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NEW BICYCLIC ORGANYLBORONIC ESTERS DERIVED FROM IMINODIACETIC ACIDS

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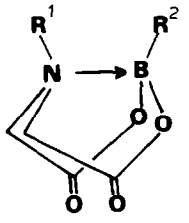
Summary

The reactions of phenylboronic acid or dimethylthexylboronic ester with iminodiacetic- or *N*-methyliminodiacetic acids lead in high yield to the air-stable bicyclic esters (N–B)phenyl[iminodiacetate-*O*,*N*]borane (**1**), (N–B)phenyl[*N*-methyliminodiacetate-*O*,*N*]borane (**2**), (N–B)thexyl[iminodiacetate-*O*,*N*]borane (**3**) and (N–B)thexyl[*N*-methyliminodiacetate-*O*,*N*]borane (**4**). These are shown by ^{1}H, ^{11}B and ^{13}C NMR spectroscopy to have rigid bicyclic structures of strong intramolecular N–B coordination.

Introduction

Boron heterocycles with intramolecular N–B coordination (for some leading references, see 1–5) are useful compounds for studying steric interactions, stereochemical relationships (e.g. to corresponding hydrocarbons) and dynamic effects. Our current interest in this area [6–9] prompted us to look for compounds of this type with a rigid cyclic structure. Boron aminoacid derivatives have been little studied [10] in spite of the possibility of obtaining heterocycles with a high degree of hydrolytic stability and potentially useful for biological studies. This paper describes a synthesis of the new compounds **1–4**, derivatives of iminodiacetic acids, which are shown to be highly stable to hydrolysis. Models indicate a particularly rigid structure for **1–4**, and we studied them in solution by dynamic ^{1}H, ^{11}B and ^{13}C NMR spectroscopy in order to confirm this.



R^1	R^2	Nr.
H	C_6H_5	**1**
CH_3	C_6H_5	**2**
H	$C(CH_3)_2CH(CH_3)_2$	**3**
CH_3	$C(CH_3)_2CH(CH_3)_2$	**4**

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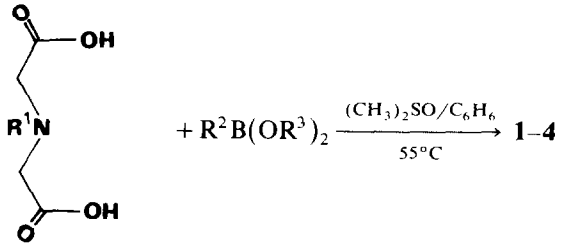
Results

Synthesis

The iminodiacetic acids **5** and **6** react with phenylboronic acid (**7**) or dimethylthexylboronic ester (**8**) to give the bicyclic compounds **1**–**4**.

Compounds **1**–**4** are obtained pure as colourless air-stable solids by recrystallization from methanol/hexane.



(**5**, $R^1 = H$; (**7**, $R^2 = C_6H_5$, $R^3 = H$;

6, $R^1 = CH_3$) **8**, $R^2 = C(CH_3)_2CH(CH_3)_2$, $R^3 = CH_3$)

The ^1H NMR spectra (Table 1) prove the rigid structure of **1**–**4**. Thus, an ABX (**1**, **3**, X = N*H*) or AB (**2**, **4**)-coupling pattern is observed for the methylenic protons (Fig. 1). These protons are diastereotopic as long as the ring inversion (Scheme 1) is slow on the NMR time scale. Rapid H/D exchange in **1** and **3** occurs upon addition of D_2O, as shown by the disappearance of the splitting due to ^3J(HNCH). Since other ^1H resonances are not affected the B–N or B–O bonds are not broken.

The ^1H NMR spectra of **3** (in DMSO-d_6/CD_2Cl_2) and **1**, **2**, **4** (in $C_2D_2Cl_4$) were observed at 140 and 125°C, respectively. In no case was there a change in the coupling pattern. From this and from the data in Table 1 the free energy of activation $\Delta G^{\ddagger}$ of the B–N bond can be shown [12] to be > 90 kJ M^{-1}. Comparison with corresponding $\Delta G^{\ddagger}$ values obtained for **9** (59.6 kJ M^{-1}) and **10** (49.2 kJ M^{-1}) reveals the increased stability of the bicyclic structures in **1** to **4**.

