Grant No. CHE 80-19041, the Alfred P. Sloan Foundation for a fellowship to R.D.A., and Engelhard Industries for a loan of osmium tetroxide.

Registry No. III, 83928-37-4; IV, 83928-36-3; V, 86177-67-5; VI, 72282-40-7; VII, 61817-93-4; $HOs_3(CO)_{10}(\mu\text{-SPh})$, 23733-19-9; $Os(CO)_5$, 16406-49-8.

Supplementary Material Available: A table of structure factor amplitudes (10 pages). Ordering information is given on any current masthead page.

Epimerization of α-Chloro Boronic Esters by Lithium and Zinc Chlorides

Donald S. Matteson* and Ender Erdik[1]

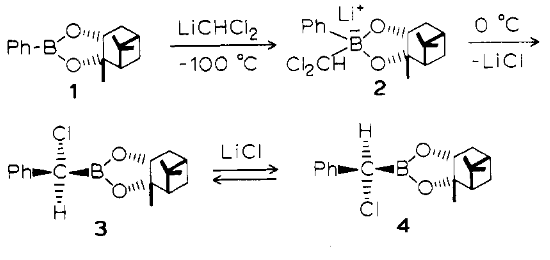
Department of Chemistry, Washington State University, Pullman, Washington 99164

Received March 11, 1983

The epimerization of (+)-pinanediol (αS)-α-chloro-α-phenylmethaneboronate (**3**) to the (αR)-isomer **4** is catalyzed by lithium chloride in tetrahydrofuran (THF). The rate is first-order in **3** and approximately 0.75 order in lithium chloride over the range 0.04–0.45 M LiCl. No epimerization takes place in the absence of lithium chloride. The rate is greatly increased by reagents which promote ionization of lithium chloride, including water and dimethyl sulfoxide. Accordingly it appears that the active catalyst is free chloride ion. Zinc chloride also catalyzes the epimerization, and the rate shows approximately 1.6-order dependence on the $ZnCl_2$ concentration, as if acid catalysis is involved together with chloride catalysis. Mixtures of lithium chloride and 0.5–1.0 equiv of zinc chloride are less active catalysts than either salt by itself, implying formation of relatively inactive $LiZnCl_3$ and Li_2ZnCl_4, but rates of epimerization by these reagents are still significant in terms of limiting the stereoselectivity of the synthesis of α-chloro boronic esters by homologation of boronic esters with (dichloromethyl)lithium. The rate of epimerization of (+)-pinanediol (αS)-α-chlorallylboronate by lithium chloride was 0.7 that of the α-chloro α-phenylmethaneboronate (**3**), and the rates for (+)-pinanediol 1-chloro-2-phenylethane-1-boronate and 1-chloropentane-1-boronate were about an order of magnitude less than that for **3**.

Introduction

The chirally selective reaction of pinanediol boronic esters with dichloromethyllithium to form homologous α-chloro boronic esters provides a promising new approach to directed chiral synthesis.[2] A side reaction which can decrease the stereoselectivity of this process is the epimerization of the α-chloro boronic ester product in the presence of the other reaction product lithium chloride. Thus, the reaction of (+)-pinanediol benzeneboronate (**1**) with (dichloromethyl)lithium forms the borate complex **2**, which rearranges primarily to (+)-pinanediol (αS)-α-chloro-α-phenylmethane boronate (**3**), which in turn epimerizes significantly to its (αR)-isomer (**4**) if the reaction mixture is not worked up quickly enough.[2] Although conditions were found which yielded ratios of **3** to **4** as high as 30:1,[2] the present kinetic study was undertaken in order to understand the factors which affect the rate of epimerization of **3** and related compounds, with the aim of learning how to minimize this side reaction for synthetic purposes.



Experimental Section

General Data. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Lithium chloride and zinc chloride were reagent grade and were dried to constant weight under vacuum (0.01 torr) at up to 100 °C while pulverizing with the aid of a small magnetic stirrer in a volumetric flask. The flask was cooled with an ice-water bath when THF was added to zinc chloride. Solutions were made up under argon, and all transfers of solvents or solutions were made by syringe through rubber septums with pressure equalization by argon-filled balloons. Protection from air was not entirely rigorous as the rubber septum was exchanged for a Teflon plug after filling the polarimeter cell. Slow leakage of THF through the rubber septums was observed, and solutions were used within a few days of preparation. Proton NMR spectra were measured at 60 MHz with a Varian EM-360 instrument or at 200 MHz with a Nicolet NT-200. Optical rotations were measured at 546 nm (Hg line) with a Jasco DIP-181 digital polarimeter, except for exploratory studies before this instrument became available to us, which were done with an ancient Rudolph visual instrument at 589 nm.

(+)-Pinanediol (αS)-α-Chlorobenzylboronate (3). A. Modified Previous Method.[2] The published procedure[2] was followed, 10-mmol scale, up to the point where the reaction mixture was kept at 0 °C for 1 h in order to rearrange **2** to **3**. If the solution was concentrated at this point and **3** was distilled directly from the residual lithium chloride as described for other α-chloro boronic esters,[3] epimerization of **3** to **4** approached the equilibrium value. To avoid this problem, the cold solution of

---

(1) Visiting NATO Fellow from Organic Chemistry Research Institute, Faculty of Science, Ankara University, Ankara, Turkey.

