J. Am. Chem. Soc. **1982**, *104*, 522–525

Preliminary Studies of the Mechanism of Metal–Halogen Exchange. The Kinetics of Reaction of *n*-Butyllithium with Substituted Bromobenzenes in Hexane Solution

Harold R. Rogers* and Janette Houk[1]

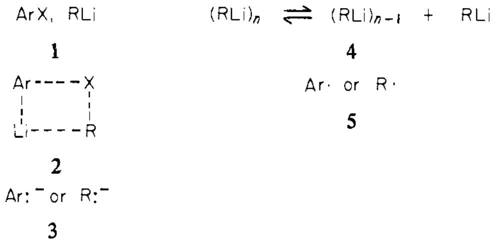
Contribution from the Department of Chemistry, California State University, Fullerton, Fullerton, California 92634. *Received March 3, 1981*

Abstract: Initial measurements of the rate of reaction of bromobenzene with *n*-butyllithium in hexane solution have shown the exchange to be first order in bromobenzene and first order in *n*-butyllithium, with an activation energy of 12 kcal mol^{-1} (52 kJ mol^{-1}). A Hammett relationship for the reaction of substituted bromobenzenes with *n*-butyllithium suggests negative charge character in the transition state ($\rho \simeq 2$). The addition of a Lewis donor (*p*-methylanisole) to the hexane solution was found to result in an increase in the rate of exchange, but did not affect the Hammett reaction constant. Several transition-state structures are considered; available evidence suggests that the exchange may be concerted, with either a four-centered structure, or S$_N$2-type attack of the *n*-butyl anion at the bromine of the aryl bromide.

The exchange of a halogen atom for a metal atom is one of the more widely applicable synthetic methods for the preparation of, in particular, aromatic lithium reagents (eq 1);[2] very little, however, is known about the mechanism of this reaction. The aromatic halide is often an intermediate in a complex synthetic scheme and not necessarily readily available. It would be of great value, therefore, to know how the position of the equilibrium described by eq 1 might be affected by changing various reaction parameters, including the structure of the alkyllithium component, solution dielectric strength, and temperature. It would also be of value to answer basic questions concerning the mechanism of the metal–halogen exchange: What is the rate-determining step? What are the steric and electronic constraints on the reaction? Which of the halogens is/are best suited for the reaction?

$$\mathrm{ArBr + RLi \rightleftharpoons ArLi + RBr} \qquad (1)$$

We have studied the kinetics of the reaction of substituted bromobenzenes with *n*-butyllithium (*n*-BuLi) in an effort to answer the first of these three questions. The nature of the rate-limiting transition state might be described by one of several structures; initially we shall consider five of the more plausible limiting transition states, summarized by structures **1–5**: **1**, the unperturbed starting materials would represent the transition state if the exchange were diffusion controlled; **2**, bond-breaking and bond-forming processes may be concerted in the rate-limiting step; **3**, the rate-limiting transition state may involve a partially- or fully-formed carbanion derived from either the aryl halide in a substitution process such as nucleophilic attack by R:$^-$ at bromine[3] (eq 2a) or the alkyllithium reagent by dissociation into a solvent-separated or intimate ion pair (eq 2b); **4**, the dissociation



$$\mathrm{Ar{-}Br + R{-}Li \rightleftharpoons Ar{:}^{-}Li^{+} + R{-}Br} \qquad (2a)$$

$$\mathrm{R{-}Li \rightleftharpoons R{:}^{-}Li^{+}} \qquad (2b)$$

of monomeric alkyllithium reagent in the solution from the normally aggregated form may be rate limiting; and **5**, the transition state may resemble a carbon-based free radical if the rate-determining step involves homolytic bond scission.

Results and Discussion

The rate of reaction can be expressed as shown by eq 3. By

$$\text{rate} = -\mathrm{d}[\mathrm{ArBr}]/\mathrm{d}t = k[\mathrm{ArBr}]^1[\mathrm{RLi}]^1 \qquad (3)$$

following the disappearance of bromobenzene (initial concentration, 0.57 M) in 2.4 M *n*-butyllithium as a function of time, we have found the exchange to be first order in aryl bromide: Plots of ln [ArBr] vs. time were linear to >80% consumption of halide (Figure 1) and a plot of ln *k* vs. ln *C* was found to be linear with a unit slope. Hence, structure **4**, which would require a zero-order dependence on aryl halide, can be eliminated as a description of the rate-limiting step. In another series of experiments, the initial concentration of bromobenzene was fixed at 0.57 M, and its rate of disappearance was followed as the initial concentration of lithium reagent was varied. A plot of ln *k* vs. ln [$(n\text{-BuLi})_6$] yields[4] a linear relationship with a unit slope (Figure 2). Thus the exchange reaction is first order in *n*-butyllithium, a result which suggests reaction with bromobenzene occurs through the *n*-butyllithium hexamer, and also precludes **4** as representative of the rate-limiting step: A rapid preequilibrium would result in a fractional order in *n*-BuLi, with the most likely value of $^1/_6$.[5]

