 9 Hz), 7.09 (d, 8 H, $J$ = 9 Hz), 7.76 (s, 2 H), and 8.17 (s, 4 H).

Anal. Calcd for **1** ($C_{46}H_{42}N_2O_8$): C, 73.58; H, 5.64; N, 3.73. Found: C, 73.60; H, 5.57; N, 3.65.

**Route b: Direct 2:2 Cyclization under High Dilution Conditions.** A solution of **2** (1854 mg, 6 mmol) in THF (200 mL) and a solution of **3** (1370 mg, 6 mmol) and *t*-BuOK (1392 mg 12 mmol) in ethanol (200 mL) were simultaneously added dropwise with vigorous stirring to a mixture of EtOH/THF/$C_6H_6$ (250/250/50 mL) in a period of 10 h under refluxing. The reaction mixture was treated in a similar manner to the case of the stepwise method to give the **1**–benzene complex (591 mg, 23%).

**Direct 2:2 Cyclization without High Dilution.** A solution of **2** (1854 mg, 6 mmol), **3** (1370 mg, 6 mmol), and *t*-BuOK (1392 mg, 12 mmol) in a mixture of EtOH/THF/$C_6H_6$ (450/450/50 mL) was refluxed for 10 h under vigorous stirring. The reaction mixture was treated in a similar manner to the case of the stepwise method to give the **1**–benzene complex (522 mg, 21%).

**Preparation of the Inclusion Complexes. General Procedure.** Into a solution of free **1** in a minimum amount of $CHCl_3$ was added a proper quantity f a guest compound. The mixture was magnetically stirred at room temperature to give the stoichiometrically 1:1 inclusion complex as a whitish crystalline powder. The crystals were collected by filtration, washed with methanol, and dried at room temperature under reduced pressure (0.1 torr) for 6 h. The structures of the complexes were confirmed by $^1$H NMR spectral studies. The data of the stoichiometry and the thermal stability for each complex are given in Table II.

**Competitive Inclusion.** Into a solution of free **1** in a minimum amount of $CHCl_3$ was added an equimolar mixture of guests (ca. one-half the volume of $CHCl_3$). The mixture was treated in a similar manner to that of general procedure as described above. The ratios were determined by $^1$H NMR spectra.

**X-ray Structure Determination of the Benzene-Included Complex of 1.** Colorless crystals of the **1**–benzene complex were obtained by slow recrystallization of **1** from a $CHCl_3$/benzene mixture. Crystal data for the **1**–benzene complex ($C_{46}H_{42}N_2O_8C_6H_6$) at 20 °C are as follows: $M_r$ = 829.0, triclinic; $a$ = 14.606 (4) Å, $b$ = 13.220 (6) Å, $c$ = 6.419 (2) Å; $\alpha$ = 100.42 (4)°, $\beta$ = 104.78 (3)°, $\gamma$ = 66.41 (3)°; $V$ = 1093.9 (8) Å$^3$, space group $P\bar{1}$, $Z$ = 1, $D_c$ = 1.269 g cm$^{-3}$. The intensities of 2801 reflections (3° < 2$\theta$ < 50°) from a small crystal (0.5 × 0.1 × 0.05 mm) were measured ($\omega - 2\theta$ scans) on the Rigaku AFC-5 diffractometer (Mo K$\alpha$ radiation, graphite monochromator, $\lambda$ = 0.71069 Å). Unique 1780 reflections with $F_o > 3\ \sigma F_o$ were used in refinement of the structure. The structure was solved by a direct method with MULTAN 78.[9] The final refinement including isotropic hydrogen atoms reduced the $R$ value to 0.082.[10] The ORTEP drawing was carried out by using UNICS III program.[5]

**Acknowledgment.** We gratefully acknowledge Dr. Kazuhide

(8) (a) Sherrod, S. A.; da Costa, R. L.; Barnes, R. A.; Boekeiheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1565. (b) Vöglte, F.; Böckman, K. *Ber.* **1979**, *112*, 1400.

(9) Germain, G.; Main, P.; Wooltson, M. M. *Acta Crystallogr., Sect. A* **1971**, *A27*, 368.

