

NMR determination of enantiomeric composition of 1-substituted 3-amino-1,2-dicarba-*closo*-dodecaboranes using $\text{Eu}(\text{hfc})_3$

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Abstract

Experimental conditions for determination of enantiomeric composition of 1-substituted 3-aminocarboranes by ^1H and ^{13}C NMR spectroscopy using chiral shift reagent $\text{Eu}(\text{hfc})_3$ have been found.

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1. Introduction

Chiral NMR shift reagents (CSRs) are widely used for the determination of enantiomeric composition of chiral organic compounds [1]. Commercially available lanthanide chelates, i.e., europium(III) tris[3-(trifluoromethylhydroxymethylene)camphorate] and europium(III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate], $\text{Eu}(\text{tfc})_3$ and $\text{Eu}(\text{hfc})_3$ are most frequently used as such reagents. It has been reported in literature that in many cases $\text{Eu}(\text{hfc})_3$ is more effective CSR than $\text{Eu}(\text{tfc})_3$, ensuring greater differentiation of the enantiomers resonances [2]. However, this methodology has not been previously applied for carborane derivatives with asymmetry resulting from relative position of substituents in the carborane cage (Fig. 1) [3].

Recently we turned our attention to the preparation of enantiomers of 1-*R*-3- NH_2 -1,2-*closo*- $\text{C}_2\text{B}_{10}\text{H}_9$, *R* = Me (**1**), Ph (**2**), and *i*-Pr (**3**) [4], so needing a good analytical method for determination of enantiomeric excess. For this purpose a systematic study of determining the

enantiomeric composition of 3-aminocarboranes **1–3** by NMR spectroscopy using $\text{Eu}(\text{hfc})_3$ as a chiral shift reagent has been undertaken. Herein, we report the results of these investigations.

2. Results and discussion

In nonpolar aprotic solvents lanthanide shift reagents being weak Lewis acids, are able to bind Lewis bases, e.g., amides, amines, etc. The organic solutes rapidly exchange between bound and unbound states. Addition of CSRs to racemic compounds in solution gives rise to diastereomeric complexes, so externally enantiotopic groups become diastereotopic. On the other hand, the added CSRs result in peak broadening caused by the paramagnetic character of the metal and chemical exchange. So, the acquisition of well-resolved resonances in shifted spectra that are suitable for integration is a matter of trial and error. It should be mentioned that in the case of chiral carboranes the additional line broadening due to the quadrupole moment of B atoms complicates the integration of the spectra.

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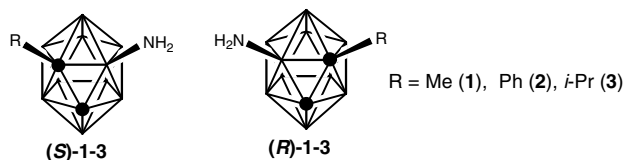


Fig. 1. In icosahedral cage structures, closed circles (●) represent carbon atoms and other vertices represent boron atoms. Hydrogen atoms are omitted for clarity.

In order to find the conditions resulting in optimum enantiomeric and spectrum resolution we systematically studied the relationships between ^1H , ^{13}C chemical shift differences in two enantiomers, $\Delta\delta = \delta^R - \delta^S$, and half-height widths of NMR peaks ($\Delta\nu$), and the ratio between the number of moles of CSR, $\text{Eu}(\text{hfc})_3$, and the number of moles of substrate (carborane), $n_{\text{CSR}}/n_{\text{S}}$.

Addition of $\text{Eu}(\text{hfc})_3$ to racemic 3-aminocarboranes **1–3** in CDCl_3 resulted in a marked change in all chemical shifts of both enantiomers and enantiomeric resolution simultaneously with line broadening. The most indicative resonances in ^1H NMR spectra are those of carborane CH protons. Spectral area of BH protons had poor resolution with broad lines, and alkyl protons in 1-alkyl-3-aminocarboranes **1**, **3** were overlapped by camphorate signals.

