73-9; $[MoBr_2(CO)_4]_2$, 80594-72-5; $Mo(CO)_3(S_2CNEt_2)_2$, 18866-21-2; $Mo(CO)_3(S_2CN(CH_2)_4)_2$, 80664-72-8; $WBr_2(N_2CHPh)(S_2CNMe_2)_2$, 80664-71-7; $MoBr_2(N_2CHPh)(S_2CNMe_2)$, 80664-70-6; $Mo(CO)(N_2CHPh)(S_2CNMe_2)_2$, 80664-69-3; $MoOBr_2(S_2CNMe_2)_2$, 57146-53-9; PhCH=O, 100-52-7; PhCH=N—N=CHPh, 588-68-1; PhCH=NPh, 538-51-2; $PhCH{=}N{-}N{=}PPh_3$, 1103-87-3; $PhCH{=}N{-}NH{-}C_6H_4NO_2$, 3078-09-9; $PhCH{=}N{-}NH_2$, 5281-18-5; PhCH=NΔbdN, 766-91-6; $WBr_2(CO)_3(PPh_3)_2$, 18130-07-9; $p\text{-}CH_3C_6H_4CHN_2$, 23304-24-7; $ToCH{=}NNH_2$, 52693-87-5; *p*-tolualdehyde, 104-87-0; 1-*p*-tolydiazoethane, 64252-52-4; 4-methylacetophenone, 122-00-9; tungsten hexacarbonyl, 14040-11-0; molybdenum hexacarbonyl, 13939-06-5.

Covalently Bound Paramagnetic Shift Reagents. 1. A Versatile Lithium Reagent Derived from Bis[(4-bromophenyl)tris(1-pyrazolyl)borato]cobalt(II)

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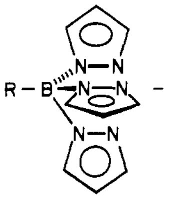
Abstract: A versatile precursor for the attachment of covalently bound paramagnetic probes has been prepared. Sodium (4-bromophenyl)tris(1-pyrazolyl)borate, $4\text{-}BrC_6H_4B(pz)_3Na$, was converted to the 4-lithio derivative via a metal–halogen exchange with butyllithium in THF at −70 °C. Deuteration of this lithium reagent could be effected by treatment with D_2O; carbonation, however, led to decomposition. Conversion of $(4\text{-}BrC_6H_4B(pz)_3)_2Co^{II}$ to the corresponding 4-lithio compound followed by deuteration, coupling with 1-iodobutane, or carbonation gave $(4\text{-}RC_6H_4B(pz)_3)_2Co^{II}$, with R = D, *n*-Bu, or CO_2H, respectively. The latter compound was converted to the methyl ester by reaction with diazomethane. The large isotropic shifts observed for protons on the phenyl ring and its substituents can be accurately predicted by using conventional expressions for the dipolar shift.

Hydrotris(1-pyrazolyl)borate, I, and its alkyl and aryl analogues



$RBpz_3^-$

I, R = H
II, R = C_6H_5
III, R = $4\text{-}BrC_6H_5$
IV, R = $4\text{-}LiC_6H_5$

constitute a class of unique uninegative tridentate ligands possessing C_{3v} symmetry. Trofimenko[1] has reported the preparation of a number of these compounds and their complexes with alkaline-earth and transition-metal ions. However, the emphasis heretofore has been on the physical properties of the coordinated metal ions rather than the chemistry of the ligand or the potential applications of the complexes. The kinetic stability and the high symmetry of tris(1-pyrazolyl)borate transition-metal chelates should make this ligand an attractive choice for attaching metal ion probes to drug molecules, proteins, etc., so that their binding to substrates could be investigated. In particular, the very large isotropic shifts of NMR resonances associated with paramagnetic Co(II) in a pseudooctahedral environment with axial symmetry[2] should constitute a powerful probe for the detailed geometry of such complexes. Accordingly, we have synthesized the Na^+ and Co^{2+} complexes of (4-bromophenyl)tris(1-pyrazolyl)borate and studied the formation and reactions of the lithium reagents derived from them. The synthesis of the ligand itself involved a modification of one of the procedures originally described by Trofimenko.[3,4]

Experimental Section

General Comments. Reactions involving lithium reagents were carried out in flame-dried glassware under an atmosphere of prepurified nitrogen. THF and ether were distilled under nitrogen from sodium benzophenone ketyl. Organic reagents were purchased from Aldrich or Eastman Organic Chemicals and used without further purification. *n*-BuLi in hexane solution and NaH in mineral oil dispersion were purchased from Alfa. NMR spectra were recorded on a JEOL FX90-Q 90-MHz or a Bruker 270-MHz spectrometer. Chemical shifts are given in parts per million from internal Me_4Si or DSS with resonances downfield of the reference being positive. IR spectra were recorded on a Beckman IR-4250. HPLC was carried out on a C-8 reversed phase column with 80% CH_3CN–20% aqueous phase (1% aqueous NH_4OAc adjusted to pH 8.5 with concentrated aqueous ammonia). Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, IN, or Atlantic Microlab Inc., Atlanta, GA.