The pseudo-first-order rate constant, *k*, for the disappearance of bromobenzene under the given conditions (see Experimental Section for details) was found to be 0.010 ± 0.002 min^{-1}, which agrees qualitatively with the results of Trepka.[6] The rate of disappearance of bromobenzene was found to be insensitive to small added quantities of phenyllithium (5 mmol as a solid) or *n*-butyl bromide (20 mM), and insensitive to small quantities of lithium bromide (5 mmol as a solid), or lithium butoxide (20 mM). The sensitivity of the exchange to temperature changes is summarized in Figures 1 and 3. The activation energy is estimated from the slope of the Arrhenius plot (Figure 3) to be 12 kcal mol^{-1} (52 kJ mol^{-1}).

Electronic effects on the rate of exchange were studied using appropriately substituted bromobenzenes. The rates of exchange relative to that of bromobenzene are presented in Table I, along

---

[1] National Science Foundation URP Fellow, Summer 1980.

[2] Gilman, H.; Jones, R. G. "Organic Reactions"; Wiley: New York, 1951; Vol. VI, Chapter 7. Prakham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 2407 and references cited therein.

[3] Wittig. G.; Schollkopf, V. *Tetrahedron* **1958**, *3*, 91.

[4] *n*-Butyllithium has been shown to exist as a hexamer in hydrocarbon solvents: Margerison, D.; Newport, J. P. *Trans. Faraday Soc.* **1963**, *59*, 2058.

[5] Evans, A. G.; George, D. B. *J. Chem. Soc.* **1961**, 4653; **1962**, 141.

[6] Trepka has found the time required for the complete reaction of equimolar (0.17 M) quantities of bromobenzene with *n*-BuLi (toluene, sealed tube, 50 °C) to be 300 min.: Trepka, W. J.; Sonnenfeld, R. J. *J. Organomet. Chem.* **1969**, *16*–2, 317.

0002-7863/82/1504-0522$01.25/0

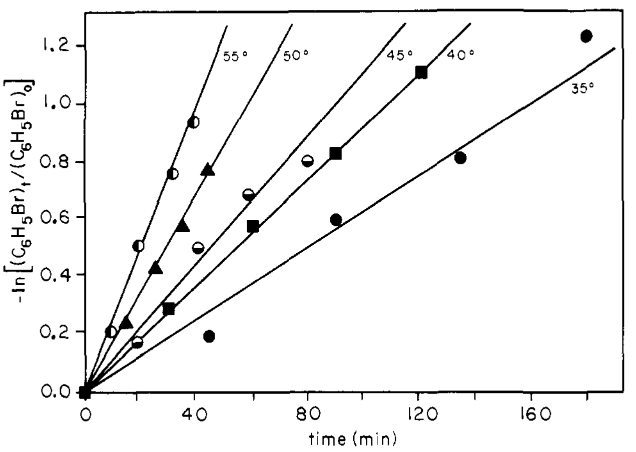


Figure 1. First-order plots for the disappearance of bromobenzene in 2.4 M n-BuLi at various temperatures.

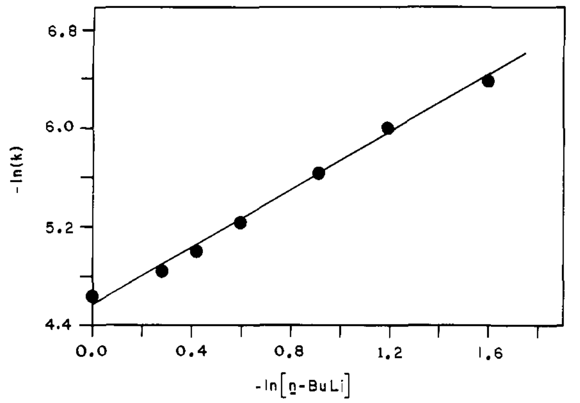


Figure 2. Plot of ln k for the disappearance of bromobenzene vs. ln $[(n\text{-BuLi})_6]$. The order of the exchange with respect to n-BuLi is determined from the slope to be first order. Data were collected in hexane solution at 40 °C.