(10) Stewart, J. M. "Technical Report TR-446 of the Computer Science Center"; University of Maryland: Baltimore, 1985.

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**Registry No. 1**, 97350-55-5; **1**-$C_6H_6$, 97350-56-6; **1**-$CHCl_3$, 100813-06-7; **1**-*o*-$CH_3C_6H_4CH_3$, 100813-07-8; **1**-*m*-$CH_3C_6H_4CH_3$, 100813-08-9; **1**-*p*-$CH_3C_6H_4CH_3$, 100813-09-0; **1**-1,3,5-$(CH_3)_3C_6H_3$, 100813-10-3; **1**-PhCOOMe, 100813-11-4; **1**-MePh, 100813-12-5; **2**, 51760-20-4; **3**, 80-05-7; **4**, 97345-97-6.

**Supplementary Material Available:** A list of potential parameters, bond distances, and bond angles with their estimated standard deviations (6 pages). Ordering information is given on any current masthead page.

# S–C–P Anomeric Interactions. 4. Conformational Analysis of 2-(Diphenylphosphinoyl)-1,3-dithiane[1,2]

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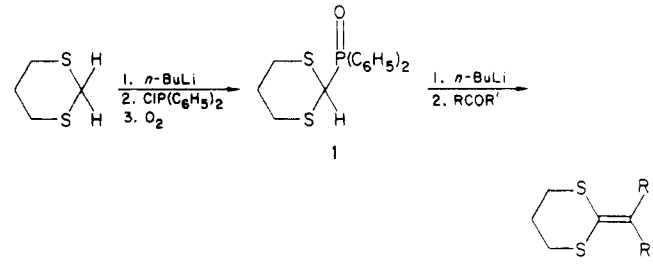
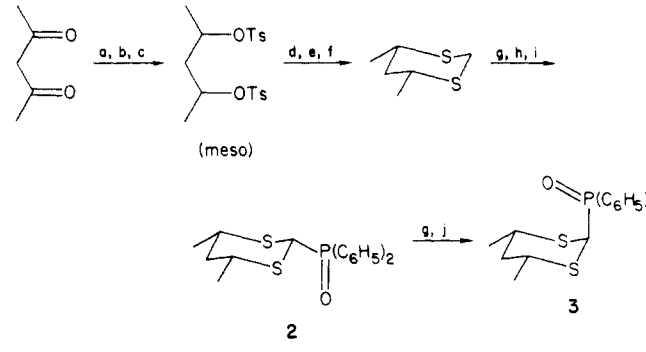
**Abstract:** Proton NMR spectroscopy and X-ray crystallographic studies demonstrate the predominance of the axial conformer of 2-(diphenylphosphinoyl)-1,3-dithiane (**1**). Chemical equilibration of anancomeric models (**2** ⇄ **3**) allows quantitative determination of the conformational free energy in **1**, 1.0 kcal/mol, which corresponds to an anomeric effect of 3.74 kcal/mol, the largest yet measured. Comparison of the structural data for **1**-ax and **2** (equatorial) provides information contrary to what would be expected if an $n_S \rightarrow \sigma^*_{C-P}$ interaction were responsible for the preferred axial conformation in **1**. Also, solvent effects do not show the trend to be expected if dipole/dipole interactions dominated the conformational behavior in **1**. Alternative rationalizations of the phenomenon are discussed. In particular, the possible importance of electrostatic, attractive interactions between the phosphoryl oxygen and the axial hydrogens at C(4,6) is suggested.

2-[1,3]Dithianyldiphenylphosphine oxide (**1**) has been studied in our laboratory as a potential precursor of ketene dithioketals (i.e., as a new Wittig–Horner/Corey–Seebach reagent[3,4] (Scheme I). It soon became obvious that the conformational behavior of **1** could provide useful information concerning the nature of the anomeric effect,[5,6] a phenomenon whose general chemical implications have recently been reviewed.[7,8] While much work has been dedicated to studies of the effect involving first-row elements, much less effort has been devoted to systems containing second-row elements.[9–11] The present work constitutes the first quantitative evaluation of a S–C–P anomeric interaction[2,12,13]

**Scheme I**




**Scheme II**[a]




[a] (a) $NaBH_4$. (b) *p*-TsCl (2 equiv), pyridine. (c) Fractional crystallization. (d) $AcS^-K^+$ (2 equiv.), EtOH. (e) $(CH_2NH_2)_2$. (f) $CH_2(OCH_3)_2$, $BF_3 \cdot Et_2O$. (g) *n*-BuLi, THF–TMEDA. (h) $ClP(C_6H_5)_2$. (i) Air oxidation. (j) $NH_4Cl$, $H_2O$.