$C_6H_5B(pz)_3Na$ (3). A 250-mL round-bottom flask equipped with mechanical stirrer, thermometer, and 20-cm Vigreaux column topped with a distilling head was charged with 16 g (0.24 mol) of pyrazole and 100 mL of diglyme. To this solution at 120 °C was added dropwise over 30 min a solution of 4.9 g (0.04 mol) of $PhB(OH)_2$ in 50 mL of 10% aqueous acetone. Acetone and water were removed from the reaction mixture by fractional distillation until the head temperature reached the boiling point of diglyme (161 °C). The reaction mixture then was cooled to 50 °C and treated portionwise with 3.0 g of 50% NaH dispersion in mineral oil (0.06 mol of NaH). After the foaming had subsided, the mixture was again heated and diglyme was removed by distillation. This required ca. 45 min, and the pot temperature was not allowed to exceed 220 °C. The pot residue solidified upon cooling to room temperature under nitrogen. It was treated with filter aid and 50 mL of water, and the resulting suspension was filtered. Water was removed from the filtrate in vacuo at room temperature. The residue was first triturated with ether and then with hexane to yield 3.7 g of finely divided white powder containing 69% by weight of $PhB(pz)_3Na$ (20% of theory). (The product was assayed by reaction of an aliquot with 0.5 M $CoCl_2$ in 1 M acetate buffer at pH 5.5, extraction with CH_2Cl_2, and HPLC determination of $(PhB(pz)_3)Co$ in the extract.) The ether washes and other residues contained an additional 7% of product.

$4\text{-}BrC_6H_4B(pz)_3Na$. This compound was prepared as above from $4\text{-}BrPhB(OH)_2$. The crude product was 68% pure, and the yield was

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(1) Trofimenko, S. *Chem. Rev.* **1972**, *72*, 497–509.
(2) LaMar, G. N.; Horrocks, W. D., Jr.; Holm, R. H. "NMR of Paramagnetic Molecules"; Academic Press: New York, 1973.
(3) Trofimenko, S. *J. Am. Chem. Soc.* **1967**, *89*, 6288–6294.
(4) Trofimenko, S. *J. Am. Chem. Soc.* **1967**, *89*, 3170–3177.

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25%. This product was purified by repeated trituration with ether. Drying in vacuo at room temperature gave a freely flowing, hygroscopic white powder that displayed the following properties: NMR (D$_2$O) δ 6.29 (approx t, J = 1.75 Hz, 2 H, pz 4-H), 7.29 (AA′BB′, J = 26 Hz, J = 8.4 Hz, 4 H, Ar-H), 7.27 (dd, J = 2.19 and 0.44 Hz, 3 H, pz 3- or 5-H), 7.65 (dd, J = 1.75 and 0.44 Hz, 3 H, pz 3- or 5-H), and 7.44 (s, variable but approx 1 H, H$_2$O); IR (Nujol mull) 3605 (m) cm^{-1}; IR (KBr) 3295 (m), 1650 (w), 1575 (m), 1500 (m), 1495 (s), 1480 (s), 1435 (s), 1412 (s), 1385 (s), 1373 (s), 1288 (sh), 1278 (s), 1245 (w), 1205 (s), 1186 (s), 1160 (m), 1090 (s), 1070 (m), 1050 (s), 1010 (s), 971 (w), 960 (w), 920 (m), 885 (m), 868 (s), 845 (w), 828 (w), 810 (s), 790 (s), 755 (s), 625 (m), 625 (m), 495 (m), 480 (w), 390 (m), 338 (w) cm^{-1}.

Anal. Calcd for C$_{15}$H$_{13}$N$_6$BBrNa·2H$_2$O: C, 42.18; H, 4.01. Found: C, 42.17; H, 3.54.

(4-BrC$_6$H$_4$B(pz)$_3$)$_2$Co^{II}. The above procedure was followed by using 5.02 g (0.025 mol) of 4-BrPhB(OH)$_2$ as starting material. The aqueous filtrate containing the 4-BrPhB(pz)$_3$Na was added to 50 mL of 0.5 M CoCl$_2$ in 1 M pH 5.5 acetate buffer. The resulting precipitate was isolated by centrifugation, washed with water, taken up in CH$_2$Cl$_2$, and dried with Na$_2$SO$_4$. Two recrystallizations from CH$_2$Cl$_2$–MeOH gave 3.6 g (36%) of light yellow crystals: mp 300 °C dec; NMR (CDCl$_3$, 298 K) δ 27.51 (s, 2 H, Ph 3,5-H's), 36.5 (br s, 3 H, pz 4-H), 62.33 (very br s, 2 H, Ph 2,6-H's), 80.89 (very br s, 3 H, pz 5-H); IR (KBr) 1582 (m), 1500 (m), 1429 (m), 1405 (s), 1386 (m), 1292 (s), 1228 (m), 1200 (s), 1190 (sh), 1163 (m), 1092 (s), 1058 (s), 1008 (m), 972 (m), 920 (w), 900 (m), 880 (s), 792 (s), 780 (s), 758 (s), 710 (m), 623 (m), 398 (m), 350 (w) cm^{-1}; mass spectrum, *m/e* (relative intensity) 798 (9.3), 797 (31.7), 796 (32.8), 795 (63.4), 794 (38.5), 793 (35.7); 428 (100), 427 (40.7), 426 (98.9) (M$^+$ – BrPhB(pz)$_3$), 360 (82.8), 359 (33.8), 358 (80.5) (428 – pz).

Anal. Calcd for C$_{30}$H$_{26}$N$_{12}$Br$_2$B$_2$Co: C, 45.32; H, 3.30; N, 21.15; Br, 20.10. Found: C, 45.10, 44.94; H, 3.36, 3.48; N, 20.10, 20.44; Br, 19.46.

