J. Org. Chem. 1984, *49*, 2608–2613

(1*RS*,4*SR*,5*RS*)-4-(5-Hydroxy-4,8-dimethyl-7-nonen-1-yl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetic Acid Hemihydrate (3). $NaOH-H_2O$ (2 N, 2.0 mL) was added to **42** (79 mg, 0.19 mM) in methanol (2.0 mL) while stirring under nitrogen at 2 °C. After 10 min of stirring, it was allowed to come to room temperature and stirred under nitrogen for 72 h. The methanol was evaporated in vacuo at room temperature and the residue was extracted with Et_2O. The aqueous basic solution was cooled with ice water, stirred, acidified with 6 N $HCl-H_2O$, and extracted with Et_2O. It was washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to give the bicyclic hydroxy acid **3** (70 mg, 91%): IR (neat) 3500–3300, 2500–2300 (OH), 1720 (CO), 1090, 1050, 1010 cm^{-1} (ether bonds); NMR ($CDCl_3$) 5.43 (br m, 2 H, -OH and $-CO_2H$), 5.12 (t, 1 H, C=CH), 3.90 (m, 1 H, H-C), 3.58 (q, $J = 11$ Hz, 2 H, $-C_2-CH_2$), 3.33 (m, 1 H, $-CHOH$), 2.65 (br s, $-CH_2CO_2H$), 1.75 and 1.67 (2 × br s, 2 × 3 H, vinyl methyls), 1.35 (s, 3 H, C_4-CH_3), 0.92 (d, $J = 7$ Hz, 3 H, $-CHCH_3$); GC/MS of bis Me_3Si derivative, M^+ 498. Anal. Calcd for $C_{20}H_{34}O_5\cdot{}^1/_2H_2O$: C, 66.08; H, 9.74. Found: C, 65.81; H, 9.29.

(1*RS*,4*SR*,5*RS*)-4-(5-Hydroxy-4,8-dimethyl-8-nonen-1-yl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-acetic Acid Monohydrate (43). $NaOH-H_2O$ (2 N, 5.0 mL) was added to **41** (1.06 g, 2.5 mM) in methanol (5.0 mL) while stirring at 0 °C under nitrogen. The cooling bath was removed after 15 min and the reaction mixture was stirred at room temperature for 3 days. The methanol was evaporated in vacuo at room temperature and the residue was extracted with Et_2O. The aqueous basic solution was cooled with ice water, stirred, acidified with 6 N $HCl-H_2O$, and extracted with Et_2O. This extract was washed with saturated brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to give 608 mg (69%) of crude acid **43** which was purified by column chromatography on SilicAR CC-7 to give the pure acid **43** (305 mg): IR ($CHCl_3$) 3000, 2800–2500 (sh), 1750, 1720, 1650, 730 cm^{-1}; NMR ($CDCl_3$) 6.10 (m, 2 H, CO_2H, and HO), 4.70 (m, 2 H, $C=CH_2$), 3.86–3.31 (m, 4 H, -CH(OH)-, C_2-CH_2, C_5-H), 2.63 (m, 2 H, CH_2CO_2H), 1.71 (br s, 3 H, $CH_3C=C$), 1.30 (s, 3 H, C_4-CH_3), 0.88 (d, $J = 6$ Hz, 3 H, $-CHCH_3$); MS (CI), bis Me_3Si derivative. $M^+ + 1 = 493$, $M^+ - 1 = 491$, $M - Me_3SiO = 409$ (base peak). Anal. Calcd for $C_{20}H_{34}O_5\cdot H_2O$: C, 64.49; H, 9.74. Found: C, 64.00; H, 9.28.

Acknowledgment. We thank Dr. A. Fabian and Mr. E. Deegan for the large-scale preparation of some of the intermediates, Dr. M. L. Cotter for spectroscopic results, and Mr. C. Shaw for GC/MS data. We also thank Dr. S. D. Levine and Prof. J. A. Marshall for many helpful discussions.

Registry No. **3**, 67441-54-7; (*E*)-**4**, 106-24-1; **5**, 15580-05-9; (±)-(*E*)-**6**, 90460-03-0; (±)-(*Z*)-**6**, 90460-04-1; **7**, 77878-45-6; **8**, 77878-47-8; (*E*)-**9**, 79756-30-2; (±)-**10**, 79756-34-6; **12**, 38237-34-2; (±)-**13**, 90432-82-9; (±)-**13** (benzyl ether), 90432-92-1; (±)-14, 90432-83-0; (±)-(*E*)-**15**, 90432-84-1; (±)-(*Z*)-**15**, 90432-85-2; (±)-(*E*)-**16**, 90460-05-2; (±)-(*Z*)-**16**, 90460-06-3; (±)-(*Z*)-**17**, 90432-87-4; (*E*)-**4**, 106-24-1; (±)-(*E*)-**18**, 90432-86-3; (±)-(*E*)-**19**, 90432-88-5; (±)-(*Z*)-**19**, 90432-89-6; (*E*)-**20**, 3796-70-1; (*E*)-**21**, 79756-27-7; (*E*)-**22**, 79756-28-8; (±)-(*E*)-**23**, 90432-90-9; (*E*)-**24**, 79772-32-0; (*E*)-**25**, 77878-39-8; **26**, 77878-41-2; **27**, 77878-43-4; **28**, 77878-62-7; **29**, 79756-31-3; **30**, 90528-01-1; (±)-**31**, 79756-33-5; (±)-**32**, 77878-46-7; **33**, 20038-12-4; (±)-**34**, 90432-91-0; **36a**, 79756-36-8; (±)-**37**, 90528-02-2; **38**, 77878-48-9; **39**, 77878-49-0; 41, 77878-50-3; **42**, 77878-51-4; **43**, 79756-39-1; $H_2C=C(CH_3)CH_2CH_2COCH(CH_3)CO_2Et$, 18034-04-3; $Ph_3P=CHCO_2Et$, 1099-45-2; ethyl acetoacetate, 141-97-9.

