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Kinetic resolution of 1-methyl- and 1-phenyl-3-amino-1,2-dicarba-*closo*-dodecaboranes *via* acylation with chiral acyl chlorides

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A study of the kinetic resolution of racemic 1-substituted 3-amino-1,2-dicarba-*closo*-dodecaboranes by chiral acyl chlorides has shown that *N*-tosyl-(*S*)-prolyl and *N*-phthaloyl-(*S*)-alaninyl chlorides are more efficient resolving agents than (*S*)-naproxen chloride.

The icosahedral carboranes (dicarba-*closo*-dodecaboranes or 'carboranes') are compounds featuring an unusually high boron content.[1] Compounds containing the carborane cage are of great interest as building blocks in drug design, especially as radiopharmaceuticals for the boron neutron capture therapy (BNCT) of cancer.[2,3] It is clear that the physiological activity of these compounds may significantly depend on their stereo structure. However, the biological properties of chiral carboranes have not so far been studied.

Recently, we prepared both of the enantiomers of 3-amino-1-methyl-1,2-dicarba-*closo*-dodecaborane **1** using (*S*)-naproxen chloride as a chiral resolving agent (CRA).[4] Structural isomerism of such carboranes is caused by relative positions of substituents in the carborane cage (Figure 1).†

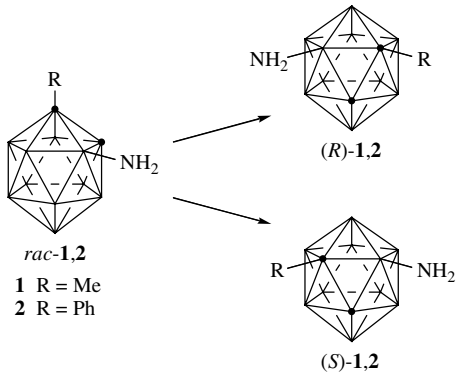
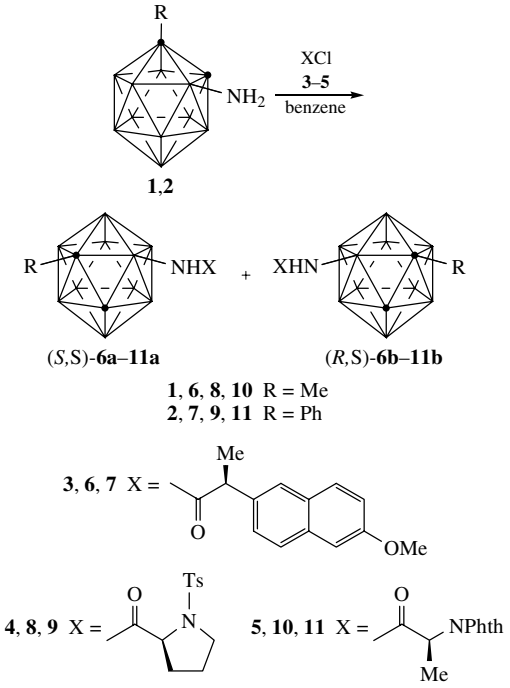


Figure 1

The aim of this work was to study the acylative kinetic resolution of 1-substituted 3-aminocarboranes **1** and **2**. Previously, we found that optically active acyl chlorides **3**–**5** are convenient CRAs for the kinetic resolution of heterocyclic amines,[6–10]

† In icosahedral cage structures, closed circles represent carbon atoms and other vertices represent boron atoms. For convenience in the designation of the configuration of planar-chiral carboranes and their derivatives, we used the approach suggested for chiral 7,8-dicarba-*nido*-undecaboranes.[5] The observer looks onto the plane of $C^1R–C^2H–B^3NHX$ face of a carborane cage and then examines the positions of substituents according to the Cahn–Ingold–Prelog rule.



Scheme 1

enabling one to obtain enantiomers of heterocyclic amines of high stereoselectivity. Therefore, it was reasonable to use these agents for the kinetic resolution of 3-aminocarboranes **1** and **2**.