The $\delta(^{13}C)$values (Table 2) shows no unusual features [11,13]. The assignment is based on the typical $\delta(^{13}C)$values, $^1J(^{13}C^1H)$ and on the presence of broad ^{13}C resonances (owing to partially relaxed scalar coupling $^1J(^{13}C^{11}B)$ [11,14]). The negative inductive effect of the carboxylic groups is reflected by the $\delta(^{13}C_{para})$ values in **1** and **2**. Deshielding is observed relative for $\delta(^{13}C_{para})$ for $[B(C_6H_5)_4]^-$ (125.8 [14]), $(C_6H_5)_3B{-}NC_5H_5$ (125.3 [14]) or in $(C_6H_5)_2\overline{BO(CH_2)_2}\overline{NH_2}$ (126.5 [16]).

NMR measurements

^1H and ^{11}B NMR data are given in Table 1 and $\delta(^{13}C)$ data in Table 2. All the NMR data are consistent with the proposed bicyclic structure and intramolecular N–B coordination.

The $\delta(^{11}B)$ values (Table 1) confirm the tetrahedral environment of the ^{11}B nucleus, since they lie in the range reported previously for the heterocycles **9** and **10** [6] and similar compounds [4a,b]. The increase in shielding relative to organylboronic esters [11] (typical range of $\delta(^{11}B) + 28$ ($R^2 = C_6H_5$); $+33$ (R^2 = alkyl)) was found to be independent of temperature (from 28 to 130°C). This is in contrast to

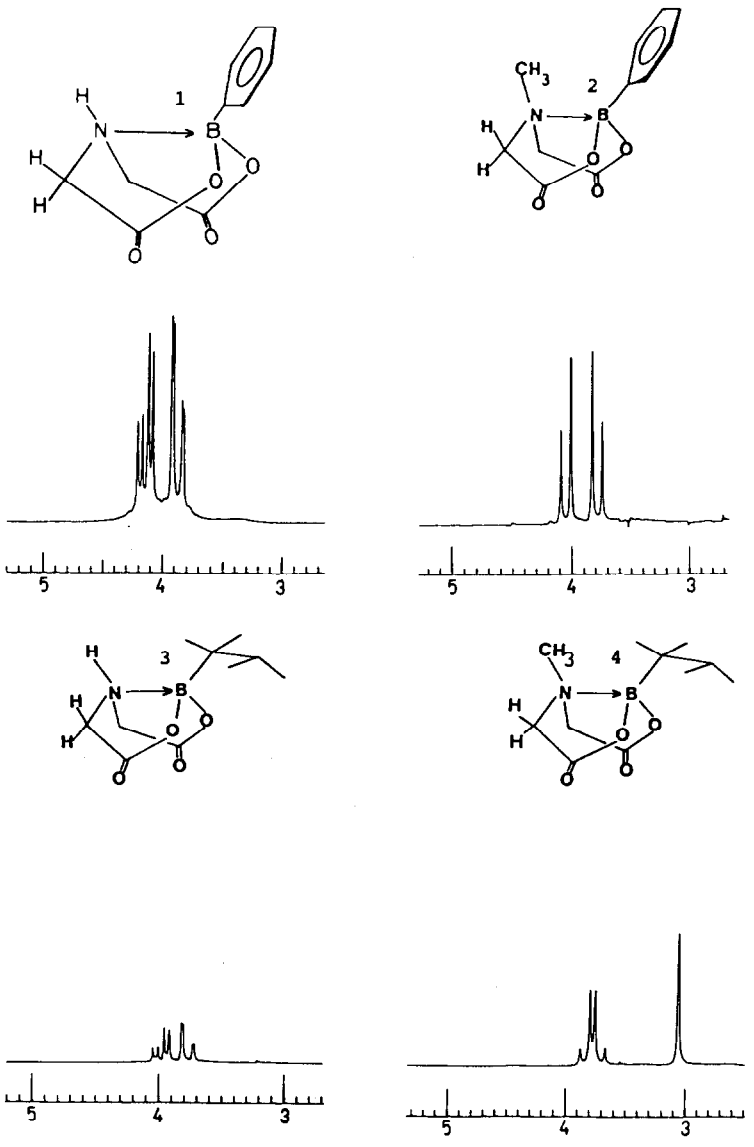
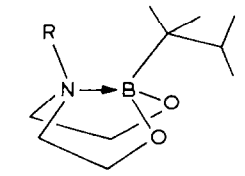