Kinetics and Mechanism of the Reaction of Ketones with Lithium Reagents in Cyclohexane

Munther A. Al-Aseer and Stanley G. Smith*

Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

Received October 27, 1983

The kinetics of the reaction of *sec*-BuLi and *n*-BuLi with several substituted phenyl *sec*-butyl ketones in cyclohexane at 25.0 °C have been examined by stopped-flow infrared spectroscopy. Experiments in which reacting solutions of the ketones were scanned over the carbonyl region of the infrared spectrum revealed the presence of an intermediate which was characterized as a reversibly formed complex between ketone and alkyllithium aggregate. The rates of disappearance of the ketones in the presence of excess alkyllithium exhibited complex dependence on reagent concentration. Further, the dependence of the pseudo-first-order rate constant on lithium reagent concentration varied with each compound. These results are accommodated by a mechanism in which product is formed by rearrangement of the ketone–alkyllithium aggregate complex and by reaction of uncomplexed ketone with alkyllithium monomer.

The addition of alkyllithium reagents to ketones is a widely used reaction in organic synthesis. In contrast to the corresponding Grignard reagent reactions with ketones which give high ratios of reduction to addition products, the use of alkyllithiums leads to the predominant formation of the addition product.[1]

The mechanism of this reaction has been the subject of several reports by Smith and co-workers. For example, the reactions of methyllithium with 2,4-dimethyl-4′-(methylthio)benzophenone[2a] and 4-(methylthio)acetophenone[2b] in ether was found to be $^1/_4$ order with respect to methyllithium which supports a dissociative mechanism in which the tetrameric methyllithium is in rapid equilibrium with a small concentration of monomer which is

---

[1] Hurt, F.; Emptoz, G. *J. Organometal. Chem.* **1975**, *101*, 139. Young, W. G.; Roberts, J. D. *J. Am. Chem. Soc.* **1944**, *66*, 1444. Barlett, P. D.; Lefferts, E. B. *Ibid.* **1955**, *77*, 2804. Whitmore, F. C.; George, R. S. *Ibid.* **1942**, *64*, 1239. Tomboulian, P.; Stehower, K. *J. Org. Chem.* **1968**, *33*, 1509.

[2] (a) Smith, S. G.; Charbonneau, L. F.; Novak, D. P.; Brown, T. L. *J. Am. Chem. Soc.* **1972**, *94*, 7059. (b) Allison, B. D. Ph.D. Thesis, 1978, University of Illinois, Urbana, IL. (c) Ultraviolet spectroscopic evidence was reported recently for the formation of a ketone-lithium reagent complex in the reaction of di-*tert*-butyl ketone with trimethyl-3,5,7-adamantyl-1-lithium in pentane: Lozach, D.; Molle, G.; Bauer, P.; Dubois, J. E. *Tetrahedron Letters* **1984**, *24*, 4213.

0022-3263/84/1949-2608$01.50/0

the reactive species (Scheme I).

Scheme I

$$^1/_4\mathrm{Me_4Li_4} \rightleftharpoons \mathrm{MeLi}$$

$$\mathrm{MeLi} + \text{ketone} \rightarrow \text{product}$$

$$k_{\text{obsd}} = [\mathrm{Me_4Li_4}]kK$$

Scheme I has been postulated for several lithium reagent reactions in ethereal solvents including the addition of *n*-butyllithium to benzonitrile[3] and the initiation of vinyl polymerization.[4]

Monomeric alkyllithium appears to be the predominant reactive species in many lithium reagent reactions in aromatic solvents. These include the addition of butyllithiums to 1,1-diphenylethylene,[5] styrene,[6] and fluorene[7] in benzene and initiation of polymerization of 2,3-dimethyl-1,3-butadiene by *sec*-butyllithium and *tert*-butyllithium[8] in benzene. However, reaction through aggregates has been reported for some reactions in aromatic solvents such as the coupling reaction of ethyllithium and benzyl chloride[9] and the alkylation of naphthalene with *tert*-butyllithium.[10] Hsieh reported[11] that the order in alkyllithium for the reaction of *n*-butyllithium with butadiene in toluene varied from $^1/_3$ to 1 over the concentration range employed. Charbonneau and Smith[12] have examined the kinetics of the reaction of *n*-butyllithium with 4-(methylthio)acetophenone in benzene. The continuous-flow UV spectrum of the reacting solution showed a broadening of the π–π^* absorption of the ketone and a bathochromic shift in its λ_{max} suggesting the formation of a ketone–*n*-butyllithium complex. The kinetic data were consistent with two mechanisms: reaction through monomeric butyllithium or ireaction via a ketone–lithium reagent complex (Scheme II).

Scheme II

$$n\text{-}\mathrm{Bu_6Li_6} + \text{ketone} \overset{K}{\rightleftharpoons} \text{complex}$$

$$\text{complex} \xrightarrow{k} \text{product}$$

$$k_{\text{obsd}} = \frac{kK[n\text{-}\mathrm{Bu_6Li_6}]}{1 + K[n\text{-}\mathrm{Bu_6Li_6}]}$$

Alkyllithium aggregates have been suggested as the reactive species in lithium reagent reactions occurring in saturated hydrocarbon solvents. The ethylenation of isopropyl-, *sec*-butyl, and *tert*-butyllithium is first order with respect to the alkyllithium tetramer in *n*-heptane.[13] Reaction through tetrameric alkyllithium has also been noted in the polymerization of isoprene, butadiene, and styrene.[14] Allison,[2b] in 1978, was the first to report kinetic data on the reaction of ketones with alkyllithium reagents in saturated hydrocarbon solvents. He observed a shift of −10 cm^{-1} in the carbonyl stretching frequency of cyclopentyl phenyl ketone immediately upon mixing with cyclopentyllithium in cyclohexane at 25 °C. The shift to lower wavenumber was attributed to the formation of a ketone–cyclopentyllithium complex (**2c**). The order in alkyllithium was found to vary with cyclopentyllithium concentration.

