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# Acidic hydrolysis of *N*-acyl-1-substituted 3-amino-1,2-dicarba-*closo*-dodecaboranes

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**Abstract**

Acidic hydrolysis of *N*-acyl 1-methyl- and 1-phenyl-3-amino-1,2-dicarba-*closo*-dodecaboranes has been studied. It has been shown that acidic hydrolysis of diastereomeric amides of 1-methyl-3-amino-1,2-dicarba-*closo*-dodecaborane results in the partial racemization of the target 3-amino-1-methylcarborane. Under the similar conditions, the hydrolysis of *N*-acyl-3-amino-1-phenyl-1,2-dicarba-*closo*-dodecaboranes resulted in amide bond cleavage accompanied by simultaneous deboronation with the removal of boron atom at position 6 of carborane cage and formation of 7,8-dicarba-*nido*-undecaborane derivative according to $^{11}B$ and $^{1}H$ NMR spectroscopy.


*Keywords:* 3-Amino-1,2-dicarba-*closo*-dodecaboranes; Amides; Acidic hydrolysis; Racemization; Deboronation; NMR spectroscopy

## 1. Introduction

The icosahedral carboranes (dicarba-*closo*-dodecaboranes or "carboranes") are compounds featuring a high boron content [1]. Compounds containing the carborane cage are of great interest as building blocks in the field of drug design, especially as radiopharmaceuticals for the boron neutron capture therapy of cancer [1b,2]. The physiological activity of such compounds should significantly depend on their stereo structure.

Recently, we have obtained both enantiomers of 3-amino-1-methyl-1,2-dicarba-*closo*-dodecaborane (**1**) using (*S*)-naproxen chloride as a chiral resolving agent (CRA) [3]. Structural isomerism of such carboranes is caused by relative position of substituents in the carborane cage (Fig. 1). For convenience in the designation of the configuration of planar-chiral carboranes and their derivatives we have used the approach suggested for chiral 7,8-dicarba-*nido*-undecaborane derivatives [4]. The observer looks onto the plane of $C^1R–C^2H–B^3NHX$ face of carborane cage and then examines the position of substituents according to the Cahn–Ingold–Prelog rule.

Previously, we have shown that chiral acyl chlorides, such as (*S*)-naproxen chloride, *N*-tosyl-(*S*)-prolyl chloride and *N*-phthaloyl-(*S*)-alanyl chloride are convenient and efficient CRAs for the kinetic resolution of heterocyclic amines [5]. To optimize the process of optical resolution of 1-substituted 3-aminocarboranes **1** and **2**, we studied the kinetic resolution of racemic carboranes

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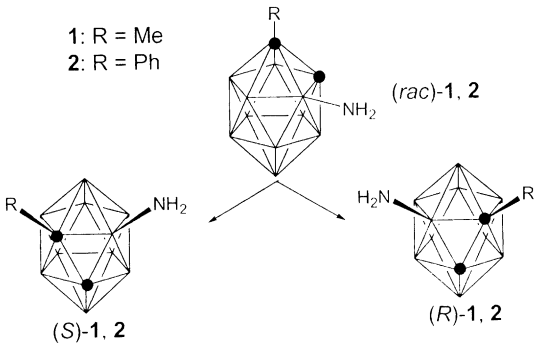



Fig. 1. In icosahedral cage structures, closed circles (•) represent carbon atoms and other vertices represent boron atoms. Hydrogen atoms are omitted for clarity.

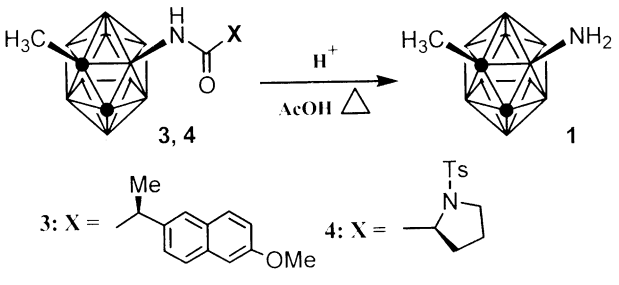
via acylation with these CRAs [6]. The individual diastereomeric amides obtained were isolated from diastereomeric mixtures by column chromatography or fractional crystallization. The next step in preparation of enantiomers of 1-substituted 3-aminocarboranes **1** and **2** is hydrolysis of amide bond. In this communication, we present the results of acidic hydrolysis of amides of carboranes **1** and **2**.

## 2. Results and discussion

Hydrolysis of the amides was carried out in a mixture of glacial AcOH and concentrated HCl under reflux. Recently, it has been shown that acidic hydrolysis of both (*R*, *S*) and (*S*, *S*) diastereomeric amides **3** results in the partial racemization of the target 3-aminocarborane **1** [3]. Hydrolysis of *N*-tosyl-(*S*)-prolyl amide **4** of 3-amino-1-methylcarborane (*de* 92%) during 14 h also resulted in the racemization of the target carborane **1** (*ee* 46%) (Scheme 1) [7].