(2) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590–7591.

(3) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7588–7590.

0276-7333/83/2302-1083$01.50/0

3 was treated with 200 mL of ice water and 100 mL of cold ether and the organic phase was dried over magnesium sulfate and distilled rapidly to yield **3**, bp 118–126 °C (0.5 torr), containing 5–10% unchanged **1** in most samples by 60-MHz proton NMR analysis, $[\alpha]^{25}{}_{D}$ variable from −17.6° to +1.0° in THF. Samples of **3** prepared in this manner yielded erratic kinetic results in epimerization studies, which appeared to become more erratic as the samples aged a few days.

B. Zinc Chloride Method.[4] The use of zinc chloride in the synthesis of α-chloro boronic esters is described elsewhere.[4] (Dichloromethyl)lithium prepared from 83 mmol of butyllithium and excess dichloromethane in 75 mL of THF at −100 °C was treated with 1..2 g (75 mmol) of optically pure (+)-pinanediol benzeneboronate (**1**) in 50 mL of ether, resulting in a solid precipitate which made stirring difficult. To the slurry at −100 °C was added 7.58 g (56 mmol) of powdered anhydrous zinc chloride. On warming to −30 to −25 °C for 45 min, the zinc chloride dissolved. The solvent was distilled immediately under vacuum from a bath kept below −10 °C, and the residue was treated with petroleum ether (250 mL) followed by ice water (200 mL). Chromatography on 80 g of silica gel with petroleum ether yielded 19.1 g (83.6%) of crystalline (+)-pinanediol (α*S*)-α-chloro-α-phenylmethaneboronate (**3**), which contained 6% (±1%) of the (α*R*)-epimer **4** by 200-MHz proton NMR analysis. The two epimers are readily distinguished by a doublet (J = 4.0 Hz) which for **3** appears at δ 1.142, for **4** at δ 1.03. Two recrystallizations from hexane yielded a pure sample of **3**: mp 63–64 °C; $[\alpha]^{25}{}_{577}$ −38.06°, $[\alpha]^{25}{}_{546}$ −43.69°, $[\alpha]^{25}{}_{435}$ −80.82°, $[\alpha]^{25}{}_{365}$ − 139.4° (c = 1.25, THF). Anal. Calcd for $C_{17}H_{22}BClO_2$: C, 67.03; H, 7.28; B, 3.55; Cl, 11.64. Found: C, 67.23; H, 7.03; B, 3.74; Cl, 11.22. After brief exposure to air and storage for 2 weeks at room temperature, the sample had yellowed. Material used for kinetic runs was stored in the freezer under argon. Some of the kinetic runs were carried out with an early sample of **3** which had been allowed to stand at room temperature overnight in the presence of the zinc chloride during its preparation and was thereby about 60% epimerized, but identical k values were obtained, within experimental error, on checking with a highly purified sample of **3**.

Other α-Chloro Boronic Esters. These compounds were available from studies reported elsewhere.[2,4,5] All had been prepared with the aid of zinc chloride.[4] Specific rotations: (+)-pinanediol 3-chloro-1-propene-3-boronate, from $[\alpha]^{25}{}_{546}$ +69.4° initially to +31.2° after epimerization; (+)-pinanediol 1-chloro-2-phenylethane-1-boronate, $[\alpha]^{25}{}_{546}$ from +17.6° to +26.1; (+)-pinanediol 1-chloropentane-1-boronate, $[\alpha]^{25}{}_{546}$ from +36.2° to +26.8°.

Kinetics. Samples of **3** (50–200 mg) were weighed under argon in 10-mL volumetric flasks, and the required amounts of THF and lithium chloride or other solutions were added by syringe. Tabulated concentrations are estimated to be accurate to 1–3%. Solutions were transferred to water-jacketed polarimeter cells, which were kept at 24.9 °C (±0.3 °C) with a circulating thermostated bath. Rotations were read at convenient intervals, with 30 or more points generally recorded during the first half-life, the interval used as the basis for most of the tabulated k's. Infinity points were measured after 10 half-lives for several of the faster runs, and these values were used to estimate the remainder. For a pure equilibrium mixture of **3** and **4**, $[\alpha]^{25}{}_{546}$ is +20.3° (c = 1.1, THF with 0.45 M lithium chloride). The equilibrium constant K = 1.0, estimated from the doublets at δ 1.14 and 1.03 in the 200-MHz NMR spectrum of material recovered after a kinetic run. The k values were calculated directly from the experimental data with the aid of a calculator programmed to store and read back the data, to convert rotations to $\ln (a_0/a)$ where a/a_0 is the fraction of **3** unconverted, and to calculate the least-squares slope. For visualization of the quality of the data, a typical run is plotted in Figure 1. The k values determined for varying amounts of lithium chloride are summarized in Table I, approximate data involving various additives in Table II, k's for other boronic esters in Table III, and k's for zinc chloride/lithium chloride mixtures in Table IV.