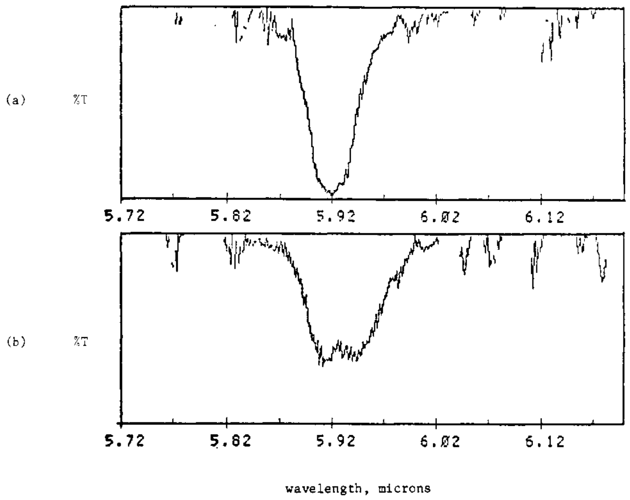


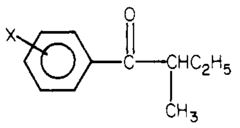
Figure 1. Plot of percent transmission vs. wavelength. (a) 9.0 × 10^{-3} M Phenyl *sec*-butyl ketone. (b) Reacting mixture of 9.0 × 10^{-3} M phenyl *sec*-butyl ketone and 1.34 × 10^{-2} M *sec*-butyllithium at 25 °C. The spectra are digitized by using 384 data points and are generated by subtracting the absorbance spectrum of the solvent, cyclohexane, from the absorbance spectrum of interest.

Table I. Infrared Carbonyl Wavenumber Shifts and Equilibrium Constants of Complexation for the Reaction of *sec*-Butyllithium with Substituted Phenyl *sec*-Butyl Ketones in Cyclohexane at 25.0 °C

substituted phenyl *sec*-butyl ketone	$\Delta\nu_{\text{CO}}$,^{a} cm^{-1}	K_c, M^{-1}
4-C_6H_5O	−13	49 ± 5
H	−11	37 ± 3
4-Cl	−11	29 ± 4
3-CF_3	−9	26 ± 3

^{a} $\Delta\nu_{\text{CO}}$ ± 2 cm^{-1}.

In this paper we report on a kinetic investigation of the reactions of *sec*-butyllithium (tetrameric) and *n*-butyllithium (hexameric) with a series of substituted phenyl *sec*-butyl ketones (**1a–h**) in cyclihexane at 25.0 °C. Reacting solutions were observed by infrared stopped-flow spectroscopic techniques. The role of alkyllithium aggregates in reaction is considered and a mechanism is proposed.



1a, X = H
b, 4-C_6H_5O
c, 4-CH_3O
d, 4-CH_3
e, 4-Cl
f, 3-F
g, 3-CF_3
h, 3,5-$(CF_3)_2$

Results

The kinetics of the reactions of (2–30 × 10^{-2} M) *sec*-BuLi with (7–9 × 10^{-3} M) substituted phenyl *sec*-butyl ketones (**1a–h**) in cyclohexane at 25.0 °C were investigated by

---

[3] Holm, T. *Acta. Chem. Scand.* **1969**, *23*, 1829; *Ibid.* **1971**, *25*, 833.

[4] Waack, R.; Doran, M. A. *J. Organometal. Chem.* **1971**, *29*, 329.

[5] Evans, A. G.; George, D. *J. Chem. Soc.* **1961**, 4653. Castling, R. A.; Evans, A. G.; Rees, N. H. *Ibid.* **1966**, 519.

[6] Bywater, W.; Worsfold, D. J. *J. Organometal. Chem.* **1967**, *10*, 1. Wosfold, D.; Bywater, S. *Can. J. Chem.* **1960**, *38*, 189.

[7] Evans, A. G.; Rees, N. H. *J. Chem. Soc.* **1963**, 6039. Evans, A. G.; Gore, C.; Rees, N. H. *Ibid.* **1965**, 5110.

[8] Mechin, R.; Kaempf, B.; Tameban, C. *Eur. Polym. J.* **1977**, *13*, 493.

[9] West, R.; Glaze, W. *J. Chem. Phys.* **1961**, *34*, 685.

[10] Eppley, R. L.; Dixon, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 1606.

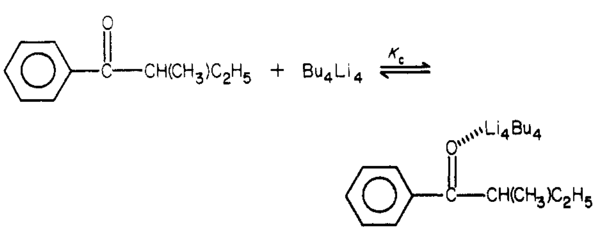
[11] Hsieh, H. L.; Glaze, W. *Rubber Chem. Technol.* **1970**, *43*, 22.

[12] Charbonneau, L. F.; Smith, S. G. *J. Org. Chem.* **1976**, *41*, 808.

[13] Bartlett, P. D. Goebel, C. V.; Weber, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 7425.

[14] Roovers, J. E.; Bywater, S. *Macromolecules* **1968**, *3*, 328. Guyot, A.; Vialle, J. *J. Macromol. Sci. Part A* **1970**, 79. Hsieh, H. L. *J. Polym. Sci. Part A-1* **1965**, *3*, 163.

infrared stopped-flow spectroscopy. Immediately after mixing, a new carbonyl band appears in the infrared spectrum of the reacting solution of ketone and alkyllithium reagent. Figure 1 presents the infrared spectrum of the carbonyl stretching region of **1a** and the continuous-flow rapid-scan spectrum of the reacting solution recorded within 3 ms after mixing. The appearance of a new band, which is shifted to lower wavenumber relative to the carbonyl band of the ketone, has been attributed to the reversible formation of a ketone–*sec*-BuLi tetramer complex (eq 1). The equilibrium constant for complex formation, K_c was deduced from initial absorbance measurements of the ketone as it was mixed with reagent solutions of various concentrations (eq 2–4). b and ϵ are



(1)

$$K_c = [\text{Ket}\cdot sec\text{-Bu}_4\text{Li}_4]/[\text{Ket}][sec\text{-Bu}_4\text{Li}_4] \qquad (2)$$

$$K_c = ([\text{Ket}]_0 - [\text{Ket}])/[\text{Ket}]([sec\text{-Bu}_4\text{Li}_4]_0 - [\text{Ket}]_0 + [\text{Ket}]) \qquad (3)$$

$$[\text{Ket}] = A_{\text{Ket}}/b\epsilon_{\text{Ket}} \qquad (4)$$

the infrared cell path length and extinction coefficient of the ketone, respectively. A_{Ket} is the absorbance of the ketone solution immediately after mixing with reagent but before any reaction has occurred. Values of K_c and the carbonyl wavenumber shift for selected substituted phenyl *sec*-butyl ketones are found in Table I. These K_c values were correlated with Hammett constants. A plot of log (K_c^x/K_c^H) vs. σ has a slope (ρ) of −0.86 ± 0.05.