Table I. Relative Rates (k_R/k_H) for the Reaction of Bromobenzenes (RC_6H_4Br) with n-Butyllithium[a]

R	k_R/k_H		σ_R[b]
	n-BuLi	n-BuLi + p-MeC_6H_4OMe	
4-OCH_3	12 (0.91)[c]	0.91[d]	−0.27
4-CH_3	0.74	0.59	−0.17
3-CH_3	0.91	0.73	−0.07
H	1	1	0.00
4-F	3.6	2.8	0.06
3-OCH_3	41 (3.1)[c]	3.1[d]	0.12
4-Cl	1.8	4.2	0.23
4-Br	4.0[e] (2)[f]	4.0[e]	0.23
3-F	9.4		0.34
3-Cl	5.3	5.8	0.37
3-Br	13[e] (10)[f]	10.7	0.39

[a] All kinetics reactions were carried out at least in duplicate at 40 °C, using conditions described in the text. [b] J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, 1963, p 173. [c] Corrected for the donor effects of oxygen. See text for a discussion of this point. [d] No p-methylanisole added. [e] Statistically corrected for the presence of two identical carbon–bromine bonds by dividing the observed rate constant by two.[7,8] [f] Reference 6.

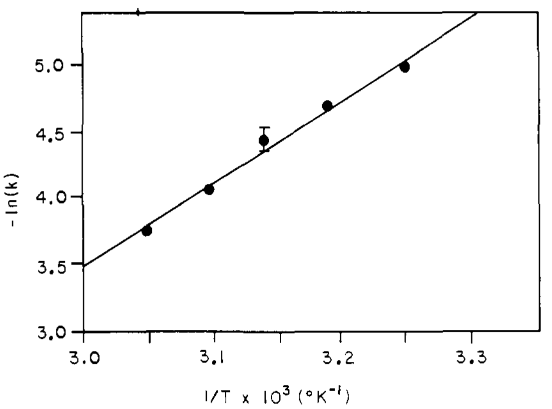


Figure 3. Arrhenius plot for the reaction of bromobenzene with n-BuLi. The activation energy is estimated from the slope to be 12 kcal mol^{-1} (52 kJ mol^{-1}). Typical reproducibility is indicated by the error bar.