(C$_6$H$_5$B(pz)$_3$)(4-BrC$_6$H$_4$(pz)$_3$)Co. Approximately equimolar amounts of C$_6$H$_5$B(pz)$_3$Na and 4-BrC$_6$H$_4$B(pz)$_3$Na were combined, dissolved in water, and reacted with Co^{2+} as above. Workup yielded a mixture of (C$_6$H$_5$B(pz)$_3$)$_2$Co, (4-BrC$_6$H$_4$B(pz)$_3$)$_2$Co, and (C$_6$H$_5$B(pz)$_3$)(4-C$_6$H$_4$B(pz)$_3$)Co. The latter was isolated by HPLC (k' = 11.5): NMR (CDCl$_3$, 298 K) δ 25.42 (s, 1 H, Ph 4-H), 29.79 (s, 2 H, Ph 3,5- or 3′,5′-H's), 29.86 (s, 2 H, Ph 3′,5′- or 3,5-H's), 37.06 (br s, 3 H, pz 4- or 4′-H), 37.37 (br s, 3 H, pz 4′- or 4-H), 63.32 (br s, 4 H, Ph 2,2′,6,6′-H's), 95.44 (very br s, 6 H, pz 5,5′-H's); mass spectrum, *m/e* (relative intensity) 718 (7.9), 717 (26.4), 716 (21.0), 715 (29.4), 714 (13.3); 639 (2.7), 638 (7.9), 637 (21.0), 636 (10.1) (M$^+$ – Br); 429 (4.3), 428 (24.2), 427 (9.2), 426 (25.0), 425 (6.6) (M$^+$ – C$_6$H$_5$B(pz)$_3$); 361 (4.5), 360 (24.7), 359 (10.4), 358 (24.4) (427 – pz); 350 (27.0), 349 (16.9), 348 (100), 347 (22.4) (M$^+$ – BrC$_6$H$_4$B(pz)$_3$).

(4-*n*-BuC$_6$H$_4$B(pz)$_3$)$_2$Co. (4-BrC$_6$H$_4$B(pz)$_3$)$_2$Co, 0.100 g (0.126 mmol), was dissolved in 5 mL of THF, and this solution was cooled to −70 °C and then treated with 0.17 mL of 1.6 M *n*-BuLi in hexane. After the solution stirred for 5 min, 0.5 g (2.8 mmol) of 1-iodobutane was added and the reaction mixture was allowed to warm to room temperature. Hydrolysis, extraction with CH$_2$Cl$_2$, and recrystallization of the CH$_2$Cl$_2$-soluble material from CHCl$_3$–MeOH gave 0.079 g (83%) of yellow crystals: mp 248 °C dec; NMR (CDCl$_3$, 298 K) δ −124.0 (br s, 3 H, pz 3-H), 7.28 (approx t, J = 8.1 Hz, 3 H, 4′-CH$_3$), 10.30 (approx d, J = 2.7 Hz, 2 H, 3′-CH$_2$), 13.09 (s, 2 H, 2′-CH$_2$), 15.73 (s, 2 H, 1′-CH$_2$), 29.24 (s, 2 H, Ph 3,5-H's), 36.81 (br s, 3 H, pz 4-H), 62.50 (br s, 2 H, Ph 2,6-H's), 94.34 (br s, 3 H, pz 5-H); IR (KBr) 2950 (m), 2922 (m), 2850 (w), 1608 (w), 1500 (m), 1430 (w), 1406 (s), 1385 (w), 1295 (s), 1230 (m), 1198 (s), 1162 (m), 1095 (s), 1060 (s), 975 (w), 921 (w), 893 (w), 885 (m), 790 (s), 755 (s), 720 (m) cm^{-1}; mass spectrum, *m/e* (relative intensity) 750 (3.2), 749 (8.1), 748 (3.6) (M$^+$); 404 (14, M$^+$ – C$_4$H$_9$C$_6$H$_4$B(pz)$_3$); 91 (85, C$_7$H$_7$$^+$); 44 (100, C$_3H_8$$^+$).

(4-HOOCC$_6$H$_4$B(pz)$_3$)$_2$Co. (4-BrC$_6$H$_4$B(pz)$_3$)$_2$Co, 1.01 g (1.26 mmol), in 30 mL of THF at −70 °C was treated with 1 mL of 1.6 M *n*-BuLi in hexane. After being stirred for 10 min, the cold reaction mixture was quickly added to a slurry of excess CO$_2$ in THF. This mixture was allowed to warm to room temperature, hydrolyzed, and then adjusted to pH 5 by the addition of dilute acetic acid. THF was removed on a rotary flash evaporator, leaving a yellow solid suspended in the aqueous phase. This material was filtered, washed with water until the washes were neutral, and dried in vacuo at room temperature to yield 0.81 g of crude product. Its NMR spectrum displayed a resonance at 24.8 ppm that was assigned to the Ph 4-H of the mixed product (4-HOOCC$_6$H$_4$B(pz)$_3$)(C$_6$H$_5$B(pz)$_3$)Co resulting from hydrolysis concomitant with carbonation. The IR spectrum of this material had a carbonyl band at 1678 cm^{-1}.

The product was purified (with significant loss) by conversion to the potassium salt with ethanolic KOH and three recrystallizations from EtOH. The pure material (shiny gold plates when wet) displayed the following properties: IR (Nujol mull) 3400 (w) cm^{-1}; IR (KBr) 3170 (w), 3140 (w), 1588 (s), 1533 (m), 1455 (w), 1403 (sh), 1382 (s), 1286 (m), 1195 (m), 1090 (m), 1055 (m), 880 (m), 822 (w), 750 (s), 615 (s) cm^{-1}; NMR (CD$_3$OD, 298 K) δ 29.58 (s, 2 H, Ph 3,5-H's), 36.71 (br s, 3 H, pz 4-H), 61.86 (br s, 2 H, Ph 2,6-H's), 93.47 (br s, 3 H, pz 5-H).

Anal. Calcd for C$_{32}$H$_{26}$N$_{12}$B$_2$CoK$_2$O$_4$·2.5H$_2$O: C, 45.40; H, 3.69; N, 19.86. Found: C, 45.37; H, 3.57; N, 19.81, 19.77.