We used acyl chlorides of (*S*)-naproxen **3**, *N*-tosyl-(*S*)-proline **4** and *N*-phthaloyl-(*S*)-alanine **5** as CRAs. Acylation of racemic carboranes **1** and **2** with acyl chlorides **3–5** (in a 2:1 molar ratio) was carried out in benzene at room temperature (Scheme 1).‡ The ratio of resulting diastereomeric amides was determined by HPLC§ and ^{1}H NMR¶ spectroscopy.

Higher diastereoselectivity was observed when N-protected amino acid chlorides **4** and **5** were used as CRAs as compared with (*S*)-naproxen chloride (**3**). We also found that, in the case of acyl chloride **4** as a resolving agent, (*S*,*S*)-amides **8a**, **9a** were formed predominantly (de 28 and 36%, respectively), while kinetic resolution by acyl chloride **5** resulted in the formation of (*R*,*S*)-amides **10b** and **11b** as major products (de 30 and 39%, respectively). Acylation by acyl chloride **3** proved to result in a lower diastereoselectivity of the (*S*,*S*)-amides (**6a**, de 8% and **7a**, de 16%). Unreacted isomers of 3-amino-

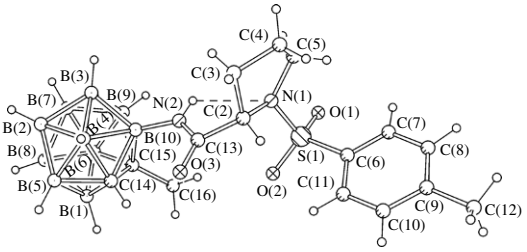


Figure 2 X-Ray crystal structure of (*R*,*S*)-amide **8b**.

‡ To a stirred solution of carborane **1** or **2** (2 mmol) in dry benzene (5 ml) a solution of acyl chloride **3–5** (1 mmol) in dry benzene (5 ml) was added dropwise. The reaction mixture was stirred at room temperature for 24 h, then washed consequently with 1 N HCl, water, 5% $NaHCO_3$ and water and dried ($MgSO_4$). The resulting solution was evaporated to dryness to give a yellow oily residue, which was subjected to column chromatography or crystallization.

§ The de values of amides **6–11** 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–Pr^{i}OH, 80:1 (A), hexane–Pr^{i}OH, 200:1 (B), hexane–Pr^{i}OH, 40:1 (C), flow rate of 1 ml min^{-1}; UV detection at 230 nm; $\tau_{\mathbf{6a}}$ 10.1 min, $\tau_{\mathbf{6b}}$ 6.0 min (A); $\tau_{\mathbf{7a}}$ 10.4 min, $\tau_{\mathbf{7b}}$ 8.6 min (B); $\tau_{\mathbf{8a}}$ 15.4 min, $\tau_{\mathbf{8b}}$ 10.6 min (C); $\tau_{\mathbf{9a}}$ 24.0 min, τ_{9b} 18.6 min (A); $\tau_{\mathbf{10a}}$ 15.4 min, $\tau_{\mathbf{10b}}$ 20.3 min (A); $\tau_{\mathbf{11a}}$ 17.5 min, $\tau_{\mathbf{11b}}$ 16.7 min (A).

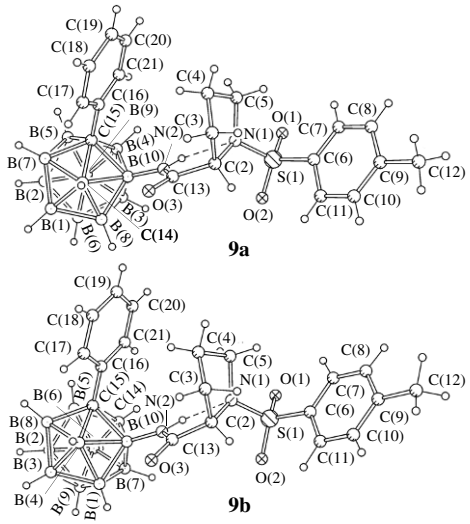


Figure 3 X-ray crystal structures of (*S*,*S*)-amide **9a** and (*R*,*S*)-amide **9b**.