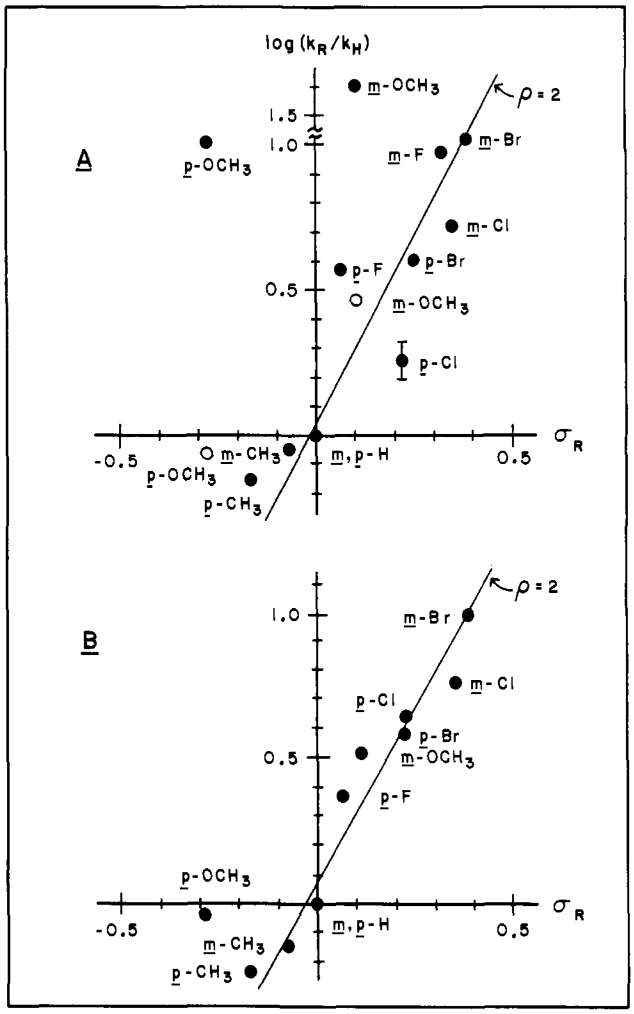


Figure 4. (A) Hammett plot for the reaction of substituted bromobenzenes with n-BuLi in hexane at 40 °C (●). The open circles (○) denote corrected values (see text for a discussion of this point). (B) Hammett plot for the reaction of substituted bromobenzenes (0.57 M) with n-BuLi in hexane containing p-methylanisole (0.57 M) at 40 °C. The points for m- and p-bromoanisole were determined *without* added p-methylanisole. Reproducibility is indicated by the error bar and is approximately the same for each point.

with Hammett σ parameters. Also included in Table I are the relative rates of exchange in the presence of 0.57 M p-methylanisole (vide infra). A Hammett plot is shown in Figure 4A for the reaction of substituted bromobenzenes with n-BuLi in hexane at 40 °C. An approximate reaction constant, $\rho \simeq 2$, may be

---

(7) We have found that the statistical correction to rate constants for the reaction of multiply-substituted compounds depends upon the proximity of the reaction to diffusion limitation, at which point statistical corrections are leveled to unity: Rogers, H. R.; Swenson, L. D., manuscript in preparation.

(8) Rogers, H. R.; Deutch, J. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 226 and references therein.

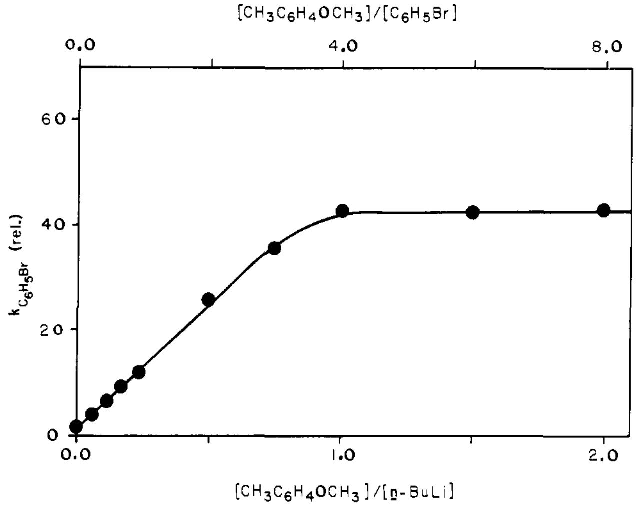


Figure 5. Relative rates of reaction of bromobenzene with *n*-BuLi in hexane containing an increasing quantity of *p*-methylanisole.

obtained; despite the scatter[9] observed in the plot, the data suggest significant negative charge buildup in the aryl group in the transition state. Some early work derived a Hammett relationship from the equilibration of substituted *aryl*lithium reagents with substituted bromobenzenes;[10] this work also suggested a positive ρ. Trepka and co-workers found that *m*- and *p*-bromo-substituted bromobenzenes were consumed at a faster rate than unsubstituted bromobenzene when allowed to react with *n*-BuLi in hexane.[6] However, although these data are consistent with a positive ρ, these authors did not clarify whether or not the rate acceleration observed was due solely to electronic effects: These two compounds have twice the number of carbon–bromine bonds as bromobenzene, which would statistically cause an observed increase in rate if the reaction were not diffusion controlled.[7,8] Since our evidence suggests that the exchange is not diffusion limited (this point is discussed later in the text), we used statistically-corrected rates in the present study.

The data for the methoxy-substituted bromobenzenes do not fit the Hammett plot shown in Figure 4A; their abnormally fast exchange rate suggests that either these compounds have an additional pathway for their disappearance (e.g., C–O bond cleavage by *n*-butyllithium),[11] or the equilibrium described by eq 1 is shifted to favor products by the donor properties of the methoxy oxygen atom, which would be expected to behave as a good donor in the hexane solvent.[12] We have tested the former possibility by adding anisole to *n*-BuLi under conditions identical with those of the kinetics runs; no change in the concentration of anisole was observed during the course of several hours (the bromoanisoles were completely consumed in ca. 10 min).