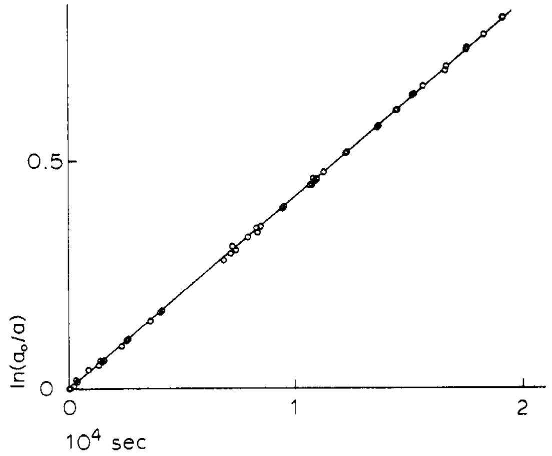


Figure 1. Plot of $\ln (a_0/a)$ vs. time for a typical kinetic run: **3** in the presence of 0.394 M lithium chloride in THF, pseudo-first-order $k = 4.25 \times 10^{-5}$ s^{1}, standard deviation of $\ln (a_0/a)$ = 0.45% of total kt interval plotted.

Table I. Pseudo-First-Order Rate Constants for Epimerization of (+)-Pinanediol (α*S*)-α-Chlorophenylmethaneboronate (3) by Lithium Chloride in THF at 24.9 °C

[LiCl], M	$10^5 K$, s^{-1}	final kt	std dev,[a] %
0	0.002[b]	0.003	10.3
0.0381	0.739	0.85[c]	0.26
0.0762	1.53	0.07	3.0
0.0953	1.81	0.79	0.42
0.183	2.41	0.11	2.3
0.191	2.68	0.76	0.59
0.213	3.05	0.58	0.77
0.248	3.33	0.79[d]	0.29
0.374	4.26	0.88	0.41
0.394	4.25	0.82	0.45
0.449	5.64	1.14	0.24
0.450	5.72	1.72	0.28

[a] Standard deviation of $\ln (a_0/a)$ from kt as percent of total kt observed. [b] Change in rotation was 0.003° over a 48-h period of observation. [c] Additional data to kt = 1.30 (2 half-lives) yield $k = 0.741 \times 10^{-5}$, std dev 0.22%. [d] Additional data to kt = 2.66 (3.8 half-lives) yield $k = 3.34 \times 10^{-5}$, std dev 0.21%.

Results

Exploratory Work. In our first expierments, solutions of (+)-pinanediol (α*S*)-α-chloro-α-phenylmethaneboronate (**3**) were prepared in THF (containing some hexane) by the published procedure[2] and then warmed to 25 °C, and the rate of mutarotation was measured. Good pseudo-first-order plots were obtained, but the k's were erratic and 2–5 times higher than the true values subsequently found with pure **3** and lithium chloride in THF (see Tables I and II).

Kinetic data for isolated samples of **3** prepared by method A (the previously published method)[2] yielded satisfactory first-order plots, but k values were still erratic, and correlation with any reasonable function of the lithium chloride concentration yielded standard deviations near ±30%, with k's about 2–3 times the reproducible values subsequently measured.

The key observation which ultimately led to solution of the problem was that the rate of epimerization of **3** was experimentally indistinguishable from zero in the presence of 0.1 M mercuric chloride or 0.1 M lithium chloride/0.1 M mercuric chloride (Table II). Thus, **3** is stable in the presence of a fairly strong complexing agent for chloride ion, permitting the incorporation of metal salts in the reaction mixture which might catalyze the rearrangement

---

(4) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077–2078.

(5) Matteson, D. S.; Sadhu, K. M.; Lienhard, G. E. *J. Am. Chem. Soc.* **1981**, *103*, 5241–5242.

Table II. Approximate Pseudo-First-Order Rate Constants for Epimerization of (+)-Pinanediol (α*S*)-α-Chloro-α-phenylmethaneboronate by Lithium Chloride under Various Conditions at 25 °C

[ClCl], M	solv	additive	$10^5 k$, s^{-1}	final *kt*	std dev,[a] %
~0.025[b]	THF	Me_2SO, 0.5 M[b]	21.9	0.73	0.53
0.449[c,d]	THF	$HgCl_2$, 0.02 M	4.47	0.61	0.91
0.1[c]	THF	$HgCl_2$, 0.1 M	<0.02[e]		
0[c]	THF	$HgCl_2$, 0.1 M	<0.02[e]		
0.019	DME		≤2.7[f]	2.4	2.2
0.025	DME		≤5.0[f]	1.7	2.7
0.098	THF	triglyme, 0.1 M	≤3.7[f]	1.25	2.5
0.096	THF	triglyme, 1.75 M	≤6.5[f]	1.8	3.6
0.10	THF	dibenzo-18-crown-6, satd[g]	≤6.7[f]	1.5	6.1
0.20[h]	THF/hexane[h]		7.6[h]	2.0	1.5
0.28[h]	THF/hexane[h]		16.5[h]	2.4	2.9
0.20[h]	THF/hexane[h]	triglyme, 1.6 M	14.0[h]	2.0	2.1

[a] See Table I for definition. [b] Estimated by difference. Addition of Me_2SO to 0.19 M LiCl in THF yielded a precipitate of LiCl·Me_2SO, which was weighed before and after removal of Me_5SO under vacuum. [c] Total LiCl added. [d] If Li_2HgCl_4 formed, remaining [LiCl] = 0.410 M, which corresponds to observed *k* (see Table I). [e] Observed *k* = 0, 22–23 °C. Maximum *k* is defined by standard deviation, 48 h. [f] The **3** was prepared without the aid of $ZnCl_2$, and the observed *k*'s may be up to twice the true values. [g] <0.1 M. [h] These are in situ runs. The LiCl is estimated from the stoichiometry, the hexane is derived from the stoichiometric quantity of 1.6 M butyllithium, and the *k* values are not closely reproducible.