The rate of disappearance of ketones **1a–h** followed at either the free ketone carbonyl band or the ketone–reagent complex carbonyl band displays pseudo-first-order behavior in the presence of excess reagent. The dependence of the observed pseudo-first-order rate constant, k_{obsd}, on *sec*-BuLi is complex and varies with each compound. For ketones **1a–e**, k_{obsd} reaches a maximum and then decreases at higher reagent concentrations; whereas, with ketones **1f–h** k_{obsd} increases with increasing *sec*-BuLi concentration (Figure 2). The pseudo-first-order rate constant was found to be slightly dependent on initial ketone concentration. The addition of the product alcohol (di-*sec*-butylphenylmethanol) to the lithium reagent prior to reaction has been found to cause a rise in the observed rate constant.

The reaction of *n*-BuLi with phenyl *sec*-Butyl ketone in cyclohexane at 25.0 °C gives rise to a broadened carbonyl stretch in the infrared spectrum of **1a** which indicates the formation of a ketone–*n*-butyllithium hexamer complex. The disappearance of this complex followed at 1682 cm^{-1} exhibits pseudo-first-order kinetics. The observed pseudo-first-order rate constant increases slowly with increasing *n*-BuLi concentration.

The reaction of *sec*-BuLi with **1a** in benzene has also been examined by infrared stopped-flow spectroscopy. Upon reaction with excess reagent phenyl *sec*-butyl ketone **1a**, displays a broadened carbonyl stretching band. Compared to the reaction in cyclohexane, broadening of the **1a** carbonyl band in benzene is significantly smaller. The rate of disappearance of the ketone at 1678 cm^{-1} follows pseudo-first-order kinetics. Values of k_{obsd} were 3–4 times greater than those obtained for the reaction in cyclohexane.

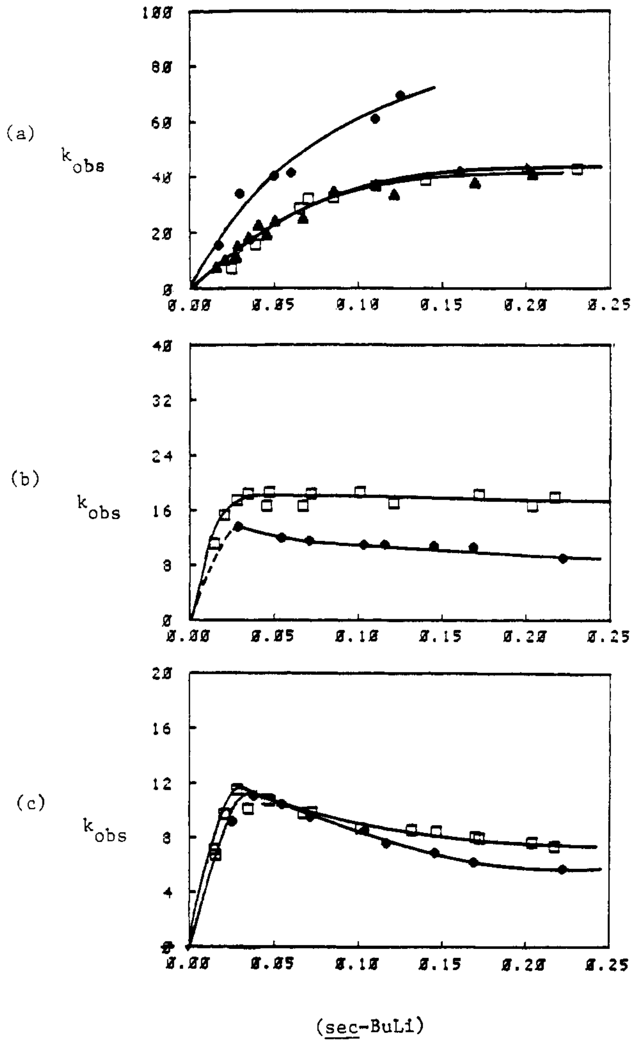
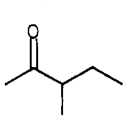
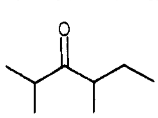
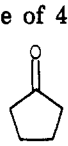


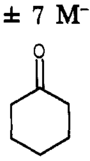
Figure 2. Plot of observed pseudo-first-order rate constant vs. *sec*-BuLi concentration. (a) Reaction with 7.5 × 10^{-3} M **1h** (●), 8.2 × 10^{-3} M **1g** (▲), and 8.2 × 10^{-3} M **1f** (□). (b) Reaction with 8.3 8.6 × 10^{-3} M **1a** (□) and 8.1 × 10^{-3} M **1d** (●). (c) Reaction with 9.2 × 10^{-3} M **1c** (●) and 8.0–8.15 × 10^{-3} M **1b** (□). Reaction rates measured in cyclohexane at 25.0 °C.

Aliphatic ketones **2–5** have been observed to exhibit broadened carbonyl bands upon reaction with *sec*-BuLi in cyclohexane at 25 °C. A value of 40 ± 7 M^{-1} was


2


3


4


5

determined for the complexation equilibrium constant of 3-methyl-2-pentanone (**2**) with a carbonyl wavenumber shift of ca. −10 cm^{-1}. Rates of the reactions of **2–5** with excess *sec*-BuLi were measured by following the disappearance of the broadened carbonyl bands. The dependence of k_{obsd} on *sec*-BuLi concentration varied with each ketone: k_{obsd} was nearly independent of reagent concentration for ketones **1** and **2**, but with ketones **3** and **4** k_{obsd} attained a maximum and declined with increasing *sec*-BuLi concentration (Figure 3).

