Isolation of equatorial conformers of chloro- and bromocyclohexane in a pure state as inclusion complexes with a host compound

Shinya Hirano, Shinji Toyota and Fumio Toda*

Department of Chemistry, Faculty of Science, Okayama University of Science, Ridai-cho 1-1, Okayama 700-0005, Japan. E-mail: toda@chem.ous.ac.jp; Fax: +81 86 256 9604; Tel: +81 86 256 9604

The equatorial conformers of chloro- and bromocyclohexane were isolated in a pure state as inclusion complexes with a host compound, and their structures were studied by IR spectra and X-ray analysis.

Conformational studies of cyclohexanes substituted with sterically less bulky group, such as chloro- (**1**) and bromocyclohexane (**2**) are of considerable interest. Nevertheless, it is not easy to isolate conformational isomers of halocyclohexanes in a pure state at room temperature due to dynamic equilibrium between the equatorial and axial conformers, although in the solid state at sufficient low temperature or high pressure **1** and **2** exist only in the equatorial form (**1a, 2a**).[1]

Some attempts to isolate conformational isomers of **1** and **2** in a pure form at room temperature have been reported. Chlorocyclohexane (**1**) which is included with thiourea as host has been shown by IR and Raman spectroscopy to adopt the axial conformation (**1b**).[2] However, X-ray crystal structural study of the inclusion complex of **1** with thiourea showed that substructure of **1** is substantially disordered and its structure was not analyzed clearly.[3] Conformational studies by IR spectra and X-ray analysis of **1** which is included in tri-*o*-thymotid host compound has been reported.[4] The data showed that a 2:1 inclusion complex of the host and **1** contains both an axial chair (**1b**) and axial boat conformers (**1c**) in a 2:1 ratio and that these two are overlapping in the same crystalline lattice. Finally, the equatorial (**1a, 2a**) and axial conformers (**1b, 2b**) have never been isolated in a pure form at room temperature so far. As the sole example of the successful isolation, (*R,R*)-(−)-diequatorial isomer (**3a**) of *trans*-1,2-dichlorocyclohexane (**3**) has been isolated in a pure form as an inclusion complex with the chiral host, (*R,R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane (**4**), and the diequatorial structure was elucidated by X-ray study.[5] This is the first X-ray structural report that has confirmed the conformation of **3a** directly. In this case, however, it is easier to isolate **3a**, since the diaxial conformer (**3b**) is energetically very unfavorable.

We report isolation of the equatorial conformers of chloro- (**1a**) and bromocyclohexanes (**2a**) by inclusion complexation with racemic *p*-fluoro-substituted derivative of **4** (**5**), and structural study on these conformers by IR spectra and X-ray analysis. Inclusion complexes of **1** and **2** with the host **5** were prepared by recrystallization of the host from neat **1** and **2** to give 1:1 inclusion complexes of **1a** with **5** (**6**) (mp 227.5–228.0 °C) and of **2a** with **5** (**7**) (mp 226.5–227.0 °C), respectively, as colorless crystals.† These complexes showed sharp mp as indicated. The host:guest molar ratios were determined by ^{1}H NMR spectra.

The equatorial conformations of **1a** and **2a** in their inclusion complexes were first studied by IR spectra with using ATR (attenuated total reflection) method. As shown in Fig. 1, **1** showed in its neat IR spectrum equatorial and axial C–Cl strechings at 732 and 685 cm^{-1}, respectively. In the spectrum of **6**, very strong equatorial C–Cl stretching appeared at 726 cm^{-1} in addition to a weak absorption at 685 cm^{-1}. However, it is not clear whether the latter absorption is due to axial C–Cl or the host compound **5**. In Fig. 2, **7** also showed very strong equatorial C–Br absorption at 684 cm^{-1}. However, a weak absorption also appeared at around 660 cm^{-1} which is possibly assignable to the axial C–Br. Finally, it could not be concluded that only equatorial isomers **1a** and **2a** are included exclusively in the complex **6** and **7**, respectively.