Table III. Pseudo-First-Order Rate Constants for Epimerization of (+)-Pinanediol (α*S*)-α-Chloro Boronates by Lithium Chloride in THF at 24.9 °C

R of RCHCl-$BO_2C_{10}H_{16}$	[LiCl], M	$10^5 k$	rel *k*[a]	final *kt*	std dev,[b] %
CH_2=CH	0.384	2.94	0.69	0.79	0.46
$PhCH_2$	0.389	0.46	0.11	1.60	2.1
$CH_3(CH_2)_3$	0.443	0.25	0.047	0.88	1.7

[a] Compared to **3**, *k* defined as 1.00 at same LiCl concentration. [b] See Table I for definition.

of **2** to **3** or at least suppress the epimerization of **3** to **4**.

The search for a good Lewis acid additive for promoting the rearrangement of **2** to **3** and analogous preparations of α-chloro boronic esters involved a number of factors was best carried out on different compounds and is reported elsewhere.[4] Mercuric chloride was found not to interfere with the rearrangement of **2** to **3** or analogous reactions,[6] though it did not improve the yields of α-chloro boronic esters. A sample of **3** prepared in the presence of mercuric chloride and kept overnight before workup was epimerized to about the same extent as a sample similarly prepared with zinc chloride. This result is not inconsistent with our "zero" rate of epimerization of **3** by 0.1 M $LiHgCl_3$, inasmuch as the extrapolated *k* for 0.1 M $LiZnCl_3$ (Table IV) would also have been below the threshold of detectability with the visual polarimeter then available. Mercuric chloride proved difficult to separate from **3** by extraction and distillation, and the impure sample of **3** obtained yielded a *k* with 0.24 M lithium chloride that was 30% below the *k* subsequently obtained with **3** prepared in the presence of zinc chloride.

The first sample of **3** prepared with the aid of zinc chloride crystallized, even though it had partially epimerized, and reproducible epimerization kinetics were immediately obtained.

Lithium Chloride. Excellent pseudo-first-order epimerization data were obtained with a digital polarimeter and samples of **3** prepared by method B. A plot of a typical run is shown in Figure 1, observed *k* values are shown in Table I, and a plot of *k* vs. the 0.75 power of the lithium chloride concentration is shown in Figure 2. The reproducibility (±3%) is particularly illustrated by the pairs of *k*'s near 0.38 and 0.45 M lithium chloride, which were obtained from different preparations of samples and lithium chloride solutions. The 0.75-order dependence on lithium chloride is a purely empirical correlation based on the least-squares slope of a log/log plot. The data between 0.075 and 0.25 M lithium chloride are optimally correlated by the 0.62 power of the lithium chloride concentration.

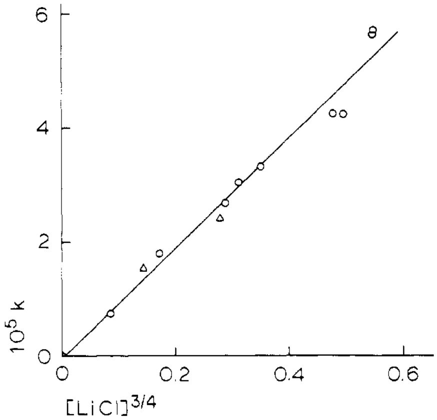


Figure 2. Plot of pseudo-first-order *k* vs. the 0.75-power of lithium chloride for the epimerization of **3** in THF. The least-squares slope, $9.72 \times 10^{-5}\ L^{0.75}\ s^{-1}$, is based on the data represented by circles, including the origin, standard deviation 5.8%. The triangles represent runs for which only initial rate data (5–10% reaction) were obtained.

In the absence of lithium chloride, the rate of epimerization of **3** in THF was barely detectable (Table I). The sample was one which had been purified but then stored several months at −15 °C. The slight epimerization may be attributed to impurities.

The effects of various additives on the rate of epimerization of **3** are summarized in Table II. These data are only of qualitative or semiquantitative significance in most instances but are reliable enough to illustrate significant features of the reaction. Thus, the rate is greatly accelerated by a small amount of water (doubled by 11 mg in 10 mL of THF) or dimethyl sulfoxide (Me_2SO) and is depressed by mercuric chloride. The data for **3** in dimethoxyethane (DME) indicate that at saturation with lithium chloride (~0.025 M), *k* is not greater than in THF saturated with lithium chloride (>0.45 M).