When bromobenzene containing an equivalent amount of *p*-methylanisole was allowed to react with *n*-BuLi in hexane at 40 °C, a rate enhancement of 12-fold was observed. If the relative rates of reaction of *m*- and *p*-bromoanisole are adjusted to account for this rate acceleration caused by 1 equiv of oxygen–donor functionality, the estimated rates of exchange for these two compounds are more consistent with the Hammett relationship $\rho \simeq 2$ (see open circles on Figure 4A). A Hammett plot constructed from the relative rates of exchange at 40 °C in hexane with ArBr:*p*-methylanisole = 1:1 (Table I) is shown in Figure 4B. The reaction constant obtained from this plot, $\rho \simeq 2$, is the same as the reaction constant obtained without the *p*-methylanisole donor in the system. This suggests that although the rates of exchange are uniformly increased in the presence of the donor, the electronic effects with respect to the aryl group remain essentially constant.

The extent to which added *p*-methylanisole affected the rate of exchange of bromobenzene with *n*-BuLi was studied, and the results are summarized in Figure 5. The rate of disappearance of bromobenzene was found to increase in a linear fashion with low concentrations of *p*-methylanisole, reaching a plateau at a molar ratio of *p*-methylanisole:*n*-BuLi = 1:1. This result is consistent with the proposal that the exchange, in the absence of a good donor, takes place through the *n*-BuLi hexamer (vide supra); with *p*-methylanisole present, the *n*-BuLi hexamer is disrupted, and a new, more reactive species that is monomeric in lithium reagent is formed. The exchange in the presence of the donor then occurs through an *n*-BuLi-donor adduct.

It is possible to interpret the data of this study to exclude several of the remaining plausible transition-state structures (**1–3**, **5**). The reaction of bromobenzene with *n*-BuLi in hexane is clearly not diffusion controlled (**1**): The activation energies for diffusion-controlled processes lie in the 2–5 kcal mol^{-1} range;[8] a nonzero value for ρ is also inconsistent with a transport-limited process.[13] Several considerations suggest qualitatively that the transition state probably does not resemble a free radical (**5**): First, the magnitude of ρ seems larger than those for reactions which generate an aryl radical.[13] Second, no correlation is apparent from a plot of the relative rates of exchange vs. the relative rates of photochemical reduction by tri-*n*-butyltin hydride. This latter reaction is known to generate aryl radicals.[13] Third, when an exchange reaction was conducted in a sealed NMR tube and the 60-MHz spectrum recorded at several times during the reaction, no CIDNP signals were observed. Fourth, none of the bromobenzenes gave >5% coupling products with either the *n*-BuLi (which would yield *n*-BuAr) or with themselves (which would give the biaryls, Ar–Ar).[14] Hence, **5** is probably not representative of the transition state.

It is difficult to exclude carbanionic structures (**3**) without knowing an accurate magnitude for ρ. However, the magnitude of ρ is considerably smaller than that estimated for reactions generating aryl anions.[13] Thus, a concerted transition state seems more likely: Either a four-centered structure (**2**) or S_N2-type structure (eq 2a) could involve negative charge buildup in the aryl group to the extent observed; it is possible, for example, that alkyl carbon–bromine bond formation is slightly ahead of aryl carbon–bromine bond breaking.

One attempt to differentiate a four-centered transition state from an S_N2 transition state involved following the exchange in

---

[9] Data for the reaction of *n*-BuLi with *m*- and *p*-bromobenzo trifluoride were not included. These compounds react with *n*-BuLi in several different ways in addition to metal–halogen exchange, complicating the interpretation of the results with respect to this study: Roberts, J. D.: Curtin, D. Y. *J. Am. Chem. Soc.* **1946**, *68*, 1658. Fuller, G. *Manuf. Chem. Aerosol News* **1964**, *35*, 43. The scatter observed in the data for the compounds that were used might be attributed to an equilibrium between $(n\text{-BuLi})_6$ and the aryl halide prior to the exchange:

$$\mathrm{ArBr} + (n\text{-BuLi})_6 \overset{K_{eq}}{\rightleftharpoons} \mathrm{ArBr}\cdot(n\text{-BuLi})_6 \qquad \text{fast}$$

$$\mathrm{ArBr}\cdot(n\text{-BuLi})_6 \xrightarrow{k} \mathrm{ArLi} + n\text{-BuBr} \qquad \text{slow}$$