Discussion

The rapid and reversible formation of a ketone–alkyllithium aggregate complex constitutes the initial step in the reaction of lithium reagents with ketones in cyclohexane. Association between the carbonyl group of the ketone and

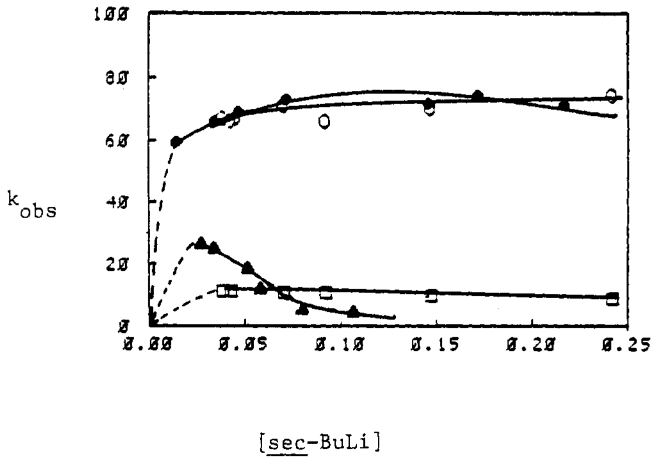


Figure 3. Plot of observed pseudo-first-order rate constant vs. *sec*-BuLi concentration. Reaction with 8.74×10^{-3} M **5** (●), 8.31×10^{-3} M **4** (○), 7.5×10^{-3} M **3** (▲), and 9.12×10^{-3} M **2** (□) in cyclohexane at 25.0 °C.

the lithium of the reagent aggregate in such a complex is indicated by the shift to lower energy of the carbonyl stretching band of the ketone. A trend is recognizable in the equilibrium constants of the complexation of the substituted aromatic compounds. The more electron withdrawing the substituent on the phenyl ring the smaller the equilibrium constant for complex formation. Also, there exists a qualitative correlation between the carbonyl wavenumber shift of the complexed ketone and the equilibrium constant, K_c. The negative value of ρ from the log K_c^x/K_c^H vs. σ plot indicates the development of positive charge at the carbonyl carbon in the complexation process.

The dependence of k_{obsd} on *sec*-BuLi concentration for the reactions of the substituted aromatic ketones **1a–h** has been shown to vary with the substituent on the phenyl ring of the compound. Electron-releasing groups cause k_{obsd} to go through a maximum with increasing *sec*-BuLi concentration. On the other hand, substitution of the phenyl ring with an electron-withdrawing substituent leads to the common behavior of increasing k_{obsd} with rising reagent concentration. Thus, the shape of a plot of k_{obsd} vs. concentration of lithium reagent is related to the nature of the substituent. The substituent effect on rate curves parallels that found in the ketone reagent complexation equilibrium data. Those ketones which exist predominantly in the complexed state give rate constants which are inversely related to the *sec*-BuLi concentration whereas ketones which to a large extent remain uncomplexed give rate constants which are directly dependent on alkyllithium concentration.

The kinetic data are accommodated by the reaction sequence shown in Scheme III.[2b] In this scheme, ketone

Scheme III

$$^{1}/_{4}\mathrm{Bu_4Li_4} \xrightleftharpoons{\text{fast}} \mathrm{BuLi} \tag{5}$$

$$\mathrm{Ket} + \mathrm{Bu_4Li_4} \xrightleftharpoons{K_c} \mathrm{Ket{\cdot}Bu_4Li_4} \xrightarrow{k_3} \text{product} \tag{6}$$

$$\mathrm{Ket} + \mathrm{BuLi} \xrightarrow{k_4} \text{product} \tag{7}$$

$$k_{obsd} = \frac{k_3K_c(\mathrm{Bu_4Li_4}) + k_4(\mathrm{BuLi})}{1 + K_c(\mathrm{Bu_4Li_4})} \tag{8}$$

is transformed to product by two competing pathways: initial complexation with *sec*-BuLi tetramer and subsequent rearrangement of the complex, and reaction with the more reactive monomeric reagent which is in equilibrium with the tetramer. As reagent concentration increases the aggregated fraction increases much more rapidly than the monomeric fraction. The change in the monomer–aggregate ratio over a certain reagent concentration range underlies the occurrence of the maximum in the rate constant that is observed in the reactions of **1a–d**. Increasing the concentration of the lithium reagent increases the fraction of the ketone that is complexed with alkyllithium aggregates which cause k_{obsd} to level off and decline. The substituent effect on the rate data is manifested through the value of K_c. Ketones with a large K_c would be largely complexed at high reagent concentrations and thus go to product via the complexation pathway. Ketones with a small K_c, on the other hand, would remain relatively uncomplexed and tend to go to product by the monomer pathway.

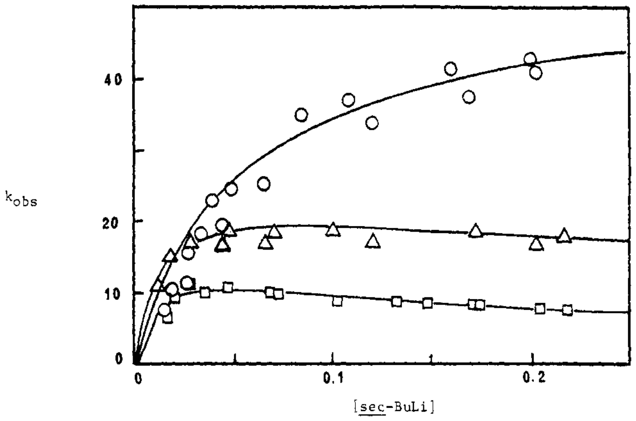


Figure 4. Plot of k_{obsd} vs. *sec*-BuLi concentration for the reaction of 8.2×10^{-3} M 3-(trifluoromethyl)phenyl *sec*-butyl ketone (○), 8.3–8.6 $\times 10^{-3}$ M phenyl *sec*-butyl ketone (▲), and 8.0–8.15 $\times 10^{-3}$ M 4-phenoxyphenyl *sec*-butyl ketone (□). The solid curves were calculated from eq 8 (Scheme III) with $K_D = 5 \times 10^{-6}$ M^3, $K_C = 49$ M^{-1}, $k_3 = 1.2$ s^{-1}, $k_4 = 1000$ s^{-1}; $K_1 = 5 \times 10^{-6}$ M^3, $K_2 = 37$ M^{-1}, $k_3 = 9$ s, $k_4 = 1500$ s^{-1}; $K_1 = 5 \times 10^{-5}$ M^3, $K_2 = 26$ M^{-1}, $k_3 = 50$ s^{-1}, $k_4 = 900$ s^{-1}, respectively.