Other α-Chloro Boronic Esters. A very brief study, summarized in Table III, has indicated that (+)-pinanediol (α*S*)-α-chlorallylboronate epimerizes almost as fast as **3**, and that two saturated α-chloro boronic esters epimerize an order of magnitude more slowly. The observed muta-

---

(6) Matteson, D. S.; Jesthi, P. K., manuscript in preparation.

Table IV. Pseudo-First-Order Rate Constants for Epimerization of (+)-Pinanediol (αS)-α-Chloro-α-phenylmethaneboronate (3) by Zinc Chloride and Lithium Chlorozincates in THF at 24.9 °C

[ZnCl$_2$], M	[LiZnCl$_3$], M	[Li$_2$ZnCl$_4$], M	10^5k, s^{-1}	final kt	std dev,[a] %
0.079			0.13	0.30	0.26
0.172			0.34	0.27	0.90
0.430			1.82	0.63[b]	0.59
0.780			5.4[c]	0.72	1.2
0.292	0.260		1.99[d,e]	0.29	3.2
0.580	0.516		8.7[d,f]	0.63	3.4
0.026	0.286		0.215	0.57	0.50
0.052	0.572		0.67	0.63	1.8
0.002	0.170		0.044	0.009	9.0
	1.08	0.01	1.4[d,g]	0.31	6.7
	0.0874	0.0821	0.385	0.26	1.0
	0.0529	0.0608	0.354	0.68	0.56
	0.106	0.122	0.618	1.09	0.26
	0.264	0.304	1.59	0.49	1.7
	0.514	0.591	4.5	0.30	3.5
	0.012	0.156	1.05	0.70	0.51
	0.001	0.606	5.10	0.49	0.37
	0.002	1.20	11.1[d,h]	0.96	1.0

[a] Defined in Table I. [b] If data included to $kt = 1.65$, $10^5k = 1.82$, std dev 0.26%. [c] Plot curved: to $kt = 0.28$, $10^5k = 6.0$, std dev = 0.67%; from $k = 0.09$ to 0.98, $10^5k = 5.0$, std dev 1.0%. [d] Infinity rotation higher than average. [e] Observed infinity rotation yielded $10^5k = 1.90$. [f] Observed infinity rotation yielded $10^5k = 7.9$. [g] Observed infinity rotation yielded $10^5k = 1.17$ to $kt = 0.26$, $10^5k = 0.79$ to $kt = 0.84$ (std dev 3.4%). [h] Observed infinity point yielded $10^5k = 10.5$, but infinity point drifted 0.01° in 24 h. Value tabulated gives best self-consistency for data to $kt = 2.93$, $10^5k = 1.1$, % dev 0.82.

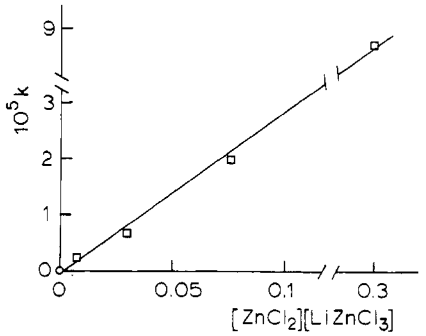


Figure 3. Least-squares plot of pseudo-first-order k vs. [ZnCl$_2$][LiZnCl$_3$] for the epimerization of **3**. The slope is 2.9×10^{-4} L^2 mol^{-2} s^{-1}.

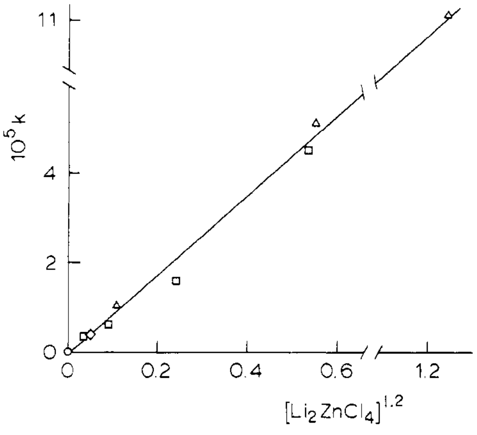


Figure 4. Least-squares plot of pseudo-first-order k vs. [Li$_2$ZnCl$_4$]$^{1.195}$, the power derived from a log/log plot of all of the data points, for epimerization of **3** in solutions containing Li$_2$ZnCl$_4$ and varying amounts of LiZnCl$_3$. The slope is 8.93×10^{-5} L$^{1.2}$ mol$^{-1.2}$ s^{-1}. The triangles represent Li$_2$ZnCl$_4$/LiZnCl$_3$ ratios in the range 13–600, the squares the ratio 1.15, and the diamonds the ratio 0.94.