Identification of the isolated product **1** was accomplished with the aid of elemental analysis, and $^{1}H$ and $^{11}B$ NMR, including complete assignment of B signals based on 2D $^{11}B$–$^{11}B$ COSY, $^{1}H$–$^{1}H\{^{11}B\}$ COSY and $^{1}H$–$^{11}B$ HMQC experiments (Table 1).

It should be mentioned that in the case of acidic hydrolysis of *N*-tosyl-(*S*)-prolyl amide **4** racemization




Scheme 1.

Table 1
$^{11}B$ Chemical shifts of compounds **1**, **2** and **7**

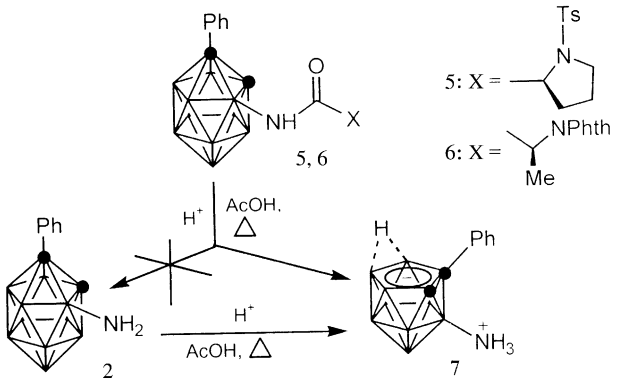
| Compound | $^{11}B$, $\delta$ (ppm) |
|---|---|
| 3-$NH_2$-1-Me-1,2-$C_2B_{10}H_9$ **1** (in $CDCl_3$) | 1.91 (B3) |
| | −4.18 (B9) |
| | −5.80 (B12) |
| | −8.27 (B8) |
| | −9.56 (B6) |
| | −10.31 (B5) |
| | −11.16 (B4) |
| | −12.77 (B7) |
| | −14.57 (B11) |
| | −16.11 (B10) |
| 3-$NH_2$-1-Ph-1,2-$C_2B_{10}H_9$ **2** (in acetone-$d_6$) | 4.53 (B3) |
| | −4.73 (B12) |
| | −6.01 (B9) |
| | −8.77 (B6, B8) |
| | −10.44 (B5) |
| | −11.58 (B4) |
| | −12.83 (B7) |
| | −15.39 (B11) |
| | −16.53 (B10) |
| 3-$NH_3^+$-7-Ph-7,8-$C_2B_9H_9^-$ **7** (in $CD_3OD$) | −5.64 (B11) |
| | −9.02 (B3) |
| | −9.74 (B9) |
| | −15.55 (B5) |
| | −17.21 (B6) |
| | −19.93 (B2) |
| | −21.65 (B4) |
| | −34.35 (B10) |
| | −35.58 (B1) |

of 3-aminocarborane **1** was greater than in the case of hydrolysis of amides **3**, cf. from *de* 98% to *ee* 83% for hydrolysis of amide **3**, and from *de* 92% to *ee* 46% for amide **4**. However, acidic hydrolysis of *N*-acyl heterocyclic amines of this kind proceeded without racemization of amine fragment [5].

Under the similar conditions the hydrolysis of 3-amino-1-phenyl-1,2-dicarba-*closo*-dodecaborane amides 5 and 6 resulted in amide bond cleavage accompanied by simultaneous deboronation with the removal of boron atom at position 6 of carborane cage and formation of 3-ammonium-7-phenyl-7,8-dicarba-*nido*-undecaborate **7** (Scheme 2) according to $^{1}H$ and $^{11}B$ NMR spectra, including 2D $^{11}B$–$^{11}B$ COSY, $^{1}H$–$^{1}H\{^{11}B\}$ COSY and $^{1}H$–$^{11}B$ HMQC experiments (Table 1).

To explain this phenomenon, we carried out the "model" experiments. Racemic 3-aminocarborane **2** was refluxed in a mixture of $CD_3COOD$ and DCl for 22 h. The reaction mixture was monitored by $^{1}H$ and $^{11}B$ NMR at intervals.

CH signal of hydrochloride of 3-aminocarborane **2** ($\delta$ 5.58 ppm) disappeared gradually with simultaneous appearance of CH signal at $\delta$ 6.41 ppm and signal of bridging H at $\delta$ −2.3 ppm. In $^{11}B$ NMR spectra we observed the gradual appearance of the signals at $\delta$ −34.17 and −35.74 ppm.




Scheme 2.