(4-CH$_3$OOCC$_6$H$_4$B(pz)$_3$)$_2$Co. Crude (4-HOOCC$_6$H$_4$B(pz)$_3$)$_2$Co, 0.11 g (0.15 mmol), was dissolved in 25 mL of 50/50 CHCl$_3$–MeOH and treated with excess ethereal diazomethane at 0 °C. The reaction mixture was allowed to warm to room temperature, and the solvent was evaporated. The residue was recrystallized from CHCl$_3$–MeOH to yield 0.081 g (72%) of product, mp 275–280 °C dec.

Analytically pure material, mp 288–290 °C dec, was obtained by chromatography on silica gel H with 60/40 hexane–CHCl$_3$: IR (KBr) 2940 (w), 1712 (s), 1490 (m), 1422 (m), 1398 (s), 1270 (s), 1227 (w), 1182 (s), 1088 (s), 1050 (s), 1019 (w), 965 (w), 915 (w), 879 (s), 805 (s), 785 (s), 745 (s) cm^{-1}; NMR (CDCl$_3$, 295 K) δ 11.42 (s, 3 H, OCH$_3$), 30.27 (s, 2 H, Ph 3,5-H's), 37.18 (br s, 3 H, pz 4-H), 63.32 (br s, 2 H, Ph 2,6-H's), 94.98 (br s, 3 H, pz 5-H); mass spectrum calcd, *m/e* (relative intensity) 752.8 (40.6), 753.6 (100), 754.6 (37.8), 755.6 (6.3), obsd, 752.2 (49.3), 753.2 (100), 754.2 (34.3), 755.2 (9.7).

Anal. Calcd for C$_{34}$H$_{32}$N$_{12}$B$_2$CoO$_{12}$: C, 54.12; H, 4.28; N, 22.32. Found: C, 54.17; H, 4.26; N, 22.56.

(4-LiC$_6$H$_4$B(pz)$_3$)$_2$Co. (4-BrC$_6$H$_4$B(pz)$_3$)$_2$Co at ca. 10 mg/mL concentration in the appropriate solvent was treated with a 10% molar excess of *n*-BuLi in hexane. At the end of the reaction period, the reaction mixture was quenched with D$_2$O. The hydrolysis mixture was extracted with CHCl$_3$, and this extract was analyzed by HPLC to obtain the ratio of diprotonated product:monoprotonated product:unreacted starting material (k' = 6.8, 9.5, and 13.5, respectively). NMR analysis of the extract in CDCl$_3$ gave the H/D ratio. The Ph 4-H proton at ca. 25 ppm could easily be detected and compared to the Ph 3,5-H protons at ca. 35 ppm.

4-LiC$_6$H$_4$B(pz)$_3$$^-Na^+$. This compound was prepared by lithium–halogen exchange from the corresponding bromo compound and *n*-BuLi as above, except that after deuteration, the hydrolysis mixture was added to a 10-fold excess of 0.5 M CoCl$_2$ in 1 M pH 5.5 acetate buffer. Extraction with CHCl$_3$ and HPLC analysis followed. Carbonation of the lithium reagent was effected by addition to a slurry of CO$_2$, warming to room temperature, and treating with Co^{2+}. Any precipitate in the hydrolysate at pH 5.5 was isolated by centrifugation, dried in vacuo, and analyzed by NMR and IR spectroscopy. The aqueous supernatant was extracted with CHCl$_3$ and analyzed by HPLC to detect hydrolysis products.

Diamagnetic Chemical Shifts. Diamagnetic [(ArB(pz)$_3$)$_2$Co^{III}]$^+$ compounds were obtained by oxidizing the corresponding paramagnetic Co(II) compounds with chloranil in CHCl$_3$ or CH$_2$Cl$_2$ solution. The solvent was removed from the resulting precipitate, which then was dissolved in Me$_2$SO-d_6. The NMR spectra of these solutions indicated that the chelates remained intact and provided the diamagnetic proton chemical shifts for reference in calculating the isotropic shifts.

Geometrical Data. Angles (θ) and distances (R) were measured on Dreiding models. When a functional group (e.g., the 2-methylene of an alkyl chain) could rotate freely on an axis off the major symmetry axis, $G(R,\theta)$ (eq 14) was evaluated at $\pi/99$ increments over the entire 2π rotation, and these values were averaged. Rotation of methylene groups (or other functional groups) further along the alkyl chain involve compound rotations and steric factors that could not be evaluated with certainty.[5] These were not considered in this study.

If the carboxylic ester group of IX is assumed to be planar, the CH$_3$–O bond nearly coincides with the major symmetry axis of the complex. This results in only a small change in θ and R, and a ±2% variation in $G(R,\theta)$ for the protons upon rotation about the CH$_3$–O bond. An average of three values was taken.

Results

[4-LiC$_6$H$_4$B(pz)$_3$]$_2$Co^{II}. The metal–halogen exchange between *n*-BuLi and (4-BrPhB(pz)$_3$)$_2$Co did not take place in ether below about −20 °C. When quenched with D$_2$O after 2 h at 0 °C, the resulting lithium reagent gave a 31% yield of [PhB(pz)$_3$]$_2$Co^{II}, 6% of [4-RC$_6$H$_4$B(pz)$_3$][PhB(pz)$_3$]Co^{II} (R = H, D, or Bu), and a 3% recovery of starting material. NMR examination of the product mixture indicated only 26% D incorporation. The remaining 74% of the lithium reagent presumably abstracted protons from the solvent.

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(5) Jesson, J. P. *J. Chem. Phys.* **1967**, *47*, 582–591.