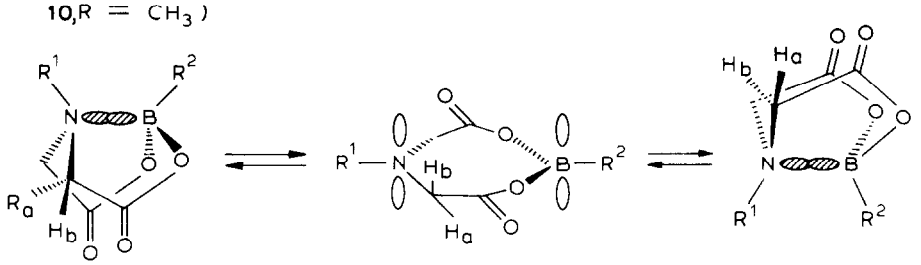
Fig. 1. Methylene ^{1}H resonances of compounds **1–4** at 25°C; these remain unchanged up to 125°C (**1**, **2** and **4**) or 140°C (**3**). The additional coupling ^{3}J(HNCH) in **1** and **4** disappears upon addition of D_2O.

the finding for compound **10** (deshielding of the ^{11}B nucleus was observed with increasing temperature), for which a rapid opening of the N–B bond has been established by ^{1}H NMR spectroscopy ($\Delta G^{\ddagger}$ 49.2 kJ M^{-1} [6]).

The extraordinary stability of the N–B bond in **1–4** (compared with **9** and **10**) is mainly the result of two effects: (i) the two carboxylic groups polarize the σ-framework much more strongly than two alkoxide groups, and the strong N–B bond compensates to some extent, for the loss of electron density at the boron atom. (ii) the introduction of a planar centre (C=O) in **1–4** reduces the flexibility of the



(**9**, R = H;
10, R = CH_3)



SCHEME 1. Ring inversion in **1** to **4** via opening and closing of the coordinative N–B bond.

bicyclic system owing to the changes in the relevant bond angles and bond lengths. Further studies (e.g. by involving introduction of other substituents at the nitrogen or at the ring carbon atoms) will be necessary to find out whether the increase in the

TABLE 1

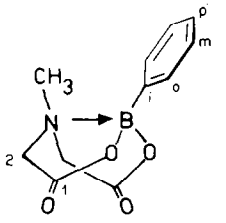
^{11}B AND ^{1}H NMR PARAMETERS [a] FOR COMPOUNDS **1–4**

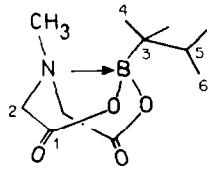
Compound	$\delta(^{11}B)$	$\delta(^{1}H)$			
		B–C_6H_{13} [d]	B–C_6H_5	N–R^1	CH_2–C(=O)
1 [b]	+10.8	–	7.2–7.6(m)	8.7(b)	H_a 4.1(dd) H_b 3.8(dd) ^2J 17.4 ^3J_a 8.1 ^3J_b 2.8
2 [c]	+12.9	–	7.3–7.5(m)	2.5(s)	H_a 4.0(d) H_b 3.7(d) ^2J 16.7
3 [b]	+14.4	0.6(s) 0.82(d) *J* 7 1.5(hep)	–	8.2(b)	H_a 3.9(dd) H_b 3.7(dd) ^2J 17.5 ^3J_a 7.9 ^3J_b 2.8
4 [c]	+14.9	0.86(s) 0.9(d) *J* 7.0 1.6(hep)	–	3.0(s)	H_a 3.8(d) H_b 3.7(d) ^2J 16.5

[a] $\delta(^{11}B)$ in ppm relative to $BF_3 \cdot OC_2H_5$, $\delta(^{1}H)$ in ppm relative to $Si(CH_3)_4$ *J* in Hz. [b] Solvent DMSO-d_6/$C_2D_2Cl_4$. [c] Solvent $C_2D_2Cl_4$. [d] δ of thexyl group are given in following order $(CH_3)_2$–C–C, $(CH_3)_2$-CH–C- and CH–C.