It should be noted that it comes as a surprise that treatment of 3-aminocarborane derivative in strongly acidic medium results in its deboronation, since to our knowledge, the deboronation of *closo*-dodecaboranes has been described in the literature under neutral conditions [8] or basic conditions, in the presence of the powerful Lewis bases [9]. Thus, instead of the individual enantiomers of carborane **2** we obtained 7,8-dicarba-*nido*-undecaborane derivative **7** as a result of acidic hydrolysis of amides **5** and **6**.

In conclusion, the mechanisms of racemization of 3-amino-1-methyl-1,2-carborane **1** and deboronation of 3-amino-1-phenyl-1,2-carborane **2** in acidic medium seem to be not obvious. So, we are currently examining acid promoted mechanisms of both racemization and deboronation to explain these phenomena.

## 3. Experimental

### 3.1. General

Racemic 3-aminocarboranes **1** and **2** were synthesized according to the procedure described [10].

$^{1}H$ and $^{11}B$ NMR spectra were recorded on a Bruker DRX 400 spectrometer operating at 400.13 and 128.38 MHz, respectively. $^{1}H$ NMR data for compounds **1**, **2** and **7** were obtained from $^{11}B$ broad-band decoupled $^{1}H$ spectra. All signals are expressed in ppm ($\delta$) with tetramethylsilane as an internal standard for $^{1}H$ NMR. Chemical shift values for $^{11}B$ NMR spectra were referenced to external $BF_3 \times OEt_2$ in deuterated solvents. Infrared spectrum was recorded in neat on a Perkin–Elmer Spectrum One FT-IR spectrometer.

The *de* values of amides **3** and **4** 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]; flow rate of 1 ml/min; UV detection at 230 nm; mobile phase: hexane: *i*-PrOH = 80:1 (A), hexane-*i*-PrOH, 40:1 (B); retention times $\tau_{3a}$ 6.0 min, $\tau_{3b}$ 10.1 min (A); $\tau_{4a}$ 15.4 min, $\tau_{4b}$ 10.6 min (B). Microanalyses were carried out on a CHNS-O model EA-1102 elemental analyzer and were in good agreement with the calculated values.

### 3.2. (*S*)-(−)-3-Amino-1-methyl-1,2-dicarba-closo-dodeca-borane (*S*)-(−)-*1*

(*S*,*S*)-Amide **3** (118 mg, 0.31 mmol, *de* 98%, HPLC, $\tau_{S,S}$ 10.1 min) was re fluxed in the mixture of AcOH (4 mL) and concentrated HCl (4 mL) for 14 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 alkalized by $Na_2C0_3$ up to pH 9 under ice-cooling. Filtration of precipitate gave compound (*S*)-**1** as a white solid (40 mg, 75%). Mp 157–159 °C; *ee* 83% (HPLC after derivatization with (*S*)-naproxen chloride); $^{1}H\{^{11}B\}$ NMR ($CDCl_3$): 1.42 (br. s, 2H, $NH_2$), 1.83 (s, 1H, $H^{10}$), 1.86(s, 1H, $H^4$), 1.91 (s, 1H, $H^{11}$), 1.97 (s, 3H, $CH_3$), 2.10 (br. s, 2H, $H^9$ and $H^{12}$), 2.13 (br. s, 2H, $H^5$ and $H^7$), 2.30 (s, 1H, $H^8$), 2.43 (s, 1H, $H^6$), 3.18 (s, 1H, CH). Anal. Calc. 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%.

Following the procedure reported above for hydrolysis of (*S*,*S*)-amide **3** and starting with (*S*,*S*)-amide **4** (201 mg, 0.47 mmol, *de* 92%) compound (*S*)-**1** was obtained as a white solid (51 mg, 63%). Mp 157–159 °C; *ee* 46% (HPLC after derivatization with (*S*)-naproxen chloride). Anal. Calc. for $C_3H_{15}B_{10}N$: C, 20.80; H, 8.73; N, 8.09. Found: C, 20.96; H, 8.85; N, 7.98%.

### 3.3. 3-Ammonium-7-phenyl-7,8-dicarba-nido-undecaborate 7

Amide **5** or **6** (0.53 mmol) was refluxed in the mixture of AcOH (4 mL) and concentrated HC1 (4 mL) for 14 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 alkalized by $Na_2CO_3$ up to pH 5 under ice-cooling, then extracted by ethyl acetate, dried ($Na_2SO_4$). Removal of the solvent under reduced pressure gave compound **7** as a white solid (88 mg, 74%). Mp 105–110 °C; IR (neat, $cm^1$): 3627, 3216, 3057, 2986, 2539, 1702, 1648, 1597, 1494, 1445, 1375, 1042, 763, 699. $^{1}H\{^{11}B\}$ NMR ($CD_3OD$): −2.38 (br. s, 1H, B–H–B), 0.13 (s, 1H, $H^{10}$), 0.97 (s, 1H, $H^1$), 1.27 (s, 1H, $H^6$), 1.35 (s, 1H, $H^5$), 1.46 (s, 1H, $H^4$), 1.87 (s, 1H, $H^2$), 2.16 (br. s, 2H, $H^9$ and $H^{11}$), 2.39 (s, 1H, CH), 6.90 (br. s, 3H, $NH_3$), 7,13 (m, 3H, Ph), 7.21 (m, 2H, Ph). Anal. Calc. for $C_8H_{18}B_9N$: C, 42.60; H, 8.04; N, 6.21. Found: C, 43.08; H, 8.15; N, 5.73%.