This scheme would yield a first-order dependence of rate upon [ArBr] and $[(n\text{-BuLi})_6]$ as well as a dependence upon the equilibrium constant K_{eq}, which would vary as the donor properties of the aryl group varied: In the absence of a good Lewis donor, the aryl halide, which would be the best donor in the system, may not be a sufficiently strong Lewis base to disrupt the *n*-BuLi hexamer. If a strong Lewis donor is added, the prior equilibrium is not involved, and reaction proceeds through a species that is monomeric in lithium reagent:

$$\mathrm{ArBr} + n\text{-BuLi}\cdot\text{donor} \rightarrow \mathrm{ArLi} + n\text{-BuBr} + \text{donor}$$

Indeed, the Hammett plot for such a system, shown in Figure 4B, does not show the scatter of Figure 4A. See text for further discussion of the exchange in the presence of a Lewis donor.

[10] Winkler, H. J. S.; Winkler, H. *J. Am. Chem. Soc.* **1966**, *88*, 964.

[11] Coates, G. E.; Green, M. L. H.; Wade, K. "Organometallic Compounds"; Methuen: London, England, 1969; Vol. 1, Chapter 1.

[12] A similar argument has been used recently to explain regioselectivity during metal–halogen exchange: Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1981**, *46*, 1384.

[13] Rogers, H. R.; Rogers, R. J.; Mitchell, H. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 231 and references therein.

[14] Large amounts (>25%) of coupling products were observed occasionally; these have been traced to the influence of iron from an exposed portion of a Teflon-covered magnetic stirring bar used in the reaction.

hexane using *p*-bromo-*tert*-butoxybenzene and *n*-BuLi. It was hoped that the bulky *tert*-butyl group would hinder coordination of the *n*-BuLi hexamer to the aryl oxygen and thus show a reduced rate of exchange; however, this compound was found to undergo exclusively base-induced elimination to give isobutene and *p*-bromophenol. Further studies in progress in this laboratory are directed toward establishing the possibly concerted (or nearly synchronous) nature of the transition state for metal–halogen exchange by examining solvent effects and steric effects with respect to the alkyllithium component.

Experimental Section

General. Aryl halides, anisole, and *p*-methylanisole (Aldrich) and *n*-butyllithium (2.4 M in hexane, Alfa-Ventron) were used as received; *n*-hexane was distilled under argon from sodium/benzophenone. Unless otherwise indicated, kinetics runs were conducted at 40 °C under argon using either syringe and cannula techniques[15] or a Vacuum-Atmospheres Dri-Lab glove box. GLC was peformed on either a 15% SE-30/Chromosorb W, $^1/_8$-in. by 3-m stainless steel column, or a 20% Carbowax 20M/Chromosorb W-AW, $^1/_8$-in. by 1.3-m stainless steel column using a Hewlett-Packard Model 810 gas chromatograph fitted with flame detectors with output to a Hewlett-Packard Model 3380S electronic integrator/plotter. NMR spectra were recorded at 60 MHz on a Varian Model EM-360 nuclear magnetic resonance spectrometer. Concentrations of *n*-BuLi in hexane were determined by the Gilman double titration procedure;[16] the concentration of the stock *n*-BuLi solution, stored at −30 °C, was checked periodically.

Kinetic Runs. Typical Procedure. A flame-dried 25-mL round-bottomed flask, equipped with a Teflon-covered magnetic stirring bar, was charged with *n*-BuLi (2.4 M in hexane, 10 mL) and *n*-decane (internal standard, 0.6 mL) while under an argon atmosphere. The system was equilibrated to 40 °C in a thermostated oil bath. With rapid stirring, the run was initiated with the addition of aryl bromide (5.7 mmol). An ca. 0.5-mL aliquot was immediately removed (time = 0); additional aliquots were removed at intervals ranging from 20 min for the slower bromides to ca. 15 s for the faster compounds. The aliquots were quenched with ice or 1,2-dibromoethane, and the organic phase was analyzed by GLC. The disappearance of aryl bromide was followed relative to the internal standard. Observed rate constants were determined by plotting ln [ArBr] vs. time and obtaining the least-squares slope.

***p*-Bromo-*tert*-butoxybenzene**, prepared in 75% yield from *p*-bromophenylmagnesium bromide[17] and *tert*-butyl peroxybenzoate following the procedure of Frisell and Lawesson[18] had bp 53–54 °C (0.04 torr) (lit.[19] bp 63–65 °C (0.4 torr)). ^{1}H NMR (CDCl$_3$, internal tetramethylsilane reference): δ 1.34 (s, 9 H), 6.97 (d of d, 4 H).