Figure 4 illustrates the fit of Scheme III to the experimental rate data for compounds **1a**, **1b** and **1g**. The values of k_3, the rate constant for conversion of complex to product, and k_4, the rate constant for reaction of monomeric lithium reagent with ketone, were deduced from the experimental rate data by rearrangement of eq 8 to a linear form in which k_3 and k_4 are the slope and y intercept, respectively. The value employed for the *sec*-BuLi dissociation constant ($5 \times 10^{-5} \pm 1 \times 10^{-5}$ M^3) was that found to provide the best fit for the rate data by Scheme III. The large ratio of k_4 to k_3 (**1a**, 1500/9, **1b**, 1000/1.2, **1g**, 900/50) in Figure 4 supports the assumption that reaction with monomer is greatly favored over reaction with tetrameric *sec*-BuLi. A comparison of k_3 values for ketones **1a**, **1b**, and **1g** (9, 1.2, and 50 s^{-1}, respectively) indicates that the presence of an electron-withdrawing substituent on the phenyl ring of the ketone increases the rate of conversion of complex to product. Within the range of values found for these compounds k_3 regulates the amount of product formed by the complex formation pathway and thereby determines the direction of the rate curves at higher lithium reagent concentrations.

Phenyl *sec*-butyl ketone has been found to react with *sec*-BuLi at a faster rate than with *n*-BuLi. The greater reactivity of the *sec*-butyl isomer may be related to its lower state of aggregation in cyclohexane. Glaze[15] has compared the reactivities of *n*-BuLi, *sec*-BuLi, and me-

---

[15] Glaze, W. H.; Freeman, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 7198.

thyllithium toward bromobenzene in pentane (halogen–lithium interchange) and toward 1,1-diphenylethylene in benzene (addition). The order of reactivities, as measured by reaction rates, was methyllithium > *sec*-BuLi > *n*-BuLi reflecting the order in states of aggregation (2, 4, 6) for these reagents in hydrocarbon solvents. Scheme III provides a good fit for the rate data from the reaction of **1a** with *n*-BuLi with the following parameter values: $K_D = 10^{-8}$ M^3, $K_c = 30$ M^{-1}, $k_3 = 4.8$ s^{-1}, $k_4 = 140$ s^{-1}.[16]

The change of solvent from cyclohexane to benzene caused a 2–3-fold increase in k_{obsd} values for the reaction of **1a** with *sec*-BuLi. Promotion of alkyllithium dissociation due to interaction of *sec*-BuLi with benzene may be responsible for the observed rate enhancement.[17]

The reaction of alkyllithium reagents with ketones in ethereal solvents is thought to proceed predominantly through monomeric reagent. This work has shown that in hydrocarbon solvents both monomeric and aggregated alkyllithium are involved in this reaction with the relative importance of each depending on the structure of the ketone. The aggregated lithium reagent participates in the reaction by the reversible formation of a complex with the ketone followed by slow conversion of the complex to product.[18]

Experimental Section

General Methods. Infrared spectra were recorded on a Perkin-Elmer Model 237B or a Beckman IR-12 spectrophotometer in 0.1-mm NaCl cells or as films. Nuclear magnetic resonance spectra were obtained on a Varian EM-390 spectrometer. Melting points were measured on a Büchi melting point apparatus in open capillaries and are uncorrected. Gas chromatographic analyses were performed on a Newlett-Packard F&M Scientific 700 laboratory chromatography equipped with a thermal conductivity detector.

Kinetic Measurements and Data Analysis. All infrared kinetic experiments were performed with a stopped-flow spectrophotometer having a rapid-scanning capability, which has been described previously.[12,19] The rapid-scanning feature is provided by a synchronous stepping motor which drives the monochromator with a variety of scanning speeds. The entire stopped-flow apparatus was maintained at 25.0 ± 0.1 °C by means of a thermostated ethylene glycol bath. Signal vs. time data were collected on either a 32-channel or 100-channel digital input buffer taking points at intervals of 0.05–1 s. These data together with zero light level and infinty readings were transferred to disk storage on the Plato V computer based teaching system. Data were collected and analyzed under pseudo-first-order conditions with excess alkyllithium. Unweighted least-squares analysis of absorbance vs. time data yielded the observed pseudo-first-order rate constants, which were typically reproducible to within ca. 5%.

Infrared spectra were recorded under rapid-scanning conditions by digitizing 382 transmittance data points at time intervals of $2.5–5 \times 10^{-3}$ s (scanning motor speed 62.5 and 125 pulses/s). The data were collected in an input buffer, transferred to an off-line Plato computer terminal, and stored on a floppy disk. Reacting mixture scans were always obtained under conditions of continuous flow on the stopped-flow instrument. The absorption spectrum of the solvent, cyclohexane or benzene, was substracted from the absorption spectrum of interest to enable spectral comparisons. The product solution absorption spectrum was identical with that of the solvent since the product does not absorb in the infrared carbonyl region.

The equilibrium constant of complexation was determined by recording 100 absorbance readings (at an interval of ca. 1.5×10^{-3} s/point) of a continuously flowing reacting mixture of carbonyl compound and *sec*-butyllithium at the carbonyl band of the compound. The time interval required for the reacting solution to travel from the mixer to the infrared cell (<3 ms) was sufficient to allow for the establishment of the rapid equilibrium between the substrate and substrate–*sec*-butyllithium complex, but not for further reaction. The average absorbance reading of the free substrate at a particular reagent concentration was then converted to concentration and substituted into eq 3 to calculate K_c.

