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Enantiomers of 3-amino-1-methyl-1,2-dicarba-*closo*-dodecaborane

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Abstract—The enantiomers of 3-amino-1-methyl-1,2-dicarba-*closo*-dodecaborane were prepared by means of resolution of the racemic mixture via acylation by (*S*)-naproxen chloride followed by separation and subsequent acid hydrolysis of each of the diastereoisomeric amides. Partial racemization of enantiomeric 3-aminocarboranes was observed during acid hydrolysis.

1. Introduction

The icosahedral carboranes (dicarba-*closo*-dodecaboranes or 'carboranes') are chemical building blocks of high boron content.[1] They have characteristic properties such as remarkable thermal and chemical stability, spherical geometry and extraordinary hydrophobic character. Compounds containing the carborane cage are of great interest in the field of drug design, especially as radiopharmaceuticals in the boron neutron capture therapy of cancer.[2]

The physiological activity of such compounds should depend significantly on their stereo structure. So, the stereoisomers of carborane derivatives with structural isomerism caused by the relative position of substituents in a carborane cage is of special interest.

Introduction of a substituent in position 3 of 1-substituted 1,2-dicarba-*closo*-dodecaboranes makes the molecule chiral. Thus, 3-amino-1-methyl-1,2-dicarba-*closo*-dodeca-borane[3] **1** can exist in the two enantiomeric forms **1a** and **1b** (Fig. 1). However, to our knowledge, there is no literature data concerning the separation of both carborane **1** and other carborane derivatives with asymmetry resulting from the relative position of substituents in a carborane cage. Herein, we report the first example of the resolution of racemic carborane **1**.

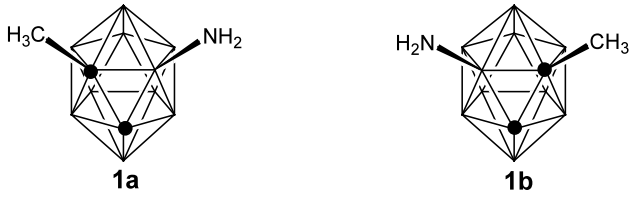

Figure 1. Structures of 3-amino-1-methyl-1,2-dicarba-*closo*-dodecaborane (**1**) enantiomers. In icosahedral cage structures, closed circles (●) represent carbon atoms and other vertices represent boron atoms.

2. Results and discussion

The resolution of carborane **1** was carried out by reaction of the racemate with (*S*)-naproxen acyl chloride[4] **2** followed by separation of the resulting diastereoisomeric amides **3a**–**3b** using column flash chromatography (SiO_2, benzene–ethyl acetate) and acid hydrolysis of each diastereoisomer (Scheme 1). The enantiomeric purity (d.e.) of amides **3a** and **3b** determined by HPLC and ^1H NMR spectroscopy was 93.7 and 98.0%, respectively.

Table 1 shows that the diastereoisomeric amides **3a** and **3b** can be distinguished easily on the basis of their ^1H NMR spectral data, and in this respect the resonance signal of the methyl group of the carborane moiety is the most indicative one with the difference in chemical shifts of 0.23 ppm.

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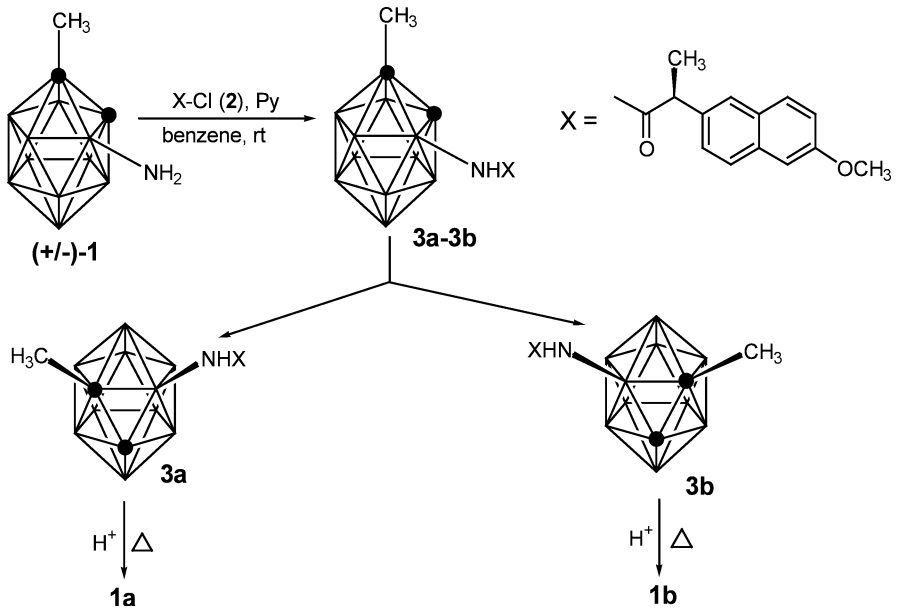

Scheme 1.