Acknowledgment. This work is supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation through Grants SCP-79-24320 and SPI-79-26855, and the Departmental Associations Council at CSUF through a grant to one of us (J.H.).

Registry No. 4-$CH_3OC_6H_4Br$, 104-92-7; 4-$CH_3C_6H_4Br$, 106-38-7; 3-$CH_3C_6H_4Br$, 591-17-3; C_6H_5Br, 108-86-1; 4-FC_6H_4Br, 460-00-4; 3-$CH_3OC_6H_4Br$, 2398-37-0; 4-ClC_6H_4Br, 106-39-8; 4-BrC_6H_4Br, 106-37-6; 3-FC_6H_4Br, 1073-06-9; 3-ClC_6H_4Br, 108-37-2; 3-BrC_6H_4Br, 108-36-1; 4-*t*-BuC_6H_4Br, 3972-65-4.

---

(15) Brown, H. C. "Organic Syntheses via Boranes"; Wiley: New York, 1975; Chapter 9.

(16) Gilman, H.; Cartledge, F. K. *J. Organomet. Chem.* **1964**, *2*, 447.

(17) Hilgetag, G.; Martini, A. "Preparative Organic Chemistry"; Wiley: New York, 1972; p 767.

(18) Frisell, C.; Lawesson, S.-O. "Organic Syntheses", Baumgarten, H. E., Ed.; Wiley: New York, 1973; Collect. Vol. V, p 924.

(19) Lawesson, S.-O.; Frisell, C. *Ark. Kemi* **1961**, *17*, 393.

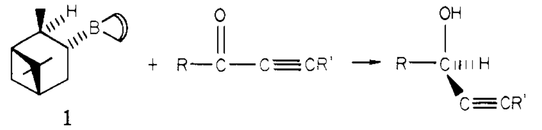
Kinetics of Reductions of Substituted Benzaldehydes with *B*-Alkyl-9-borabicyclo[3.3.1]nonane (9-BBN)

M. Mark Midland*[1] and Stephen A. Zderic

Contribution from the Department of Chemistry, University of California, Riverside, California 92521. *Received June 12, 1981*

Abstract: Second-order rate constants for the reaction of *B*-*n*-octyl-9-BBN with para-substituted benzaldehydes were obtained. Electron-withdrawing groups on the benzaldehyde increase the rate of reduction. The rate constants correlate with σ^+ (ρ +1.03). Relative rates for reduction of para-substituted benzaldehydes with *B*-3-pinanyl-9-BBN gave a ρ of +0.49. The relative rates are consistent with a hydride addition to the carbonyl carbon in the rate-determining step. Activation parameters were obtained for the reaction of three benzaldehydes with *B*-*n*-octyl-9-BBN. The major barrier to the reaction is entropy. The large negative entropies of activation (−43 to −49 eu) indicate a highly ordered transition state. It is postulated that an organoborane–carbonyl oxygen complex is an intermediate in the reduction.

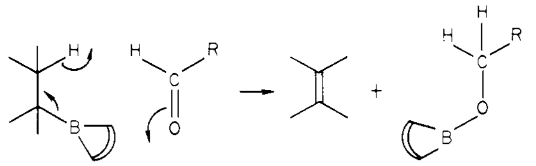
The trialkylborane *B*-3-pinanyl-9-BBN (**1**), readily prepared by hydroboration of α-pinene with 9-BBN, is a highly effective asymmetric reducing agent for aldehydes[2] and alkynyl ketones (eq 1).[3] Enantiomeric purities of nearly 100% may be obtained.



1

(1)

Likewise, *B*-3-methyl-2-butyl-9-BBN is a highly chemoselective reducing agent which is able to reduce aldehydes in the presence of unhindered ketones.[4] It has been proposed that these reactions generally proceed by a cyclic mechanism reminiscent of the Meerwein–Ponndorf–Verley (MPV) reaction (eq 2).[5,6]



(2)

---

[1] (1) Alfred P. Sloan Foundation Fellow, 1978–1982.

(2) (a) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 5211. (b) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *Ibid.* **1979**, *101*, 2352.

(3) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A.; *J. Am. Chem. Soc.* **1980**, *102*, 867.

(4) Midland, M. M.; Tramontano, A. *J. Org. Chem.* **1978**, *43*, 1470.

(5) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Organomet. Chem.* **1978**, *156*, 203.