carboranes **1** and **2** of the corresponding optical purity could be isolated after an appropriate treatment of the reaction mixtures.††

Individual diastereomers **7a**, **8a**, **8b**, **9b**, **10a**, **10b** and **11b** (de > 90%) were isolated from diastereomeric mixtures by column chromatography or fractional crystallization.‡‡

The assignment of the absolute configuration of amides **8b**, **9a**, **9b**, and **11b** was performed by X-ray analysis§§ taking into account the known absolute configurations of the acyl fragments (Figures 2–4). Assignment of configuration in carborane fragments of amides **7a–b** and **10a–b** was carried out by HPLC

¶ ^{1}H NMR spectra were recorded on a Bruker DRX 400 spectrometer in $CDCl_3$ at ambient temperature, all signals are given in ppm (δ) with TMS as an internal standard.

6a,**b**: 7.77–7.13 (m, 6H, arom.), 5.62 and 5.61 (2br. s, 1H, CH-carborane), 5.07 and 5.03 (2br. s, 1H, NH), 3.93 and 3.92 (2s, 3H, OMe), 3.78 and 3.77 (2q, 1H, CH-naproxen, *J* 7.0 Hz), 3.0–1.0 (m, 9H, 9BH), 1.85 and 1.62 (2s, 3H, Me-carborane), 1.59 and 1.57 (2d, 3H, Me-naproxen, *J* 7.1 Hz).

7a,**b**: 7.65–7.09 (m, 11H, arom.), 5.58 and 5.55 (2br. s, 1H, CH-carborane), 5.27 (br. s, 1H, NH), 3.94 and 3.93 (2s, 3H, OMe), 3.54 and 3.34 (2q, 1H, CH-naproxen, *J* 7.3 Hz), 3.0–1.0 (m, 9H, 9BH), 1.36 and 1.30 (2d, 3H, Me-naproxen, *J* 7.2 Hz).

8a,**b**: 7.75 (m, 2H, arom.), 7.37 (m, 2H, arom.), 7.19 and 7.17 (2br. s, 1H, NH), 4.97 and 4.88 (2br. s, 1H, CH-carborane), 4.10 and 3.99 (2dd, 1H, CH-proline, *J* 8.5 and 3.5 Hz, *J* 8.5 and 4.0 Hz), 3.45 (m, 1H, C^{5}H-proline), 3.24 (m, 1H, C^{5}H-proline), 3.0–1.0 (m, 9H, 9BH), 2.46 (s, Me-tosyl), 2.18–2.02 (m, 2H, C^{3}H$_2$-proline), 1.88–1.52 (m, 2H, C^{4}H$_2$-proline), 1.99 and 1.88 (2s, 3H, Me-carborane).

9a,**b**: 7.73–7.28 (m, 9H, arom.), 6.96 (br. s, 1H, NH), 5.53 and 5.42 (2br. s, 1H, CH-carborane), 3.87 and 3.59 (2dd, 1H, CH-proline, *J* 8.5 and 3.5 Hz, *J* 8.7 and 2.8 Hz), 3.44–2.93 (m, 2H, C^{5}H-proline), 3.0–1.0 (m, 9H, 9BH), 2.43 (s, Me-tosyl), 2.00–0.64 (m, 4H, C^{3}H$_2$-C^{4}H$_2$-proline).

10a,**b**: 7.88 (m, 2H, arom.), 7.76 (m, 2H, arom.), 6.17 and 6.15 (2br. s, 1H, NH), 5.03 and 5.00 (2br. s, 1H, CH-carborane), 4.99 and 4.98 (2q, 1H, CH-alanine, *J* 7.3 Hz), 3.0–1.3 (m, 9H, 9BH), 1.94 and 1.92 (2s, 3H, Me-carborane), 1.76 and 1.68 (2d, 3H, Me-alanine, *J* 7.3 Hz).