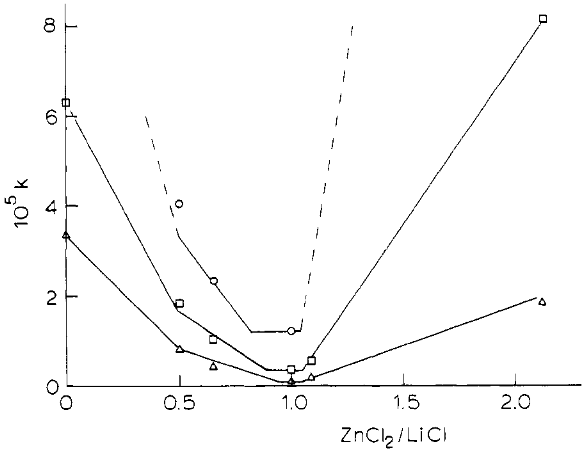


Figure 5. Plot of dependence of pseudo-first-order k for epimerization of **3** on the amount of zinc chloride added to selected constant concentrations of lithium chloride, based on interpolations from existing data. The triangular data points and lowest set of line segments are for 0.25 M LiCl, the squares and middle set of lines for 0.5 M LiCl, and the circles and highest set of lines for 1.0 M LiCl. The data points are interpolated (or extrapolated not more than 11%) from the measured k values and concentration dependences at the particular ZnCl$_2$/LiCl ratio. The solid lines are simple functions derived from the tabulated data: 2.9×10^{-4}[ZnCl$_2$][LiZnCl$_3$] at ZnCl$_2$/LiCl > 1.0; 1.2×10^{-5} [LiZnCl$_3$]$^{1.9}$ at ZnCl$_2$/LiCl = 1.0; 6.6×10^{-5}[Li$_2$ZnCl$_4$] at 0.5 < ZnCl$_2$/LiCl < 1.0; additive first-order functions of LiCl and Li$_2$ZnCl$_4$ (oversimplified but unimportant) at ZnCl$_2$/LiCl < 0.5. The dashed lines are extrapolations.

rotations for the saturated compounds spanned a relatively small range, leading to somewhat higher deviations, and were inconveniently slow for measurement.

Zinc Chloride and Lithium Chlorozincate. Since zinc chloride markedly improves the yields and diastereomeric purities of α-chloro boronic esters from the reaction of (dichloromethyl)lithium with boronic esters,[4] we have examined the rates of epimerization of **3** by zinc chloride and lithium chlorozincates. The results are summarized in Table IV and Figures 3–5.

The minimum epimerization rates are found near the composition LiZnCl$_3$, and rates at the composition Li$_2$ZnCl$_4$ remain substantially lower than for the equivalent amount of uncomplexes lithium chloride. The data for zinc chloride alone show an approximately 1.6-order dependence of k on [ZnCl$_2$]. For selected compositions between ZnCl$_2$ and LiZnCl$_3$, approximate linear dependence of k on the product of the concentrations of the two salts was observed

(Figure 3). For compositions between $LiZnCl_3$ and Li_2ZnCl_4 the dependence of k on concentration approaches first order in Li_2ZnCl_4 alone, with a slight negative dependence on $LiZnCl_3$. A plot of k vs. the 1.2 power of $[Li_2ZnCl_4]$ is shown in Figure 4. Of course, these rate laws all include the unknown and presumably large salt effects.

The rate minimum at the composition $LiZnCl_3$ is illustrated graphically in Figure 5, in which the data from Table IV are interpolated to 0.25, 0.5, and 1.0 M LiCl and the effect of adding increments of $ZnCl_2$ at fixed LiCl concentration is plotted. Concentrated salt solutions, especially of $LiZnCl_3$ and its mixtures with zinc chloride, showed some tendency toward erratic behavior. Compositions close to the stoichiometry $LiZnCl_3$ were especially erratic. Even solutions carefully prepared with cooling in ice when the THF was added to the $LiCl/ZnCl_2$ yielded initial rate constants up to 50% higher than the values estimated after 1 half-life. Infinity points showed somewhat higher values than expected and some tendency to continue to drift beyond 10 half-lives. Recovery of a sample of **3** + **4** after a week in 1.08 M $LiZnCl_3$ and analysis by 200-MHz NMR indicated that although **3** and **4** were the major constituents, 10–15% of another unknown component was present.

Discussion

Lithium Chloride. Halide exchanges on α-halo boronic esters observed previously appeared to be simple S_N2 processes with considerable rate enhancement by the neighboring boron.[7] Our present evidence regarding the epimerization of **3** by lithium chloride strongly suggests that the active nucleophile is free chloride ion, a conclusion in accord with much previous literature on S_N2 displacements by alkali-metal halides.[8,9] Lithium chloride consists largely of ion tetramers in THF in the concentration range used in our kinetic measurements.[10] Dissociation of $(Li^+Cl^-)_2$ to $(Li_2Cl)^+ + Cl^-$ would result in half-order dependence of the epimerization rate on lithium chloride concentration. (There seems no reason to expect the ion tetramers to have to dissociate all the way to $2Li^+ + 2Cl^-$, with consequent 0.25-order dependence.) Increasing salt concentration should strongly promote ionization, though perhaps not as strongly in the present system as found with lithium perchlorate in diethyl ether.[9] Thus, the observed average 0.75-order dependence on lithium chloride, which varies in the range 0.6–1.0 order if the reproducible deviations from linearity are considered, is a reasonable result.