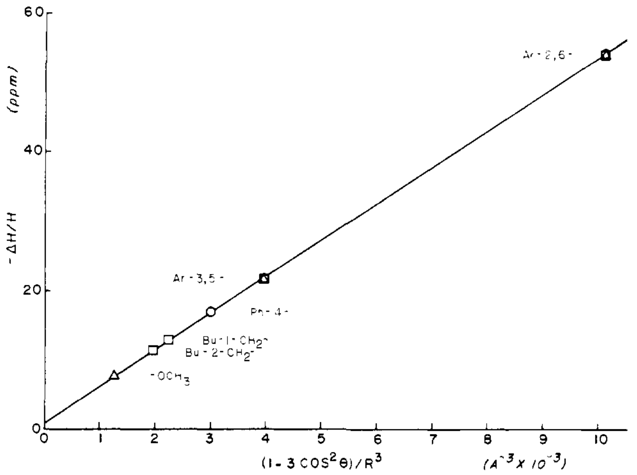


Figure 1. A test of the relationship of the proton isotropic shifts to geometry in $(ArB(pz)_3)_2Co$ complexes: ○, $(PhB(pz)_3)_2Co$; △, $(4\text{-}CH_3OOCC_6H_4Bpz_3)_2Co$; □, $(4\text{-}n\text{-}BuC_6H_4B(pz)_3)_2Co$. The slope ($D$) of the least-squares line is 5.31×10^3 A^3 ppm, its y intercept is 0.92 ppm, and the correlation coefficient is 0.9997. NMR data were obtained at 90 MHz in $CDCl_3$ at 30 °C.

In THF at −78 °C, the lithium reagent was formed immediately. D_2O quenching after 5 min gave a 74% yield of $[4\text{-}DC_6H_4B(pz)_3]_2Co^{II}$. Essentially no proton incorporation was observed. Carbonation of the lithium reagent under these conditions gave an isolated yield of 29% of $[4\text{-}HOOCC_6H_4B(pz)_3]_2Co$. No starting material or other paramagnetic products were observed.

$[4\text{-}LiC_6H_4B(pz)_3]Na$. Lithium–halogen exchange between n-BuLi and Na[4-BrPhB(pz)] also occurred in ether above about −20 °C. After 2.5 min at 0 °C, the reaction mixture was quenched with D_2O and then added to 0.5 M $CoCl_2$ in 1 M pH 5.5 acetate buffer to yield a mixture of $(4\text{-}RPhB(pz)_3)(4\text{-}R'PhB(pz)_3)Co$ (R = H, D, or Br; R′ = H, D, Br, or Bu). HPLC analysis of the chloroform extract of the hydrolysate indicated that 7% of the starting material was recovered and 26.5% was converted to the lithium reagent. NMR analysis of this mixture indicated a 41% deuteration vs. 59% proton abstraction.

At −70 °C in THF, the lithium–halogen exchange took place almost immediately. Quenching with D_2O after 5 min followed by treatment with buffered Co^{2+} solution gave a 52% yield of $[4\text{-}DPhB(pz)_3]_2Co^{II}$. No proton abstraction was observed.

When carbonation of $[4\text{-}LiPhB(pz)_3]Na$ was attempted as before, no phenyl paramagnetic products were obtained after treatment of the reaction mixture with buffered Co^{2+} solution. The chloroform extract of the hydrolysate instead contained an unknown, possibly polymeric, product containing one pyrazole per para-disubstituted benzene ring.

Dipolar Shifts. Figure 1 illustrates the relationship of the isotropic shifts vs. $[(1 - 3\cos^2\theta)R^{-3}]$ observed for $(PhB(pz)_3)_2Co$, $(4\text{-}n\text{-}BuC_6H_4B(pz)_3)_2Co$, and $(4\text{-}CH_3OOCC_6H_4B(pz)_3)_2Co$.

Discussion

Synthesis of Aryltris(1-pyrazolyl)borates. Trofimenko[3] reported two methods for the synthesis of $ArB(pz)_3^-$ compounds: reaction of an arylboron dichloride with pyrazole (eq 1) and reaction of a boronic acid with Na pyrazolide (eq 2). In our hands, the first

$$ArBCl_2 + 4pzH \rightarrow ArB(pz)_3^- + pzH_2^+ + 3HCl \tag{1}$$

$$ArB(OH)_2 + pzH + Na(pz) \rightarrow ArB(pz)_3^-Na^+ + 2H_2O \tag{2}$$

of these worked poorly, if at all. Furthermore, the reactive $-BCl_2$ group was often incompatible with other functional groups. We therefore used the boronic acid route to $ArB(pz)_3^-$ compounds.

Two modifications were made to Trofimenko's boronic acid procedure:[3] (a) diglyme (bp 162 °C) was substituted for THF, which had been used as the solvent in the early stages of the reaction; (b) the arylboronic acid was added as an aqueous acetone solution to excess pyrazole and the water was then removed by distillation before addition of NaH to generate Na(pz) in situ. The use of diglyme rather than molten pyrazole as a reaction medium made small scale preparations more convenient. The importance of temperature control should also be emphasized. If the reaction temperature was less than ca. 200 °C, essentially no desired product was obtained; if it rose above ca. 230 °C, decomposition occurred.

The use of aqueous acetone solvent for the starting arylboronic acid was prompted by large variations in product yield obtained in the original procedure. We ascribed these variations to formation of anhydrides[6] (eq 3). Nucleophilic attack on an anhydride with displacement of –OBAr (eq 4) would be expected to be less favorable than the corresponding attack on the acid with loss of water (eq 5).

$$3ArB(OH)_2 \rightarrow [B(Ar)O]_3 + 3H_2O \tag{3}$$

$$[B(Ar)O]_3 + pzH \rightarrow ArB(pz)OB(Ar)OB(Ar)OH \tag{4}$$

$$ArB(OH)_2 + pzH \rightarrow ArB(pz)OH + H_2O \tag{5}$$

The use of aqueous acetone and the changes in the order of addition of reagents were intended to prevent anhydride formation. These modifications and the use of diglyme gave consistent yields (30% ± 5%) of $(ArB(pz)_3)_2Co$.