TABLE 2

^{13}C NMR PARAMETERS [a] FOR COMPOUNDS 1–4





Compound	C^1	C^2	C^3	C^4	C^5	C^6	C_i	C_o	C_m	C_p	NCH_3
1 [b]	170.7	59.6					139.0	131.7	127.5	128.4	
2 [c]	167.9	61.8					143.0	132.2	128.5	130.1	47.6
3 [b]	170.3	53.4	24.3	19.8	33.5	18.5					
4 [c]	167.5	63.0	24.9	20.3	34.8	18.3					46.3

[a] In ppm relative to internal $(CH_3)_4Si$. [b] Solvent DMSO-d_6/$C_2D_2Cl_4$. [c] Solvent $C_2D_2Cl_4$.

$\Delta G^{\ddagger}$-values in **1–4** (with respect to **9** and **10**) originates from stabilization of the ground state or from destabilization of the transition state.

Experimental

The NMR spectra were recorded with a Bruker WP 200 PFT instrument (^1H, ^{11}B, ^{13}C NMR) and a Varian EM 390 spectrometer (^1H NMR). Mass spectra were obtained with a Hewlett Packard 5985-A instrument. Compounds **5**, **6** and **7** were commercial products, and were used without further purification. Dimethylthexylboronic ester, **8**, was prepared via hydroboration of 2,3-dimethylbut-2-ene with BH_3 in THF [17], followed by reaction with methanol.

(N–B)phenyl[iminodiacetate-O,N]borane (1)

A solution of iminodiacetic acid (0.4 g, 3 m*M*) in 100 ml of dry benzene and 20 ml of dimethylsulfoxide was placed into a 250 ml flask equipped with a stirrer and a Dean Stark trap. Phenylboronic acid (0.37 g, 3 m*M*) was added and the mixture was kept under reflux for 8 h. After removal of the solvents in vacuo the product was recrystallized from 2 ml of methanol/hexane (1/4), to give 0.51 g (79%) of compound **1**, m.p. 240°C. Found: C, 54.55; H, 4.45; N, 6.20. $C_{10}H_{10}BNO_4$ calcd.: C, 54.84; H, 4.60; N, 6.39%; MS: M^+ *m/e* 216 (28%).

(N–B)phenyl[N-methyliminodiacetate-O,N]borane (2)

In the procedure used for **1**, *N*-methyliminodiacetic acid (1 g, 6.7 m*M*) and phenylboronic acid (0.83 g, 6.7 m*M*) gave 1.2 g (77%) of compound **2**, m.p. 193°C. Found: C, 56.10; H, 5.25; N, 6.20; $C_{11}H_{12}BNO_4$ calcd.: C, 56.70; H, 5.19; N, 6.01%. MS: M^+ *m/e* 233 (58%).

(N–B)thexyl[iminodiacetate-O,N]borane (3)

In the procedure used for **1** dimethylthexylboronic ester, (**8**) (1.48 g, 9.4 m*M*) and iminodiacetic acid (1.23 g, 9.4 m*M*) gave 1.5 g (72%) of compound **3**, m.p.

219–220°C. Found: C, 52.40; H, 7.80; N, 6.05; $C_{10}H_{18}BNO_4$ calcd.: C, 52.90; H, 7.99; N, 6.17; MS: *m/e* 142 [M^+–85 (thexyl) (100%)].

(N–B)thexyl[N-methyliminodiacetate-O,N]borane (4)

In the procedure used for **1**, dimethylthexylboronic ester, **8**, (0.97 g, 6.1 m*M*) and *N*-methyliminodiacetic acid (0.9 g, 6.1 m*M*) gave 0.7 g (50%) of compound **4**, m.p. 183–185°C. Found: C, 51.45; H, 8.62; N, 6.25; $C_{11}H_{20}BNO_4$ calcd.: C, 51.99; H, 8.36; N, 6.06%; MS: *m/e* 156 [M^+–85 (thexyl) (100%)].

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