Lithium Reagents. *sec*-Butyllithium was prepared on a vacuum line which was repeatedly degassed under vacuum and kept under positive pressure of argon. Lithium sand (99.95%, 30% dispersion in mineral oil, Alfa products) was washed free of mineral oil with cyclohexane under nitrogen atmosphere. The lithium sand was then introduced into the reaction vessel on the vacuum line and dried under vacuu. *sec*-BuLi was formed by slow dropwise addition of freshly distilled and degassed *sec*-butyl chloride to the lithium sand (ca. 2-fole excess) in dry cyclohexane, previously distilled from a 0.05 M solution of *n*-butyllithium. Throughout the addition of the halide, the temperature of the reacting solution was maintained at approximately 25 °C by cooling with an ice bath. After standing 12–36 h, the reagent was twice filtered through glass frits. The clear and colorless reagent (60–70% yield) was delivered into silicon rubber serum-capped bottles and diluted with cyclohexane to prepare several different concentrations. *sec*-Butyllithium solutions were analyzed for total base and non-lithium base titers. Total base titer was determined by quenching an aliquot of reagent with aqueous ethanol and titrating with standard hydrochloric acid with neutral red indicator. Non-lithium base titer was obtained by injecting 1,2-dibromomethane into the reagent bottle to destroy the alkyllithium followed by quenching with aqueous ethanol and titration of an aliquot with hydrochloric acid. Non-lithium base varied from 0.5% to 10% depending on reagent concentration *sec*-Butyllithium was prepared in benzene utilizing the above procedure. *n*-Butyllithium was prepared by the dropwise addition of *n*-butyl chloride to excess lithium sand following the procedure described for the preparation of *sec*-BuLi.

Ketones. 2,4-Dimethyl-3-hexanone was prepared by the reaction of 2-methylbutanol with isopropylmagnesium bromide.[20]

Substituted Phenyl *sec*-Butyl Ketones (1a–h). Ketones **1a–d** were prepared by Freidel–Crafts acylation of the appropriate aryl compound with 2-methylbutanoyl chloride.[21] Aluminum chloride (0.081 mol) was dissolved in ca. 20 mL of carbon disulfide. The reaction flask was cooled in an ice bath and the aryl compound was added slowly. Acid chloride (0.080 mol) dissolved in ca. 10 mL of CS_2 was added dropwise to the mixture at 0 °C over a 15-min period. After addition of the 2-methylbutanoyl chloride, the reaction mixture was stirred for 1 h at room temperature and worked up in the usual manner. The crude product was fractionally distilled to yield the pure ketone. Below are listed the yields, boiling points, carbonyl IR absorptions, ^{1}H NMR spectra, and elemental analyses.

Phenyl *sec*-butyl ketone (1a): 62% yield; bp 110–112 °C (9.5 mm) (lit[22] 62 °C (0.25 mm)); IR (neat) 1678 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3), 1.2 (d, 3), 1.3–2.1 (m, 2), 3.25 (sextet, 1), 7.2 (m, 3), 7.6 (m, 2).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.48; H, 8.64. Found: C, 81.24; H, 8.55.

4-Phenoxyphenyl *sec*-butyl ketone (1b): 66% yield; bp 129–131 °C (0.18 mm); IR (neat) 1667 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3), 1.15 (d, 3), 1.3–211 (m, 2), 3.3 (sextet, 1), 7.2 (m, 4), 7.5 (m, 3), 8.1 (d, 2).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.31; H, 7.09. Found: C, 80.09; H, 7.06.

4-Methoxyphenyl *sec*-butyl ketone (1c): 54% yield; bp 99–100 °C (0.47 mm) (lit.[22] 105 °C (0.4 mm); IR (neat) 1667 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3), 1.15 (d, 3), 1.3–2.1 (m, 2), 3.3 (sextet, 1), 7.1 (d, 2), 8.1 (d, 2).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.0; H, 8.33. Found: C, 74.63; H, 8.39.

---

(16) Values of k_3 and k_4 were estimated by a fitting procedure.

(17) Zerger, R.; Rhine, W.; Stuckey, G. *J. Am. Chem. Soc.* **1974**, *96*, 6048.

(18) A similar mechanism is believed to operate in the reactions of lithium reagents with esters. Results from a kinetic investigation of these reactions will be reported soon.

(19) Kraus, S. R. Ph.D. Thesis 1979, University of Illinois, Urbana, IL.

(20) Kletzke, P. G. *J. Chem. Eng. Data* **1973**, *18*, 93.

(21) Desai, A. P.; Vasi, I. G.; Thacker, A. K. *J. Indian Chem. Soc.* **1970**, *47*, 117.

(22) Korver, O. *Tetrahedron* **1971**, *27*, 4643.

4-Methylphenyl *sec*-butyl ketone (1d): 50% yield; bp 87–88 °C (0.5 mm) (lit.[22] 80 °C (0.5 mm)); IR (neat) 1678 cm^{-1} (C–O); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3), 1.15 (d, 3), 1.3–2.1 (m, 2), 3.3 (sextet, 1), 7.3 (d, 2), 8.0 (d, 2).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.82; H, 9.20. Found: C, 81.29; H, 9.14.

Ketones **1e–h** were prepared by the reaction of the corresponding substituted arylcadmium reagent with 2-methylbutanoyl chloride.[23] The arylmagnesium bromide was prepared by the reaction of the substituted aryl bromide (0.14 mol) with magnesium turnings (0.145 mol) in dry diethyl ether. The Grignard solution was cooled in an ice bath and anhydrous cadmium chloride (0.08 mol) was added over a 5-min period. The resulting grey reaction mixture was heated at reflux with stirring for 2 h. Most of the ether was then removed by distillation and replaced with dry benzene. A solution of 2-methylbutanoyl chloride (0.11 mol) in 20 mL of benzene was added to the cadmium reagent at room temperature. The reaction mixture was heated at reflux for ca. 4 h and allowed to stir at room temperature overnight. Dilute sulfuric acid was added to the cooled reaction mixture to decompose the salts and give a slurry that was extracted with ether. The ether extracts were washed with 10% aqueous sodium bicarbonate and water. Drying over anhydrous magnesium sulfate and removal of solvent yielded crude product. The product was fractionally distilled, chromatographed on silica gel (methylene chloride–hexane), and redistilled to give pure ketone in 30–50% yield. The pure ketone was identified by boiling point, NMR and IR spectra, and elemental analysis.