Table 1. Selected ^{1}H NMR spectral data for carborane **1** and amides **3a** and **3b**

Compound	Chemical shifts, δ (ppm)					
	Carborane fragment			Naproxen fragment		
	CH	NH	CH_3	OCH_3	CH	CH_3
1	3.18 br. s	1.43 br. s	1.97 s		–	
3a	5.61 br. s	5.03 br. s	1.62 s	3.92 s	3.77 q	1.57 d
3b	5.62 br. s	5.07 br. s	1.85 s	3.93 s	3.78 q	1.59 d

Assignment of the absolute configuration of amide **3a** became possible on the basis of X-ray crystallography (Fig. 2) and was established from the known absolute configuration of enantiopure (*S*)-naproxen. In the unit cell there are two crystallographically independent molecules with nearly the same parameters. Considerable variation from one molecule to another consists of the orientation of substituents in naphthalene ring. The torsion angles (°) C7–C6–C10–C11 and C1–C2–O1–C9 were found to be −127.0(4) and 13.8(8), −98.2(5) and 1.9(8), respectively, for one and another molecule.

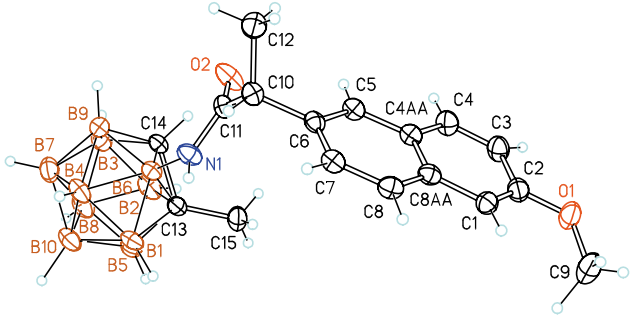

Figure 2. A perspective molecular view of amide **3a**.

Amides **3a** and **3b** were hydrolyzed while heating under reflux in a mixture of concentrated hydrochloric and acetic acids for 15 h. Enantiomers **1a** and **1b** were isolated after standard workup of the appropriate reaction mixtures. The enantiomeric purity of carboranes (+)-**1a** and (−)-**1b** was determined by HPLC with pre-column derivatization using (*S*)-naproxen acyl chloride, d.e. being 77.5 and 83.0%, respectively (Scheme 1).

While some researchers have presented evidence that complete racemization of (*S*)-naproxen was observed during a BOP-mediated esterification,[5] the interaction of the enantiopure amines or other compounds with acyl chloride **2** did not result in a loss of enantiomeric purity.[6] So, the above results suggest that acid hydrolysis of amides **3a** and **3b** is accompanied by the partial racemization of aminocarborane. This unexpected result merits further detailed investigation.

3. Experimental

3.1. General

Solvents were purified according to standard procedures. Routine monitoring of reactions was carried out using Silufol UV 254 (Kavalier) TLC aluminum plated silica gel. Melting points were determined on a Boetius

melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Bruker DRX 400 (400 MHz) spectrometer. ^{1}H NMR data for compound **1** was obtained from ^{11}B broad-band decoupled ^{1}H spectrum. All signals are expressed in ppm (δ) with tetramethylsilane as an internal standard. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Column chromatography was performed on Silica gel 60 (Lancaster Synthesis). The d.e. values of amides **3a** and **3b** were measured by HPLC on a Merck–Hitachi chromatograph with L-4000A Intelligent Pump, L-4000A UV Detector, and D-2500A Chromato-Integrator [Hibar Pre-packed Column RT250-4, Lichrosorb Si-60]; mobile phase: hexane:*i*-PrOH = 80:1, flow rate 1 mL/min; UV detection 230 nm; retention times $\tau_{\mathbf{3a}}$ 6.0 min, $\tau_{\mathbf{3b}}$ 10.1 min. Microanalyses were carried out on a CHNS-O model EA-1102 elemental analyzer and were in good agreement with the calculated values.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 190317. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.2. 3-{*N*-[(2*S*)-2-(6-Methoxynaphthyl-2)propionyl]}-amino-1-methyl-1,2-dicarba-*closo*-dodecaboranes, 3a and 3b