## Results and Discussion

**Discovery of a Strong S–C–P Anomeric Interaction in 1.** 2-[1,3]Dithianyldiphenylphosphine oxide (**1**) was prepared from 1,3-dithiane, *n*-butyllithium, and chlorodiphenylphosphine; the phosphine intermediate oxidized spontaneously to **1** during workup (Scheme I). Assignment of the proton NMR spectrum of **1**

(1) For part 3, see: Juaristi, E; López-Núñez, N. A.; Glass, R. S.; Petsom, A.; Hutchins, R. O.; Stercho, Y. accepted for publication in *J. Org. Chem.*

(2) A preliminary report on this work has appeared: Juaristi, E.; Valle, L.; Mora-Uzeta, C.; Valenzuela, B. A.; Joseph-Nathan, P.; Fredrich, M. F. *J. Org. Chem.* **1982**, *47*, 5038–5039.

(3) Juaristi, E.; Valle, L.; Mora, C. "Abstracts of Papers", 183rd National Meeting of the American Chemical Society; American Chemical Society: Washington, DC, 1982; ORGN 69. Juaristi, E.; Gordillo, B.; Valle, L. *Tetrahedron*, in press.

(4) For related examples, see inter alia: Corey, E. J.; Märkl, G. *Tetrahedron Lett.* **1967**, 3201–3204. Mikolajczyk, M.; Grzejszczak, S.; Zatorski, A.; Mlotkowska, B. *Ibid.* **1976**, 2731–2734.

(5) Szarek, W. A.; Horton, D. "The Anomeric Effect: Origin and Consequences"; American Chemical Society: Washington DC, 1979; ACS Symp. Ser. No. 87.

(6) Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen"; Springer-Verlag: Berlin, 1983.

(7) Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon Press: Oxford, 1983.

(8) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540–4552.

(9) For studies of the anomeric effect in thiane rings, see: Zefirov, N. S.; Blavoveshchenskii, V. S.; Kazimirchik, I. V.; Yakovleva, O. P. *J. Org. Chem. USSR (Engl. Transl.)* **1971**, *7*, 599–602. de Hoog, A. J. Ph.D. Thesis, University of Leiden, 1971, as cited in ref 6, p 24.

(10) For studies of the anomeric effect in 2-substituted 1,3-dithianes, see: (a) Juaristi, E.; Tapia, J.; Méndez, R. *Tetrahedron*, in press. (b) Hartmann, A. A. Ph.D. Thesis, University of Notre Dame, IN, 1971. (c) Pinto, B. M.; Sandoval-Ramirez, J.; Dev Sharma, R. *Tetrahedron Lett.* **1985**, *26*, 5235–5238.

(11) For studies of the anomeric effect in 2-substituted 1,3,5-trithianes, see: (a) Arai, K.; Iwamura, H.; Ōki, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3319–3323. (b) Ōki, M.; Sugawara, T.; Iwamura, H. *Ibid.* **1974**, *47*, 2457–2462. (c) Ōki, M.; Endo, T.; Sugawara, T. *Ibid.* **1975**, *48*, 2496–2501. (d) Sugawara, T.; Iwamura, H.; Ōki, M. *Ibid.* **1974**, *47*, 1496–1499.

(12) Mikolajczyk et al.[13] have recently found that the structurally related 2-(dimethoxyphosphoryl)-1,3-dithiane and 2-(dimethoxyphosphoryl)-1,3,5-trithiane exist largely in the axial conformation.

(13) Mikolajczyk, M.; Balczewski, P.; Wroblewski, K.; Karolak-Wojciechowska, J.; Miller, A.; Wieczorek, M.; Antipin, M. Y.; Struchkov, Y. T. *Tetrahedron* **1984**, *40*, 4885–4892.

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