The results with various additives strongly support the conclusion that free chloride ion is the active epimerization catalyst (Table II). The rate enhancement by water and dimethyl sulfoxide and the suppression by mercuric chloride support this view, as do the lesser rate enhancements by DME, triglyme, and dibenzo-18-crown-6. The 18-crown-6 is known to be only a weak chelating agent for lithium cation.[11] Our results imply that triglyme is considerably weaker. Many of the data in Table II were obtained before we learned how to purify **3** properly, and some of the k's given as upper limits could be too high by as much as a factor of 2, but no important qualitative conclusions are affected by this uncertainty. Those runs in which **3** was generated in situ all gave k values that are too high as if an active byproduct which acts as a chloride source or complexing agent for lithium ion is generated during the uncatalyzed rearrangement of **2** to **3**. However, these k's represent reality under the original conditions of our synthesis.

Other Boronic Esters. The rates of epimerization of (+)-pinanediol 1-chloropentane-1-boronate and 1-chloro-2-phenylethane-1-boronate, about an order of magnitude less than that of **3** (Table III), are sufficient to account for essentially all of the observed lack of stereospecificity in the syntheses of these and similar compounds.[2,4–6] The rate of epimerization of (+)-pinanediol 3-chloro-1-propene-3-boronate, slightly less than that of **3**, provides assurance that synthesis of chiral allylic α-chloro boronic esters will be straightforward.

Zinc Chloride and Lithium Chlorozincates. In contrast to lithium chloride, zinc chloride clearly does not catalyze the epimerization of **3** by way of liberation of free chloride ion. The deep minimum in the rate near the composition $LiZnCl_3$ (Table IV) is inconsistent with such a hypothesis, since $LiZnCl_3$ should yield a higher equilibrium concentration of chloride ion than should $ZnCl_2$. The ~1.6-order dependence on zinc chloride over a tenfold concentration range strongly suggests Lewis acid catalysis of chloride exchange. If the salt effects are comparable to those in the lithium chloride solutions, the true reaction order is about 1.5 or a little less, but probably not below 1.0.

Ionization of zinc chloride inTHF is probably dominated by the disproportionation represented by eq 1. Then

$$2ZnCl_2 \rightleftharpoons ZnCl^+ + ZnCl_3^- \quad (1)$$

equilibrium relationships are given by eq 2 and 3. An

$$K[ZnCl_2]^2 = [ZnCl^+][ZnCl_3^-] \quad (2)$$

$$[ZnCl^+] = [ZnCl_3^-] \quad (3)$$

exchange mechanism between RCl* (**3**) and $ZnCl_2$ which would show first-order dependence on the zinc chloride concentration is given by eq 4.

$$ZnCl_3^- + RCl^* \rightleftharpoons ZnCl_2 + RCl + Cl^{*-} \quad (4)$$

The principle of microscopic reversibility requires that equal numbers of chloride ions be exchanged by the forward and reverse paths.[7,12,13] Equation 4 thus requires that the concentration of free chloride ion be a constant (except for salt effects on ionization), and this is consistent with eq 2 and 3, which hold the $[ZnCl_3^-]/[ZnCl_2]$ ratio constant.

An exchange mechanism which would show second-order dependence on the zinc chloride concentration is given by eq 5. The four data points available are inconsistent with

$$ZnCl_3^- + RCl^* + ZnCl_2 \rightleftharpoons ZnCl_2 + RCl + ZnCl_3^{*-} \quad (5)$$

eq 5 being the only mechanism operating where zinc chloride alone is the catalyst, but some combination of eq

---

[7] Matteson, D. S.; Mah, R. W. H. *J. Am. Chem. Soc.* **1963**, *85*, 2599–2603.

[8] (a) Weaver, W. M.; Hutchison, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 261–265.

[9] Winstein, S.; Smith, S.; Darwish, D. *J. Am. Chem. Soc.* **1959**, *81*, 5511–5512.

[10] Wong, M. K.; Popov, A. I. *J. Inorg. Nucl. Chem.* **1972**, *34*, 3615–3622.

[11] (a) Wong, K. H.; Koniser, G.; Smid, J. *J. Am. Chem. Soc.* **1970**, *92*, 666–670. (b) Pedersen, C. J. "Synthetic Multidentate Macrocyclic Compounds", Izatt, R. M., Christensen, J. J., Eds.; Academic Press: New York, 1978; pp 1–51.

[12] (a) Matteson, D. S. "Organometallic Reaction Mechanisms"; Academic Press: New York, 1974; p 96. (b) Burwell, R. L.; Pearson, R. G. *J. Phys. Chem.* **1966**, *70*, 300.

[13] This is strictly true for exchange between $ZnCl_2$ and RCl at equilibrium. The asymmetry of **3** and **4** permits some deviation from strict equality of the forward and reverse paths with respect to the conversion of **3** to **4**, balanced by an opposite bias in the conversion of **4** to **3**.

4 and 5 seems possible. The unknown magnitude of the salt effect on ionization makes it impossible to fully define the mechanism merely by gathering more of the same kind of kinetic data.

Equation 5, perhaps modified by addition of a lithium cation to both sides, does adequately correlate the four data points involving solutions of $ZnCl_2$ and $LiZnCl_3$, in which the product of the concentrations $[ZnCl_2][LiZnCl_3]$ spans a 40-fold range and the two tested ratios $[ZnCl_2]/[LiZnCl_3]$ differ by a factor of 12 (Table IV and Figure 3). The values of $k/[ZnCl_2][LiZnCl_3]$ vary only from 2.25 to 2.91×10^{-4}. This is constant within experimental error, kinetic plots in the more concentrated range of these compositions being particularly prone to curvature.