Carborane CH resonances (δ 3.22, 3.92 and 3.33 ppm for 3-aminocarboranes **1**, **2** and **3**, respectively) moved downfield (δ 6.5–7.5, 12.5–12.9 and 7.1–7.6 [5] ppm for **1**, **2** and **3**, respectively) as $n_{\text{CSR}}/n_{\text{S}}$ ratio increased from 0 to 2. As expected, $\Delta\delta$ values increased with increasing $n_{\text{CSR}}/n_{\text{S}}$, but the maximum and inflection point of the relationship curve were observed at different $n_{\text{CSR}}/n_{\text{S}}$ (Fig. 2). For compound **1** the maximum differentiation of enantiomer chemical shifts was of the order of 100 Hz and was observed at $n_{\text{CSR}}/n_{\text{S}} = 1.5$, while for compound **2** we observed curve inflection at $n_{\text{CSR}}/n_{\text{S}}$ of about 1.0, after which $\Delta\delta$ grew insignificantly. For com-

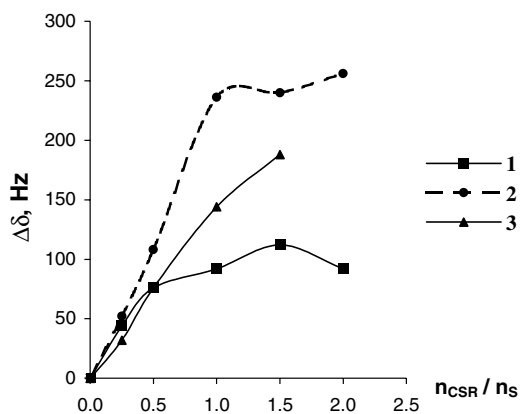


Fig. 2. Carborane CH protons chemical shift difference versus $n_{\text{CSR}}/n_{\text{S}}$ ratio for carboranes **1–3**.

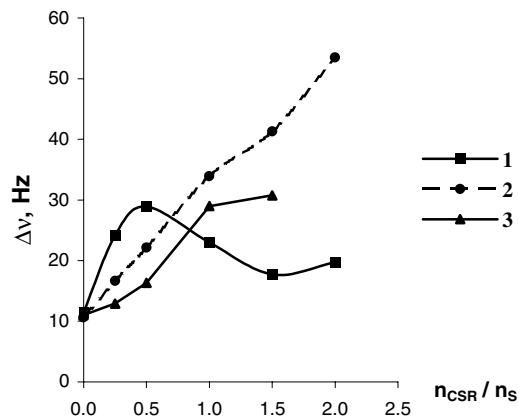


Fig. 3. Carborane CH protons half-height width versus $n_{\text{CSR}}/n_{\text{S}}$ ratio for carboranes **1–3**.

pound **3** $\Delta\delta$ value increased within the entire observed range of $n_{\text{CSR}}/n_{\text{S}}$ values. It should be mentioned, that the differentiation of enantiomer resonances in carborane **2** ($\Delta\delta \approx 230$ – 250 Hz) was substantially greater than in 1-alkylcarboranes **1** and **3**, which is likely to be due to the anisotropy of phenyl moiety.

Fig. 3 illustrates graphically the line half-width of carborane CH resonances versus $n_{\text{CSR}}/n_{\text{S}}$ for aminocarboranes **1–3**. The curves have completely different nature in the complexes of $\text{Eu}(\text{hfc})_3$ with carboranes **1**, **2** and **3**. $\Delta\nu$ Values for carboranes **2** and **3** were increasing monotonically in entire interval as $n_{\text{CSR}}/n_{\text{S}}$ was increasing, while in the case of 1-methylcarborane **1**, value of $\Delta\nu$ was initially increasing and reaching the maximum at $n_{\text{CSR}}/n_{\text{S}} = 0.5$, and then decreasing to pass its minimum at $n_{\text{CSR}}/n_{\text{S}} = 1.5$. Analysis of Figs. 2 and 3 makes it possible to find the values of molar CSR-carborane ratio that are optimal with respect to determination of enantiomeric composition of 1-*R*-3-aminocarboranes **1–3** by ^1H NMR spectroscopy. For carborane **1** the optimal $n_{\text{CSR}}/n_{\text{S}}$ is equal to 1.5, and for carboranes **2** and **3** $n_{\text{CSR}}/n_{\text{S}}$ lies in the range from 0.5 to 1.0.