The equatorial structures were finally determined by X-ray analysis of **6** and **7**.‡ In the inclusion complexes, both **1** and **2** are accommodated as an equatorial conformer, **1a** (Fig. 3) and **2a** (Fig. 4), respectively. In the both cases, no significant host-guest intereaction such as hydrogen bond or CH–π is present. Guest molecules are just accommodated in the cavity constructed by the host molecules. This is the first isolation of equatorial conformers **1a** and **2a** in a pure state as inclusion complex. The cavity is probably large enough to accommodate the relatively long equatorial conformer rather than the axial one.
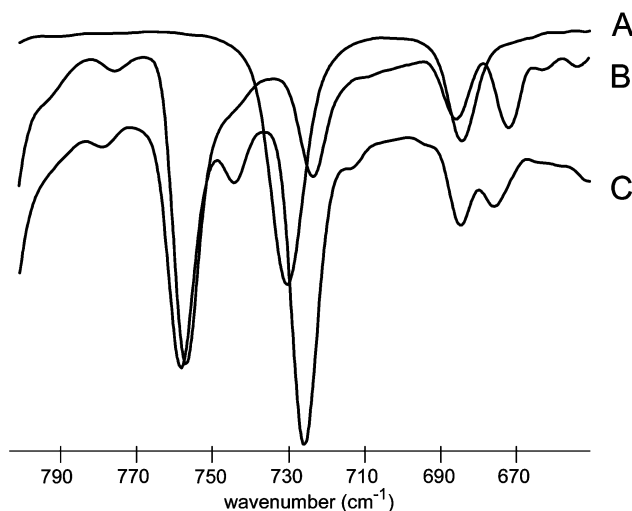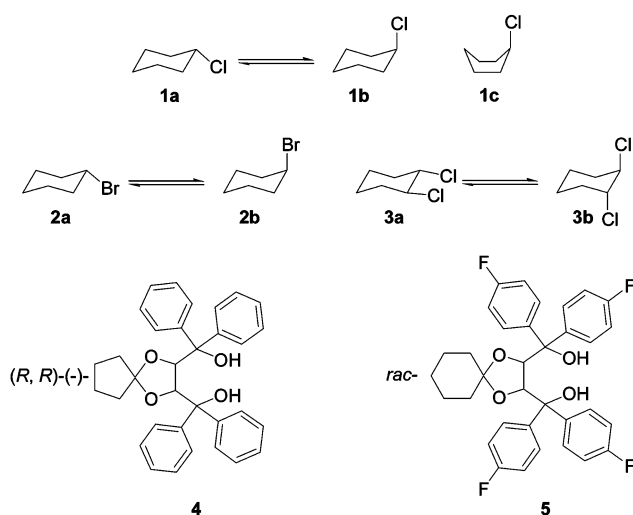