11a,**b**: 7.83–7.73 (m, 4H, C_6H_4), 7.3–7.0 (m, 5H, Ph), 6.21 and 6.20 (2br. s, 1H, NH), 5.41 and 5.39 (2br. s, 1H, CH-carborane), 4.68 and 4.63 (2q, 1H, CH-alanine, *J* 7.4 Hz), 3.0–1.5 (m, 9H, 9BH), 1.44 and 1.38 (2d, 3H, Me-alanine, *J* 7.4 Hz).

†† Unreacted 3-aminocarboranes **1** as hydrochlorides were filtered off from the reaction mixtures. Yields were about 45%, taking into account the starting racemate. Ee was determined by HPLC after pre-column derivatization with acyl chloride **3**.[4] Mp 157–160 °C. Found (%): C, 17.82; H, 7.97; Cl, 15.94; N, 6.38. Calc. for $C_3H_{16}B_{10}ClN$ (%): C, 17.18; H, 7.69; Cl, 16.90; N, 6.68.

Unreacted 3-aminocarboranes **2** were separated from the mixtures of amides by column (or flash) chromatography as the fastest eluted substances. Yields were about 30–35%, taking into account the starting racemate. Ee was determined by HPLC after pre-column derivatization with acyl chloride **3**.[4] Mp 68–70 °C. Found (%): C, 40.13; H, 7.56; N, 5.63. Calc. for $C_8H_{17}B_{10}N$ (%): C, 40.83; H, 7.28; N, 5.95.

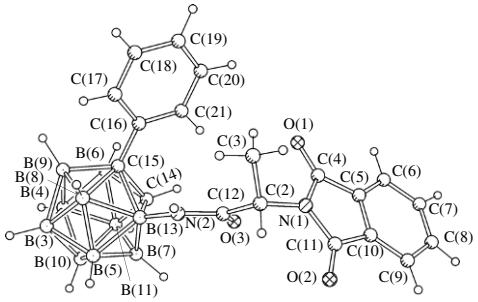


Figure 4 X-ray crystal structure of (*R*,*S*)-amide **11b**.

analysis of unreacted 3-aminocarboranes **2** and **1**, respectively, after pre-column derivatization with acyl chloride **3**.[4]

In conclusion, it should be noted that optically active acyl chlorides could be used as chiral resolving agents for the kinetic resolution of racemic 1-substituted 3-aminocarboranes. Further studies are necessary to optimise the process.

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‡‡ **7a**: 14% yield after column chromatography, oil. De 98% [HPLC: τ_R 10.4 min (B)]. ^{1}H NMR, δ: 7.65–7.11 (m, 11H, arom.), 5.55 (br. s, 1H, CH-carborane), 5.27 (br. s, 1H, NH), 3.93 (s, 3H, OMe), 3.34 (q, 1H, CH-naproxen, *J* 7.3 Hz), 3.0–1.0 (m, 9H, 9BH), 1.36 (d, 3H, Me-naproxen, *J* 7.2 Hz).

7b: 10% yield after column chromatography, oil. De 72% [HPLC: τ_R 8.4 min (B)]. ^{1}H NMR, δ: 7.60–7.08 (m, 11H, arom.), 5.58 (br. s, 1H, CH-carborane), 5.27 (br. s, 1H, NH), 3.94 (s, 3H, OMe), 3.54 (q, 1H, CH-naproxen, *J* 7.3 Hz), 3.0–1.0 (m, 9H, 9BH), 1.30 (d, 3H, Me-naproxen, *J* 7.2 Hz).

8a: 14% yield after flash chromatography. Mp 198–200 °C. De 92% [HPLC: τ_R 15.4 min (C)]. ^{1}H NMR, δ: 7.73 (m, 2H, arom.), 7.37 (m, 2H, arom.), 7.17 (br. s, 1H, NH), 4.97 (br. s, 1H, CH-carborane), 3.99 (dd, 1H, CH-proline, *J* 8.5, 4.0 Hz), 3.67 (ddd, 1H, C^{5}H-proline, *J* 10.4, 6.3, 4.4 Hz), 3.24 (m, 1H, C^{5}H-proline), 3.0–1.0 (m, 9H, 9BH), 2.46 (s, Me-tosyl), 2.18–2.02 (m, 2H, C^{3}H$_2$-proline), 1.88–1.52 (m, 2H, C^{4}H$_2$-proline), 1.88 (s, 3H, Me-carborane).