4-Chlorophenyl *sec*-butyl ketone (1e): 34% yield; IR (neat) 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3), 1.2 (d, 3), 1.3–2.1 (m, 2), 3.4 (sextet, 1), 7.4 (d, 2), 7.7 (d, 2).

Anal. Calcd for $C_{11}H_{13}C10$: C, 67.19; H, 6.62; Cl, 18.05. Found: C, 67.31; H, 6.54; Cl, 17.92.

3-Fluorophenyl *sec*-butyl ketone (1f): 40% yield; IR (neat) 1681 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3), 1.2 (d, 3), 1.3–2.1 (m, 2), 3.4 (sextet, 1), 7.5 (d, 2), 7.9 (d, 2).

Anal. Calcd for $C_{11}H_{13}FO$: C, 73.33; H, 7.22; F, 10.56. Found: C, 73.27; H, 7.28; F, 10.67.

3-(Trifluoromethyl)phenyl *sec*-butyl ketone (1g): 44% yield, bp 29–30 °C (0.36 mm); IR (neat) 1683 cm^{-1} (C=O); ^1H NMR δ 0.9 (t, 3), 1.2 (d, 3), 1.3–2.1 (m, 2), 7.5 (m, 2), 8.1 (m, 2).

Anal. Calcd for $C_{12}H_{13}F_3O$: C, 62.61; H, 5.65, F, 24.78. Found: C, 62.42; H, 5.76; F, 24.61.

3,5-Bis(trifluoromethyl)phenyl *sec*-butyl ketone (1h): 22% yield; bp 96–97 °C (0.18 mm); IR (neat) 1695 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3), 1.3 (d, 3), 1.3–2.0 (m, 2), 3.4 (sextet, 1), 8.0 (s, 1), 8.3 (s, 2).

Anal. Calcd for $C_{13}H_{12}F_6O$: C, 52.35; H, 4.03; F, 38.26. Found: C, 52.22; H, 3.93; F, 38.25.

Product Analyses. Effluents from the stopped-flow instrument were collected from the reaction of excess *sec*-BuLi with **1a–d**. Each mixture was neutralized with dilute sulfuric acid and extracted with ether. The ether extracts were washed with aqueous sodium bicarbonate and water, dried over anhydrous magnesium sulfate, and concentrated. The crude product mixture were analyzed by NMR and IR spectroscopy and gas chromatography. In all cases, the tertiary alcohol (addition product) was the predominant constituent (>70%) of the product mixture. The reduction and enolization side products (i.e., secondary alcohol and recovered ketone) accounted for the remaining portion of the product mixture. For example, the stopped-flow effluent from the reaction of **1a** with *sec*-BuLi contained 86% addition product, 12% reduction product, and 1% recovered ketone by GC.

Acknowledgment. Acknowledgement is made to the Donors of The Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

Registry No. **1a**, 938-87-4; **1a**·*sec*-Bu_4Li_4, 90269-53-7; **1b**, 90269-45-7; **1b**·*sec*-Bu_4Li_4, 90269-52-6; **1c**, 90269-46-8; **1d**, 90269-47-9; **1e**, 90269-48-0; **1e**·*sec*-Bu_4Li_4, 90269-54-8; **1f**, 49660-96-0; **1g**, 90269-49-1; **1g**·*sec*-Bu_4Li_4, 90269-55-9; **1h**, 90269-50-4; *sec*-BuLi, 598-30-1; *sec*-Bu_4Li_4, 90269-51-5; *n*-BuLi, 109-72-8; *n*-Bu_6Li_6, 90269-56-0; 2-methylbutanoyl chloride, 5856-79-1; benzene, 71-43-2; diphenyl ether, 101-84-8; anisole, 100-66-3; toluene, 108-88-3; 1-bromo-4-chlorobenzene, 106-39-8; 1-bromo-3-fluorobenzene, 1073-06-9; 1-bromo-3-(trifluoromethyl)benzene, 401-78-5; 1-bromo-3,5-bis(trifluoromethyl)benzene, 328-70-1.

---

[23] Carson, J.; Prout, F. S. *Org. Synth.* **1948**, *28*, 75. Shirley, D. A. *Org. React.* (*N. Y.*) **1954**, *8*, 28.

Notes

Evidence Defining Rate-Determining Diffusional Separation for the Hydrolysis of Acetals of Benzaldehyes

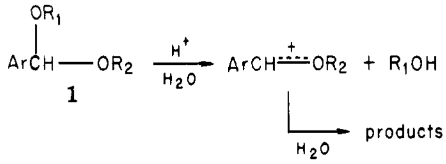
James L. Jensen* and Kenneth S. Yamaguchi

Department of Chemistry, California State University, Long Beach, California 90840

Received December 28, 1983

There has been a rekindling of interest in hydrolytic reaction mechanisms in recent years; of particular interest have been those hydrolytic reactions where catalysis (e.g., proton transfer) is concerted with other bond-making/breaking processes. In these cases the usual mechanistic tools can prove deceptive, unless one is careful to conduct experiments designed to examine both the catalytic and the bond-making/breaking process. The acetals of benzaldehydes **1** are an interesting case in point (Scheme I).

Scheme I



It has been shown that when R_1OH is an excellent leaving group (e.g., R_1 = aryl[1] or trifluoroethyl[2]), hydrolysis occurs with a rate-limiting step of proton transfer concerted with C–O bond breaking. This reaction is characterized by a large, negative Hammett ρ value of about −2 and a Brønsted α value of about 0.6. The coupling of the proton-transfer process and the C–O bond-breaking process has been measured quantitatively by Capon:[1] the Hammett ρ is more negative for weaker acid catalysts, and the Brønsted α is smaller when Ar contains electron-do-

---

[1] (a) Capon, B.; Nimmo, K. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1113–1118. (b) Capon, B.; Page, M. I. *Ibid.* **1972**, 522–529.

[2] Jensen, J. L.; Herold, L. R.; Lenz, P. A.; Trusty, S.; Sergi, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* **1979**, *101*, 4772–4677.