### 3.4. NMR experiment

3-Aminocarborane **2** (150 mg, 0.64 mmol) was refluxed in a mixture of $CD_3COOD$ (5 mL) and concentrated DCl (5 mL) for 22 h. The reaction mixture was monitored by $^1H$ and $^{11}B$ NMR spectroscopy at intervals, in 4, 7, 15, and 22 h.

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## References

[1] (a) V.I. Bregadze, Chem. Rev. 92 (1992) 209;
(b) V.N. Kalinin, V.A. Ol'shevskaya, Boron Chemistry at the Beginning of the 21st Century, Editorial URSS, Moscow, 2003, pp. xiii–xxiv.

[2] (a) M.F. Hawthorne, Angew. Chem., Int. Ed. Eng. 32 (1993) 950;
(b) A.H. Soloway, W. Tjarks, B.A. Barnum, F.-G. Rong, R.F Barth, I.M. Codogni, J.G. Wilson, Chem. Rev. 98 (1998) 1515.

[3] V.P. Krasnov, G.L. Levit, V.N. Charushin, A.N. Grishakov, M.I. Kodess, V.N. Kalinin, V.A. Ol'shevskaya, O.N. Chupakhin, Tetrahedron: Asymmetr. 13 (2002) 1833.

[4] H. Brunner, A. Apfelbacher, M. Zabel, Eur. J. Inorg. Chem. (2001) 917.

[5] (a) V.N. Charushin, V.P. Krasnov, G.L. Levit, M.A. Korolyova, M.I. Kodess, O.N. Chupakhin, M.H. Kim, H.S. Lee, Y.J. Park, K.-Ch. Kim, Tetrahedron: Asymmetr. 10 (1999) 2691;
(b) V.P. Krasnov, G.L. Levit, I.N. Andreeva, A.N. Grishakov, V.N. Charushin, O.N. Chupakhin, Mendeleev Commun. 12 (2002) 27;
(c) V.P. Krasnov, G.L. Levit, I.M. Bukrina, I.N. Andreeva, L.Sh. Sadretdinova, M.A. Korolyova, M.I. Kodess, V.N. Charushin, O.N. Chupakhin, Tetrahedron: Asymmetr. 14 (2003) 1985;
(d) V.P. Krasnov, G.L. Levit, M.I. Kodess, V.N. Charushin, O.N. Chupakhin, Tetrahedron: Asymmetr. 15 (2004) 859.

[6] G.L. Levit, V.P. Krasnov, A.M. Demin, M.I. Kodess, L.Sh. Sadretdinova, T.V. Matveeva, V.A. Ol'shevskaya, V.N. Kalinin, O.N. Chupakhin, V.N. Charushin, Mendeleev Commun. 14 (2004) 293.

[7] The stereo purity of carborane **1** was determined by HPLC and $^1H$ NMR spectra with preliminary derivatization by *(S)*-naproxen or *N*-tosyl-(5)-prolyl chlorides.

[8] E. Svantesson, J. Pettersson, A. Olin, K. Markides, S. Sjoberg, Acta Chem. Scand. 53 (1999) 731.

[9] (a) R.A. Wiesboeck, M.F. Hawthorne, J. Am. Chem. Soc. 86 (1964) 1642;
(b) L.I. Zakharkin, V.N. Kalinin, J. Gen. Chem. USSR (Engl. Transl.) 35 (1965) 1693;
(c) L.I. Zakharkin, V.A. OPshevskaya, D.D. Sulaimankulova, V.A. Antonovich, Izv. Akad. Nauk SSSR, ser. Khim. (1991) 1145;
(d) M.A. Fox, K. Wade, J. Organometal. Chem. 573 (1999) 279;
(e) M.A. Fox, A.E. Goeta, A.K. Hughes, A.L. Johnson, J. Chem. Soc., Dalton Trans. (2002) 2132.

[10] (a) L.I. Zakharkin, V.N. Kalinin, Izv. Akad. Nauk SSSR, ser. Khim. (1967) 2585;
(b) L.I. Zakharkin, V.N. Kalinin, V.V. Gedymin, J. Organometal. Chem. 16 (1969) 371.