Reactions of the Lithium Reagents. When the $4\text{-}BrC_6H_4B(pz)_3$ chelate was bound to Co^{2+} ion, the chelate was preserved intact during the straightforward formation and reaction of the reactive lithium reagent (eq 6–10). If, however, the chelate was not bound to a template transition-metal ion, decomposition occurred. Quenching of the product of reaction of n-BuLi with 4-BrPhB-$(pz)_3Na$ with D_2O indicated that lithium–halogen exchange did take place (eq 12). However, attempts to carbonate this reagent failed to yield the desired $4\text{-}HO_2CPhB(pz)_3Na$ (eq 13).[7] The initial step in the decomposition of this product may have been a boron-to-carbon migration[9] of a pyrazole to the phenyl 1-carbon, which bears a partial positive charge due to the electron-withdrawing group at the 4-position.

$$(4\text{-}BrC_6H_4B(pz)_3)_2Co + n\text{-}BuLi \rightarrow \underset{V}{(4\text{-}LiC_6H_4B(pz)_3)_2Co} \tag{6}$$

$$V + D_2O \rightarrow \underset{VI}{(4\text{-}DC_6H_4B(pz)_3)_2Co} \tag{7}$$

$$V + n\text{-}BuI \rightarrow \underset{VII}{(4\text{-}n\text{-}BuC_6H_4B(pz)_3)_2Co} \tag{8}$$

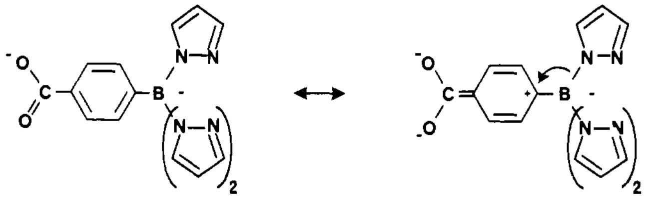
$$V + CO_2 \rightarrow \underset{VIII}{(4\text{-}HOOCC_6H_4B(pz)_3)_2Co} \tag{9}$$

$$VIII + CH_2N_2 \rightarrow \underset{IX}{(4\text{-}CH_3OOCC_6H_4B(pz)_3)_2Co} \tag{10}$$

$$4\text{-}BrC_6H_4B(pz)_3^-Na^+ + n\text{-}BuLi \rightarrow \underset{X}{4\text{-}LiC_6H_4B(pz)_3^-Na^+} \tag{11}$$

$$X + D_2O \rightarrow 4\text{-}DC_6H_4B(pz)_3^-Na^+ \xrightarrow{Co^{2+}} VI \tag{12}$$

$$X + CO_2 \rightarrow [4\text{-}LiOOCC_6H_4B(pz)_3^-Na^+] \xrightarrow{Co^{2+}} VII \tag{13}$$



Although the $(RB(pz)_3)_2Co^{II}$ moiety is generally quite stable,[1,3,4] two modes of decomposition could sometimes limit the use of these compounds: hydrolysis of the chelate in strongly acidic media and oxidation of Co(II) to diamagnetic Co(III). Air oxidation

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[6] Torsell, K. *Prog. Boron Chem.* **1964**, *1*, 369–415.

[7] An attempt to prepare a sulfonyl chloride derivative via reaction with sulfuryl chloride[8] also failed. A similar rearrangement may have been involved.

[8] Bhattacharya, S. N.; Eaborn, C.; Walton, D. R. M. *J. Chem. Soc.* **1968**, 1265–1267.

[9] Paetzold, P. I.; Grundke, H. *Synthesis* **1973**, 635–660.

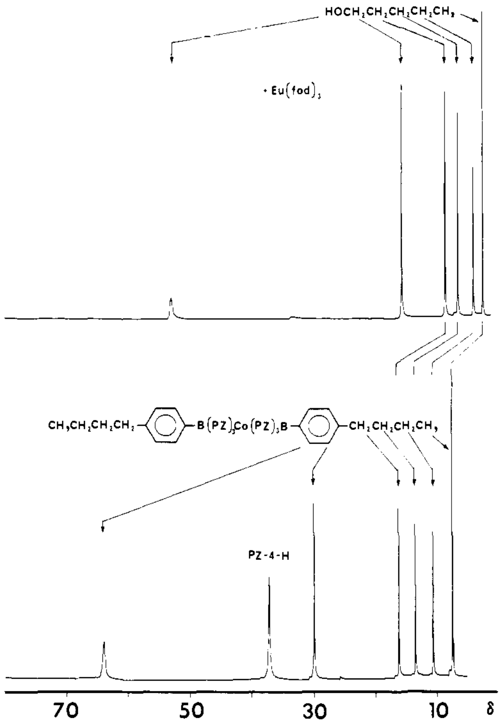

Figure 2. NMR spectra at 270 MHz in CCl_4 at 25 °C of (a) 0.04 M 1-pentanol with 0.02 M tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato-d_{30})europium added and (b) 0.02 M (4-*n*-$BuC_6H_4B(pz)_3)_2Co$.

has not been a serious problem. For example, solid $(PhB(pz)_3)_2Co$ can be stored indefinitely without special precautions, and its solutions in CH_2Cl_2 or $CHCl_3$ are stable for days to weeks without substantial air oxidation.

Validity of the Dipolar Shift Expression for These Complexes. It has been noted previously[2,5] that the isotropic shifts observed for the pyrazole protons in cobalt(II) tris(1-pyrazolyl)borates contained both contact and dipolar contributions. It was found, however, that protons on the R group attached to boron experienced predominantly dipolar contributions with essentially no contact components.[2,5] Their isotropic shifts could be expressed by eq 14,[2,10] where ΔH is the difference in the chemical shift

$$\Delta H/H = D(1 - 3\cos^2\theta)/R_3 \qquad (14)$$

between a resonance in the paramagnetic species and a diamagnetic analogue, R is the length of the vector from the metal ion to the nucleus, and θ is the angle between that vector and the principal axis of the axially symmetric magnetic susceptibility tensor (which is coincident with the principal symmetry axis of the complex). The parameter D is one-third of the magnetic susceptibility anisotropy.[2] We have confirmed that this relationship, which was first demonstrated by Jesson[5] for R = Ph and *n*-Bu, holds in the compounds reported herein, as well as a number of more extensively substituted $(R\text{-}PhB(pz)_3)_2Co$ compounds.[11] Furthermore, we have shown that the intact complexes can be functionalized and covalently coupled to substrates.