Fig. 1 IR spectra of **1** (neat), and **5** and **6** with using ATR (attenuated total reflection) method. A: **1**; B: **5**; C: **6**.
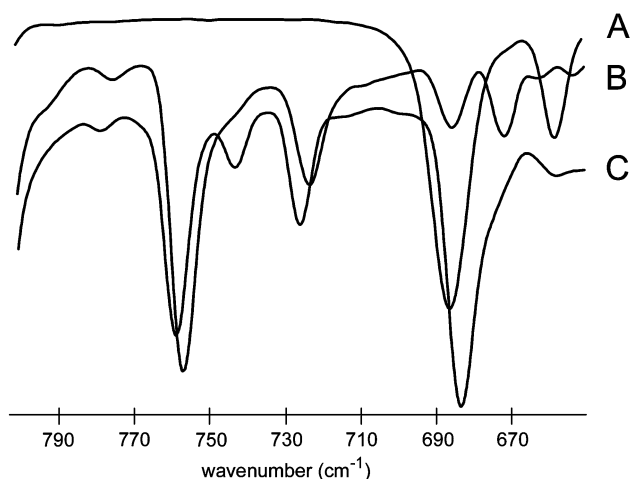
Fig. 2 IR spectra of **2** (neat), and **5** and **7** with using ATR (attenuated total reflection) method. A: **2**; B: **5**; C: **7**.
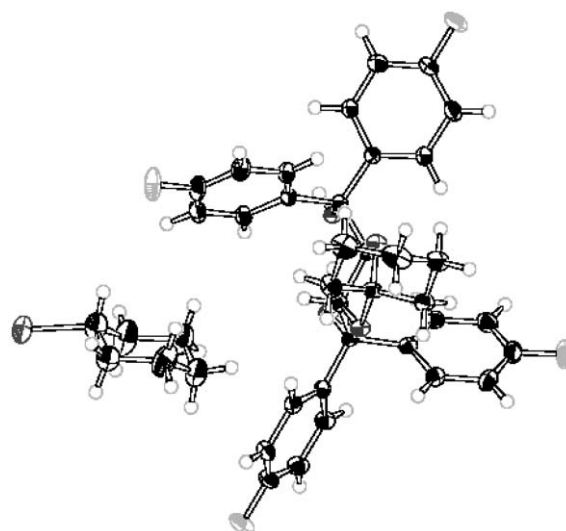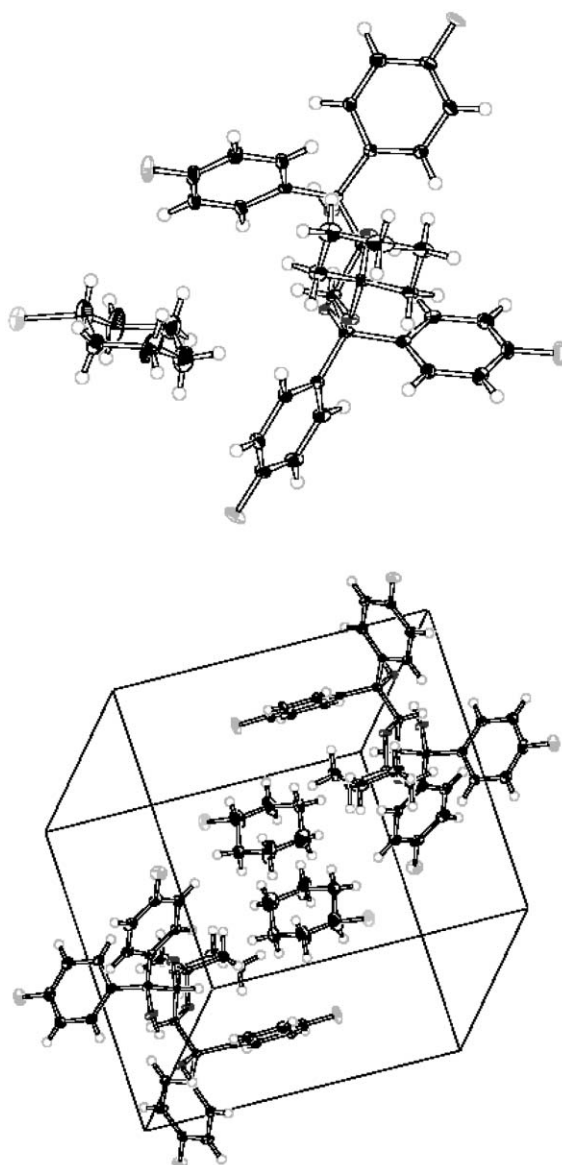

Fig. 4 X-Ray structure of **7**.

Notes and references

† Experimental section: When a solution of **5** (56 mg) in **1** (0.3 ml) was kept at room temperature for 2 days, **6** (61.7 mg, 91% yield based on **5**) was obtained as colorless needles (mp 227.5–228.0 °C). Anal. Calcd for $C_{40}H_{41}O_4F_4Cl$: C, 68.91; H, 5.93%. Found: C, 68.53; H, 5.88%. By similar method, **7** was prepared from **5** and **2** in 85% yield as colorless needles (mp 226.5–227.0 °C). Anal. Calcd for $C_{40}H_{41}O_4F_4Br$: C, 64.78; H, 5.57%. Found: C, 64.95; H, 5.57%.