It has been known that ^{13}C chemical shifts are more sensitive to the contact contributions to shielding caused by coordination with an atom of metal in comparison with protons [6]. However, in the case of 1-*R*-3-aminocarboranes **1–3** C^2 chemical shift differences ($\Delta\delta$) of *R*- and *S*-enantiomers are not great in value and, as a rule, merely exceed the width of the corresponding resonance line (Figs. 4 and 5). This significantly hinders the determination of enantiomeric excess by ^{13}C NMR with the only exception for aromatic carbons in 1-phenylcarborane **2**, especially C^{ipso} (δ 132.5 ppm). Chemical shift difference ($\Delta\delta$) of C^{ipso} reached 40–50 Hz, i.e., about 0.5 ppm, at $n_{\text{CSR}}/n_{\text{S}} \geq 1.0$, and the line width was 2–3 Hz only and slightly grew with the increase of $n_{\text{CSR}}/n_{\text{S}}$. Thus, C^{ipso} resonance can serve as a more convenient

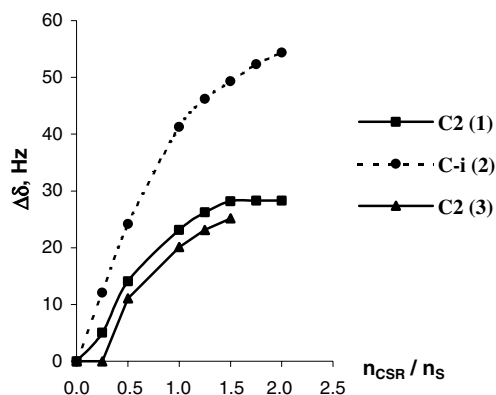


Fig. 4. Chemical shift difference of C^2 and C^{ipso} versus n_{CSR}/n_S ratio for carboranes 1–3.

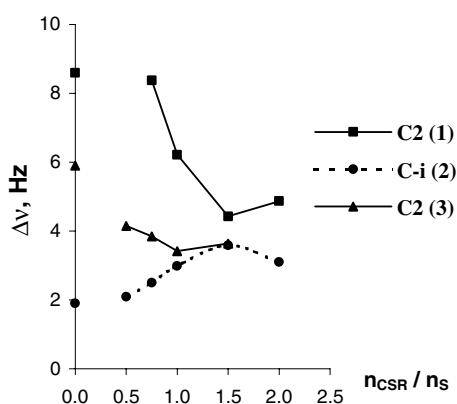


Fig. 5. Half-height width of C^2 and C^{ipso} versus n_{CSR}/n_S ratio for carboranes 1–3.

indicator for the determination of enantiomeric composition of 1-phenyl-3-aminocarborane **3**, as it is not overlapped by the carbon resonances of camphorate moiety of $Eu(hfc)_3$ as compared with protons.

The chemical shift assignment of *R*- and *S*-enantiomeric carboranes **1–3** was made based on the spectra of the samples of the known enantiomeric composition determined by HPLC [4]. In 1H и ^{13}C NMR spectra of 3-aminocarboranes **1–3** the downfield resonances of both carborane CH protons and C^2 carbons and C^{ipso} of carborane **2** relate to *S*-enantiomer.

Thus, we have found the experimental conditions for determination of enantiomeric composition of 1-*R*-3- NH_2 -1,2-*closo*- $C_2B_{10}H_9$ **1–3** by NMR spectroscopy using a chiral shift reagent. $Eu(hfc)_3$ gives observable values of $\Delta\delta$ for carboranes **1–3**, and the magnitudes of both the enantiomeric shift differences and line broadening depend on the structure of substituent R in carborane cage. The obtained optimal n_{CSR}/n_S ratio (1.0–1.5) for the studied compounds was rather high in value, which hindered the determination of enantiomeric excess due to overlapping of indicative resonances with camphorate ones.

3. Experimental

Europium(III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] was purchased from Fluka Chemie GmbH, and used as supplied. Racemic 3-aminocarboranes **1–3** were synthesized according to the procedure described [7]. Samples of 1-*R*-3-aminocarboranes **1–3** of *R*- and *S*-enantiomer ratio (30:70) were obtained as a result of kinetic resolution [4b].

1H and ^{13}C NMR spectra were measured on a Bruker DRX-400 (1H – 400.13 MHz; ^{13}C – 100.61 MHz) spectrometer at ambient temperature. 1H NMR spectra were recorded with broad-band ^{11}B -decoupling.

Standard solutions of carboranes in $CDCl_3$ were prepared by dissolving of 0.05 mmol of each compound in 0.6 ml of $CDCl_3$. The first spectrum was obtained without $Eu(hfc)_3$, then sequential portions of $Eu(hfc)_3$ (14.9 mg, 0.0125 mmol) were added. The solid increments of chiral reagent were weighed on an analytical balance and introduced by a micro funnel into the NMR tube.

Acknowledgements

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