Potential as NMR Shift Reagents. The term "paramagnetic shift reagent" is often associated with the lanthanide β-diketonates first described by Hinckley,[12] and it is to these that any new shift reagent is reasonably compared (cf. Figure 2). The lanthanide complexes have shown great utility in the analysis of the NMR spectra of compounds bearing polar functional groups.[2,13] For this purpose, the lanthanide shift reagents enjoy three major advantages: commercial availability, ease of use, and reversible binding, which in principle allows recovery of substrate and reagent. The larger isotropic shifts of the $(RB(pz)_3)_2Co$ compounds probably would not be sufficiently advantageous to lead one to choose them over a conventional lanthanide reagent for the simplification or an aid in the analysis of the NMR spectra of many substrates. However, for the purposes of obtaining structural and conformational information,[2,13] the $(RB(pz)_3)_2Co$ reagents are potentially more powerful than the lanthanide reagents. The usefulness of the lanthanide reagents is limited by several factors. Their reversible binding to substrate may reduce the magnitude of the observed shift. The geometrical information available through these reagents is also severely limited by ambiguities in the stoichiometry of the shift reagent-substrate complex,[2,13-15] its geometry,[16] and the location of the binding site where more than one is available. Further ambiguity arises from the fact that some of the observed shifts may contain significant contact contributions (the substrate is bound in the first coordination sphere of the paramagnetic ion) in addition to the dipolar interactions that contain the geometrical information.[2]

Covalently bound paramagnetic shift reagents such as those described herein do not suffer from these limitations. The synthetic procedures employed establish the stoichiometry and site of attachment to substrate. Contact contributions are essentially limited to the pyrazole rings,[2,5] and enough structural information is known about these compounds to allow empirical determination of the parameter D in the expression for the dipolar shift (eq 14), as illustrated in Figure 1. The synthetic versatility of these compounds, their large dipolar shifts, and the relationship of these shifts to the geometry of the complex combine to make them potentially powerful probes for the detailed geometry of covalently bound substrates. Moreover, the magnitude of these shifts is sufficiently large that geometrical information about indirectly bound substrates should be attainable. One can envision potential applications in which a paramagnetic probe (P) could be covalently bound to a ligand (L), which in turn binds reversibly to a substrate (S).

$$L + S = [LS]$$

$$P\text{-}L + S = [P\text{-}LS]$$

The power of this approach is illustrated by the fact that we have observed dipolar shifts of ca. 3 ppm for protons 14 Å away from the cobalt.[11]

Conclusions

The (4-bromophenyl)tris(1-pyrazolyl)borates can be readily converted to the corresponding lithium reagents in THF at ca. −70 °C. Under extreme reaction conditions the tris(1-pyrazolyl) moiety can be protected effectively by chelation of a transition metal. These lithium reagents have been used for the preparation of simple derivatives, e.g., by deuteration or carbonation; however, they provide the potential for straightforward attachment of paramagnetic probes to a wide variety of systems.[11]

Since the protons on the phenyl rings and their substituents experience large isotropic shifts that fit simple dipolar shift expressions relating them to the geometry of the complex, these probes should have numerous applications in studies of stereochemistry. Furthermore, the induced shifts can produce extremely large separations in rearranging or exchanging systems and, therefore, could provide an aid to NMR line-shape analysis of rates.

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(10) McConnell, H. M.; Robertson, R. E. *J. Chem. Phys.* **1958**, *29*, 1361-1365.

(11) We have prepared Co(II) tris(1-pyrazolyl)borate derivatives of two dyes that bind to DNA, malachite green, and 9-phenylacridine orange. Moreover, these compounds were prepared by using a different strategy in which the boronic acid functionality was added to the dye and then converted to a tris(1-pyrazolyl)borate. The potential versatility has also been expanded by devising straightforward methods of preparing mixed chelates, which contain only one pyrazolyl borate function, e.g., $[(RB(pz)_3)Co(RC(pz)_3)]^+$. White, D. L.; Faller, J. W., manuscripts to be submitted to *Inorg. Chem.*

(12) Hinckley, C. C. *J. Am. Chem. Soc.* **1969**, *91*, 5160.

(13) Orell, K. G. *Annu. Rep. NMR Spectrosc.* **1979**, *9*, 67-83 and references therein.

(14) Abraham, R. J.; Chadwick, D. J.; Griffiths, L. *Tetrahedron Lett.* **1979**, *49*, 4691-4694.

(15) Raber, D. J.; Janks, C. M.; Johnston, M. D., Jr.; Raber, N. K. *Org. Magn. Reson.* **1981**, *15*, 57-67.

(16) Richardson, F. S.; Brittain, H. G. *J. Am. Chem. Soc.* **1981**, *103*, 18-24.

One may also anticipate that since these reagents provide a straightforward method of attaching a metal chelate function to a substrate, there may be many other applications unrelated to NMR, such as the functionalization of surfaces or polymers.