8b: 36% yield after recrystallization from methanol. Mp 241–242 °C. $[\alpha]_D$ –168° (*c* 1.4, $CHCl_3$). De 98% [HPLC: τ_R 10.6 min (C)]. ^{1}H NMR δ: 7.77 (m, 2H, arom.), 7.37 (m, 2H, arom.), 7.19 (br. s, 1H, NH), 4.88 (br. s, 1H, CH-carborane), 4.10 (dd, 1H, CH-proline, *J* 8.5 and 3.5 Hz), 3.45 (m, 1H, C^{5}H-proline), 3.24 (m, 1H, C^{5}H-proline), 3.0–1.0 (m, 9H, 9BH), 2.46 (s, Me-tosyl), 2.18–2.02 (m, 2H, C^{3}H$_2$-proline), 1.88–1.52 (m, 2H, C^{4}H$_2$-proline), 1.99 (s, 3H, Me-carborane).

9a: 35% yield after recrystallization from hexane–ethyl acetate. Mp 172–178 °C. De 86% [HPLC: τ_R 24.2 min (A)]. ^{1}H NMR, δ: 7.70 (m, 2H, C_6H_4), 7.32 (m, 2H, C_6H_4), 7.42–7.32 (m, 5H, Ph), 6.96 (br. s, 1H, NH), 5.42 (br. s, 1H, CH-carborane), 3.59 (dd, 1H, CH-proline, *J* 8.7 and 2.8 Hz), 3.44 (ddd, 1H, C^{5}H-proline, *J* 10.2, 6.7 and 3.6 Hz), 3.15 (ddd, 1H, C^{5}H-proline, *J* 10.2, 9.1 and 6.9 Hz), 3.0–1.0 (m, 9H, 9BH), 2.43 (s, Me-tosyl), 2.00–1.36 (m, 4H, C^{3}H$_2$–C^{4}H$_2$-proline).

9b: 43% yield after recrystallization from methanol. Mp 238 °C. $[\alpha]_D$ –170° (*c* 0.9, $CHCl_3$). De 90% [HPLC: τ_R 18.6 min (A)]. ^{1}H NMR, δ: 7.49 (m, 2H, C_6H_4), 7.30 (m, 2H, C_6H_4), 7.46–7.34 (m, 5H, Ph), 6.96 (br. s, 1H, NH), 5.42 (br. s, 1H, CH-carborane), 3.59 (dd, 1H, CH-proline, *J* 8.7 and 2.8 Hz), 3.44 (ddd, 1H, C^{5}H-proline, *J* 10.2, 7.3 and 3.9 Hz), 3.15 (ddd, 1H, C^{5}H-proline, *J* 10.2, 9.1 and 6.9 Hz), 3.5–1.2 (m, 9H, 9BH), 2.43 (s, Me-tosyl), 2.00–1.36 (m, 4H, C^{3}H$_2$-C^{4}H$_2$-proline).

10a: 35% yield after flash chromatography. Mp 213–217 °C. De 90.4% [HPLC: τ_R 15.4 min (A)]. ^{1}H NMR, δ: 7.90 (m, 2H, arom.), 7.79 (m, 2H, arom.), 6.15 (br. s, 1H, NH), 5.03 (br. s, 1H, CH-carborane), 4.98 (q, 1H, CH-alanine, *J* 7.3 Hz), 3.0–1.3 (m, 9H, 9BH), 1.92 (s, 3H, Me-carborane), 1.68 (d, 3H, Me-alanine, *J* 7.3 Hz).

10b: 43% yield after flash chromatography. Mp 137–139 °C. $[\alpha]_D$ –47.3° (*c* 0.8, $CHCl_3$). De 92.8% [HPLC: τ_R 20.3 min (A)]. ^{1}H NMR, δ: 7.88 (m, 2H, arom.), 7.76 (m, 2H, arom.), 6.17 (br. s, 1H, NH), 5.00 (q, 1H, CH-alanine, *J* 7.3 Hz), 4.99 (br. s, 1H, CH-carborane), 3.0–1.4 (m, 9H, 9BH), 1.94 (s, 3H, Me-carborane), 1.76 (d, 3H, Me-alanine, *J* 7.3 Hz).