A solution of (*S*)-naproxen chloride **2** (0.622 g, 2.5 mmol) in benzene (5 mL) was added dropwise to a stirred solution of racemic **1** (0.433 g, 2.5 mmol) and pyridine (0.202 mL, 2.5 mmol) in benzene (5 mL). The mixture was stirred at room temperature for 20 h, then washed consequently with 1N HCl, water, 5% $NaHCO_3$, water and dried ($MgSO_4$). The solution was evaporated under reduced pressure to dryness yielding amide **3a**–**3b** as colorless crystals (0.781 g, 81%). Flash chromatography on a dry column (benzene/AcOEt: from 100:1 to 95:5) gave **3a** (faster eluting stereoisomer, 200 mg, 21%), and **3b** (slower eluting stereoisomer, 270 mg, 28%). Overall yield: 49%. Compound **3a**: d.e. 93.7% (HPLC). Mp: 161–164°C; R_f 0.46 (benzene/AcOEt: 98/2); $[\alpha]_D^{20}$ +37 (*c* 1, benzene); ^{1}H NMR ($CDCl_3$): 1.57 (d, J = 7.1 Hz, 3H, CH_3-naproxen), 1.62 (s, 3H, CH_3-carborane), 3.0–1.0 (m, 9H, 9×BH), 3.77 (q, J = 7.0 Hz, 1H, CH-naproxen), 3.92 (s, 3H, OCH_3), 5.03 (br. s, 1H, CH-carborane), 5.61 (br. s, 1H, NH), 7.73–7.13 (m, 6H, arom.). Anal. calcd for $C_{17}H_{27}B_{10}NO_2$: C, 52.97; H, 7.06; N, 3.63. Found: C, 52.73; H, 7.15; N, 3.42. Compound **3b**: *de* 98.0% (HPLC); Mp: 166-168°C; R_f 0.34 (benzene/AcOEt: 98/2); $[\alpha]_D^{20}$ +116 (*c* 1, benzene); ^{1}H NMR ($CDCl_3$): 1.59 (d, J = 7.2 Hz, 3H, CH_3-naproxen), 1.85 (s, 3H, CH_3-carborane), 3.0–1.0 (m, 9H, 9×BH), 3.78 (q, J = 7.1 Hz, 1H, CH-naproxen), 3.93 (s, 3H, OCH_3), 5.07 (br. s, 1H, CH-carborane), 5.62 (br. s, 1H, NH), 7.77–7.15 (m, 6H, arom.). Anal. calcd for $C_{17}H_{27}B_{10}NO_2$: C, 52.97; H, 7.06; N, 3.63. Found: C, 52.71; H, 7.12; N, 3.39%.

3.3. (+)-3-Amino-1-methyl-1,2-dicarba-*closo*-dodecaborane, 1a

Amide **3a** (118 mg, 0.31 mmol) was heated under reflux in a mixture of AcOH (4 mL) and HCl (4 mL) for 15 h. The reaction mixture was evaporated to dryness under reduced pressure. Then H_2O (5 mL) was added and the reaction mixture was cooled in an ice bath. The precipitate was filtered off and washed with H_2O (5 mL). The combined filtrates were treated with Na_2CO_3 until alkaline (pH 9) under ice-cooling. Filtration of precipitate gave compound **1a** as a white solid (40 mg, 75%). Mp 157–159°C; e.e. 77.5% (HPLC after derivatization with acyl chloride **2**); $[\alpha]_D^{20}$ +8.8 (C 1, EtOH); ^{1}H NMR ($CDCl_3$): 1.17–3.14 (m, 11H), 1.98 (s, 3H), 3.18 (br. s, 1H, CH). Anal. calcd for $C_3H_{15}B_{10}N$: C, 20.80; H, 8.73; N, 8.09. Found: C, 21.00; H, 8.83; N, 7.89%.

3.4. (−)-3-Amino-1-methyl-1,2-dicarba-*closo*-dodecaborane, 1b

Following the procedure reported above for the preparation of **1a** and starting with amide **3b** (138 mg, 0.36 mmol) compound **1b** was obtained as a white solid (48 mg, 77%). Mp 157–159°C; e.e. 83.0% (HPLC after derivatization with acyl chloride **2**); $[\alpha]_D^{20}$ −9.3 (*c* 1, EtOH); ^{1}H NMR ($CDCl_3$): 1.17–3.14 (m, 11H), 1.98 (s, 3H), 3.18 (br. s, 1H, CH). Anal. calcd for $C_3H_{15}B_{10}N$: C, 20.80; H, 8.73; N, 8.09. Found: C, 20.94; H, 8.95; N, 7.93%.

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