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Registry No. $C_6H_5B(pz)_3Na$, 80583-77-3; 4-$BrC_6H_4B(pz)_3Na$, 80593-37-9; 4-$LiC_6H_4B(pz)_3Na$, 80583-78-4; (4-$BrC_6H_4B(pz)_3)_2Co$. 80583-79-5; $(C_6H_5B(pz)_3)$(4-$BrC_6H_4B(pz)_3)Co$, 80583-80-8; (4-*n*-$BuC_6H_4B(pz)_3)_2Co$, 80593-38-0; (4-$HOOCC_6H_4B(pz)_3)_2Co$, 80583-81-9; (4-$CH_3OOCC_6H_4B(pz)_3)_2Co$, 80583-82-0; (4-$LiC_6H_4B(pz)_3)_2Co$, 80583-83-1; $PhB(OH)_2$, 98-80-6; 4-$BrPhB(OH)_2$, 5467-74-3; pyrazole, 288-13-1.

Hybrid Organometallic/Enzymatic Catalyst Systems: Regeneration of NADH Using Dihydrogen[1]

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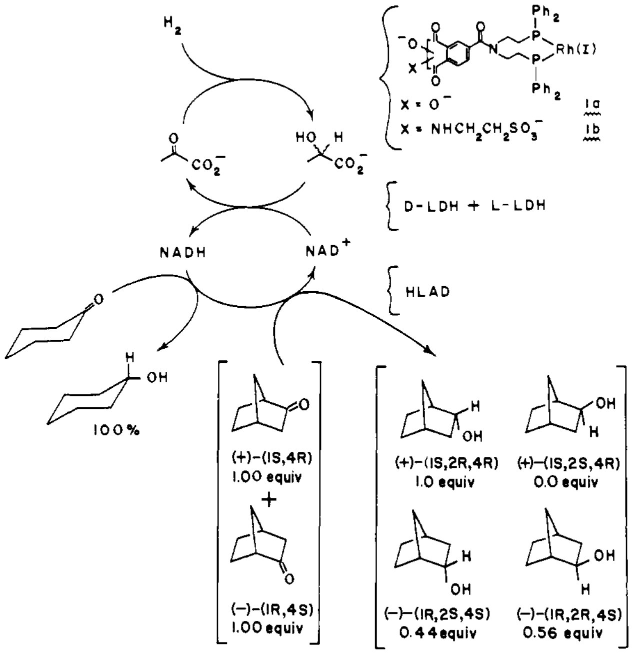
Abstract: A mixture of a water-soluble bis(phosphine)rhodium complex and D- and L-lactate dehydrogenase catalyzes the reduction of nicotinamide adenine nucleotide (NAD^+) to NADH by H_2 in an aqueous solution containing pyruvate (Scheme I). Coupling of this system to the asymmetric reduction of 2-norbornanone using horse liver alcohol dehydrogenase is demonstrated.

Organometallic and enzymatic catalysts generally exhibit their most characteristic activities on different classes of reactants: organometallic catalysts are especially effective with nonpolar substances (e.g., H_2, CO, and olefins), while enzymatic catalysts are most effective with polar, polyfunctional materials (e.g., carbohydrates, derivatives of acids, and biopolymers). Combinations of organometallic and enzymatic components which integrate these two types of substrate selectivities may have uncommon and useful catalytic activities. Here we demonstrate the operation of a hybrid system involving the combination of a water-soluble bis(phosphine)rhodium complex with two enzymes, whose overall action is to catalyze the reduction of NAD^+ to NADH by H_2.[2] The operation of this system and illustrations of its application to enzyme-catalyzed reduction reactions requiring NADH regeneration are summarized in Scheme I. The regeneration of the nicotinamide cofactors (NAD(P)–NAD(P)H) has been the subject of previous research in our laboratories. Several procedures are presently available;[3-8] the evaluation of their relative merits has not been completed.

Scheme I. Reductions of Carbonyl Compounds Using a Hybrid Organometallic-Enzymatic Catalyst System[a]



[a] D(L)-LDH = D(L)-lactate dehydrogenase; HLADH = horse liver alcohol dehydrogenase.

Results

Reduction of (±)-2-Norbornanone. Asymmetric reduction of (±)-2-norbornanone was carried out in a system containing racemic sodium lactate, NAD^+, coimmobilized horse liver alcohol dehydrogenase (HLAD), D- and L-lactate dehydrogenase (D- and L-LDH), the bis(phosphine)rhodium complex **1a** or **1b** (originally as $L_2Rh^I(norbornadiene)^+CF_3SO_3^-$), and dihydrogen at 40 psi. After 3 days, 50% reduction had occurred and no further reaction was observed. The residual activities of HLAD and D- and L-LDH at this time were respectively 80%, 85%, and 82% of the original immobilized activities. The aggregate residual activity of NAD^+ and NADH was 80% of the original value. The reaction was continued by introducing additional rhodium complex into the

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(1) Supported by the National Institues of Health (Grant GM 26543) and the National Science Foundation (Grant 8012722 CHE).

(2) We have previously described a complex between avidin and a rhodium chelate derived from biotin which was active as an asymmetric hydrogenation catalyst: Wilson, M. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1978**, *100*, 306–307.

(3) We are comparing hydrogenase-based systems with the organometallic systems described here: Wong, C.-H.; Daniels, L.; Orme-Johnson, W. B.; Whitesides, G. M. *J. Am. Chem. Soc.*, in press.

(4) Wong, C.-H.; Whitesides, G. M. *J. Am. Chem. Soc.* **1981**, *103*, 4890–4899.

(5) Shaked, Z.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 7104–7105.

(6) Shaked, Z.; Barber, J. J.; Whitesides, G. M. *J. Org. Chem.* **1981**, *23*, 4100.

(7) DiCosimo, R.; Wong, C.-H.; Daniels, L.; Whitesides, G. M. *J. Org. Chem.* **1981**, *46*, 4622–4623.

(8) Wong, C.-H.; Gordon, J.; Cooney, C. L.; Whitesides, G. M. *J. Org. Chem.* **1981**, *23*, 4676.

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