The minimum in the epimerization rates at the composition $LiZnCl_3$ (Figure 5) requires that $LiZnCl_3$ does not disproportionate to $ZnCl_2$ and Li_2ZnCl_4 to more than a slight extent. Anticooperative behavior of anions complexing with metal cations is generally observed whenever the coordination number of the cation is unchanged on substitution of an anion for a solvent molecule.[14] It would not be surprising if the coordination number of zinc ion in THF is constant at 4, and the stability of $LiZnCl_3$ is therefore expected.

In the region of composition corresponding to mixtures of Li_2ZnCl_4 and $LiZnCl_3$, the observed k's are surprisingly close to a simple first-order function of the Li_2ZnCl_4 concentration, with slightly higher k's at higher salt concentrations and slightly lower k's in solutions containing $LiZnCl_3$ nTable IV, Figures 4 and 5). For eight data points, the function $10^5k/[Li_2ZnCl_4] = 6.6 \pm 1.7$ (26%e, with its entire range being from 4.7 (with 0.082 M Li_2ZnCl_4 + 0.087 M $LiZnCl_3$) to 9.3 (with 1.2 M Li_2ZnCl_4). The lack of effect of the $LiZnCl_3$ is shown by comparison of the data for 0.606 M Li_2ZnCl_4 alone and 0.591 M Li_2ZnCl_4 + 0.514 M $LiZnCl_3$, where the values of $10^5k/[Li_2ZnCl_4]$ are 8.4 and 7.6, respectively.

Several mechanisms can account for the observed rate law, especially when the adjustable parameter of the unknown salt effect on ion pair separation is taken into account. Perhaps Li_2ZnCl_4 can attack **3** directly, and to satisfy microscopic reversibility requirements, $Li_2ZnCl_3^+ + Cl^-$ can attack as well. However, in view of the behavior of lithium chloride alone, it seems more likely that free chloride ion alone is the active catalyst in Li_2ZnCl_4 solutions. The ionization of Li_2ZnCl_4 to $Li_2ZnCl_3^+$ and Cl^- would yield half-order dependence of k on Li_2ZnCl_4, which might look like first-order dependence if the salt effect is large enough. Alternatively, the salt effect might be written into the ionization equilibria, as in eq 6 and 7. In

$$2Li_2ZnCl_4 \rightleftharpoons LiZnCl_4^- + Li_3ZnCl_4^+ \qquad (6)$$

$$LiZnCl_4^- \rightleftharpoons LiZnCl_3 + Cl^- \qquad (7)$$

order to reconcile eq 6 and 7 with the available data, k for eq 6 must be small (smaller than for $Li_2Cl_2 = Li_2Cl^+ + Cl^-$) and k for eq 7 must be somewhat greater than unity. Alternatively, the exchange process represented by adding **3** to both sides of eq 7 could be a major term in the rate law. In summary, it may be concluded that there are more than enough reasonable explanations to account for the experimental observations.

Implications for Synthesis. For synthetic purposes, the minimum possible rate of epimerization of **3**, preferably together with the maximum rate of formation of **3** from **2**, is desired. The latter has not been measured but in view of the improved yields in the presence of zinc chloride[4] presumably increases with increasing zinc chloride concentration. The effect on the epimerization rate from adding increments of zinc chloride to fixed concentrations of lithium chloride as interpolated from the available data is illustrated graphically in Figure 5. The optimally low epimerization rate is clearly achieved at the composition $LiZnCl_3$. Unfortunately, the drift in the rotation away from the expected infinity value and the observation of 10–15% impurity by NMR in a sample of **3** + **4** after a week of exposure to 1.08 M $LiZnCl_3$, as well as discouraging results when a full equivalent of zinc chloride was added in synthetic operations,[4] implies that side reactions occur under these conditions. Extrapolation from the $ZnCl_2/LiZnCl_3$ data suggests an abrupt rise in the epimerization rate if solutions made erroneously to contain a slight excess of free $ZnCl_2$ are concentrated (see Figure 5). Fortunately, the dependence of the epimerization rate on the ratio of Li_2ZnCl_4 to $LiZnCl_3$ is not very steep, and much of the range of composition between these stoichiometries may be usable for synthetic purposes.

Acknowledgment. We thank the National Science Foundation for support, Grant No. CHE-8025229, and the Boeing Corp. for a gift in support of purchase of the 200-MHz NMR instrument. E.E. thanks NATO for a fellowship.

Registry No. **3**, 76110-79-7; **4**, 85922-61-8; $CH_2{=}CHCHClBO_2C_{10}H_{16}$, 85893-32-9; $PhCH_2CHClBO_2C_{10}H_{16}$, 78902-03-1; $CH_3(CH_2)_3CHClBO_2C_{10}H_{16}$, 85167-13-1; LiCl, 7447-41-8; $ZnCl_2$, 7646-85-7.

---

[14] King, E. L. *Inorg. Chem.* **1981**, *20*, 2350–2352.