11a: 19% yield after flash chromatography. Mp 192–197 °C. $[\alpha]_D$ +93° (*c* 1.3, $CHCl_3$). De 75.4% [HPLC: τ_R 17.5 min (A)]. ^{1}H NMR, δ: 7.83–7.73 (m, 4H, C_6H_4), 7.3–7.0 (m, 5H, Ph), 6.20 (br. s, 1H, NH), 5.39 (br. s, 1H, CH-carborane), 4.68 (q, 1H, CH-alanine, *J* 7.4 Hz), 3.0–1.5 (m, 9H, 9BH), 1.44 (d, 3H, Me-alanine, *J* 7.4 Hz).

11b: 34% yield after flash chromatography. Mp 197–198 °C. $[\alpha]_D$ –143° (*c* 0.9, benzene). De 100% [HPLC: τ_R 16.7 min (A)]. ^{1}H NMR, δ: 7.85–7.72 (m, 4H, C_6H_4), 7.3–7.0 (m, 5H, Ph), 6.21 (br. s, 1H, NH), 5.41 (br. s, 1H, CH-carborane), 4.63 (q, 1H, CH-alanine, *J* 7.4 Hz), 3.0–1.5 (m, 9H, 9BH), 1.38 (d, 3H, Me-alanine, *J* 7.4 Hz).

§§ *Crystal data for* **8b**: $C_{15}H_{28}B_{10}N_2O_3S$, M = 424.55, monoclinic, a = 11.0757(9), b = 7.4986(4) and c = 13.8135(9) Å, β = 102.631(7)°, U = 1119.5(1) Å^3, space group $P2_1$, Z = 2, d_{calc} = 1.259 g cm^{-3}, μ(MoKα) = = 0.165 mm^{-1}, 2637 reflections measured, 2509 unique (R_{int} = 0.015) reflections were used in the calculations. The final R (obs.) was 0.0331.

Crystal data for **9a**: $C_{20}H_{30}B_{10}N_2O_3S$, M = 486.62, orthorhombic, a = 6.494(2), b = 15.151(5) and c = 26.375(8) Å, U = 2595.1(15) Å^3, space group $P2_12_12_1$, Z = 4, d_{calc} = 1.246 g cm^{-3}, μ(MoKa) = 0.152 mm^{-1}, 2637 unique reflections were measured and used in the calculations. The final R (obs.) was 0.0639.

Crystal data for **9b**: $C_{20}H_{30}B_{10}N_2O_3S$, M = 486.62, orthorhombic, a = 6.625(3), b = 15.422(7) and c = 26.140(11) Å, U = 2670.8(19) Å^3, space group $P2_12_12_1$, Z = 4, d_{calc} = 1.210 g cm^{-3}, μ(MoKα) = 0.147 mm^{-1}, 2696 unique reflections were measured and used in the calculations. The final R (obs.) was 0.0746.

Crystal data for **11b**: $C_{19}H_{24}B_{10}N_2O_3$, M = 436.50, orthorhombic, a = 9.2125(18), b = 11.3527(19) and c = 23.462(3) Å, U = 2453.8(7) Å^3, space group $P2_12_12_1$, Z = 4, d_{calc} = 1.182 g cm^{-3}, μ(CuKα) = 0.554 mm^{-1}, 2648 unique reflections were measured and used in the calculations. The final R (obs.) was 0.0415.

X-ray data were measured at 297 K on Bruker P4 (MoKα) and Syntex $P2_1$ (CuKα) diffractometers with graphite-monochromated radiation using $\theta/2\theta$ scans. The structures were solved by the direct methods using the SHELXS-97 program and refined in the full-matrix anisotropic (isotropic for H atoms) approximation by the SHELXL-97 program.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference numbers 256892–256895. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2004.