‡ Crystallographic data for **6** were collected at 93 K on a Rigaku RAXIS-IV Imaging Plate diffractometer with Mo–Kα. Formula = $C_{34}H_{30}F_4O_4 \cdot C_6H_{11}Cl$, MW = 697.21, crystal system = triclinic, space group = $P\bar{1}$ (#2), lattice parameters a = 10.2812(4) Å, b = 12.5651(5) Å, c = 13.8054(8) Å, α = 90.7910(1)°, β = 89.9820(1)°, γ = 107.375(4)°, V = 1701.9(1) Å^3, Z = 2, D_{calc} = 1.360 g cm^{-3}, number of unique reflections = 6791, R_{int} = 0.0350 up to 2θ = 55° , number of parameters = 442, R_1 = 0.0597, wR = 0.2056, gof = 0.991 for 5214 reflections. Crystallographic data for **7** were collected at 93 K on a Rigaku RAXIS-IV Imaging Plate diffractometer with Mo–K$_\alpha$. Formula = $C_{34}H_{30}F_4O_4 \cdot C_6H_{11}Br$, MW = 741.66, crystal system = triclinic, space group = $P\bar{1}$ (#2), lattice parameters a = 10.2862(6) Å, b = 12.7217(8) Å, c = 13.8094(8) Å, α = 91.793(3)°, β = 89.989(4)°, γ = 106.967(2)°, V = 1727.5(2) Å^3, Z = 2, D_{calc} = 1.426 g cm^{-3}, number of unique reflections = 6118, R_{int} = 0.0400 up to 2θ = 55°, number of parameters = 442, R_1 = 0.0860, wR = 0.1637, gof = 1.373 for 5360 reflections. Since no chemically significant peaks were observed on the final difference Fourier maps for **1a** and **2a** in their inclusion complexes, it is very clear that 100% pure equatorial conformers are isolated as inclusion complexes. Some residual electron density peaks (2e Å^{-3}) around C35 and C38 of **1a** and **2a** were found as follows: for **1a**, 2e Å^{-3} at the coordinates (0.205,0.477,0.248) separates 1.46 Å from C35 at the coordinates (0.281, 0.519, 0.218) and ∠C35–the peak–C36 = 74.2°; 2e Å^{-3} at the coordinates (0.430, 0.428, 0.338) separates 1.01 Å from C38 at the coordinates (0343, 0.369, 0.355) and ∠ C37–the peak–C38 = 61.4°; for **2a**, 2e Å^{-3} at the coordinates (0.198, 0.477, 0.252) separates 0.98 Å from C35 at the coordinates (0.285, 0.514, 0.221), ∠ C35–the peak–C36 = 68.8°, 2e Å^{-3} at the coordinates (0.434, 0.429, 0.349) separates 1.03 Å from C38 at the coordinates (0.345, 0.370, 0.363), ∠ C37–the peak–C38 = 59.8°. However, no any distinct structure was not derived by calculation based on the electron density. Finally, no any disorder is present in these equatorial conformers, **1a** and **2a**. CCDC numbers 235182 and 235183. See http://www.rsc.org/suppdata/cc/b4/b409905m/ for crystallographic data in .cif or other electronic format.

1 P. Klaebe, *Acta Chem. Scand.*, 1969, **23**, 2641.
2 (*a*) M. Nishikawa, *Chem. Pharm. Bull.*, 1963, **11**, 977; (*b*) K. Fukushima, *J. Mol. Struct.*, 1976, **34**, 67; (*c*) A. Allen, V. Fawcett and D. A. Long, *J. Raman Spectrosc.*, 1976, **4**, 285.
3 K. D. M. Harris and J. M. Thomas, *J. Chem. Soc. Faraday Trans.*, 1990, **86**, 1095.
4 R. Gerdil and A. Frew, *J. Inclus. Phenom.*, 1985, **3**, 335.
5 M. Kato, K. Tanaka and F. Toda, *Supramol. Chem.*, 2001, **13**, 175.

Fig. 3 X-Ray structure of **6**.