Registry No. *O*-Methyl *S*-methyl xanthate, 19708-81-7; *O*-ethyl *S*-methyl xanthate, 623-54-1; *O*-isopropyl *S*-methyl xanthate, 35200-02-3; *O*-*sec*-butyl *S*-methyl xanthate, 7694-21-5; (-)-*O*-(2-octyl) *S*-methyl xanthate, 77714-50-2; (+)-2-octanol, 6169-06-8; (-)-2-octanethiol, 10435-93-5; (+)-*S*-(2-octyl) *S*-methyl dithiocarbonate, 77629-22-2; *S*,*S*-dimethyl dithiocarbonate, 868-84-8; *S*-ethyl *S*-methyl dithiocarbonate, 10596-55-1; *S*-isopropyl *S*-methyl dithiocarbonate, 22426-84-2; *S*-*sec*-butyl *S*-methyl dithiocarbonate, 22426-85-3; trifluoroacetic acid, 76-05-1.

Kinetic Formation of Stereoisomeric Propionaldehyde Dimethylhydrazone Lithium Reagents

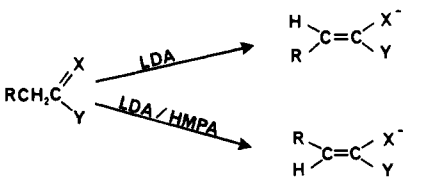
Kenneth G. Davenport, Martin Newcomb,*[1] and David E. Bergbreiter*

Department of Chemistry, Texas A&M University, College Station, Texas 77843

Received February 3, 1981

The sense and degree of stereoselectivity in deprotonations of ketones and esters and their synthetic equivalents can be critical in determining the overall stereoselectivity obtained in electrophilic substitution reactions employing enolate-like intermediates. Thus, several studies have been directed toward determining the stereochemistry of the lithio intermediates formed in deprotonations of substituted active methylene compounds and at how that stereoselectivity could be controlled experimentally.[2] Studies of deprotonations of various monosubstituted carbonyl compounds and derivatives by lithium diisopropylamide (LDA) have been found to occur as shown in Scheme I. With few exceptions,[3] deprotonation by LDA in the absence of hexamethylphosphoramide (HMPA) gives the lithium reagent wherein the substituent (R) is trans to the charge-bearing heteroatom. Deprotonation by LDA in the presence of HMPA, however, usually gives predominantly the cis lithium reagent. Products obtained in these studies were tacitly assumed to be the kinetic products of the deprotonation reactions, and rationalizations for the results involving different transition states in the deprotonations with or without HMPA have been presented.[5] Recently, Rathke and co-workers have shown that deprotonation of 3-pentanone by LDA/HMPA gives a mixture of stereoisomeric enolates, the ratio of which clearly changes during the course of the deprotonation, showing that an equilibration process occurs in this case.[6] One implication of these results is that HMPA may activate equilibration processes in other enolate-like species. In this note we show that the propionaldehyde dimethylhydrazone (DMH) lithium reagents formed by LDA deprotonation in the absence or presence of HMPA do not equilibrate under typical deprotonation conditions; thus distinctly different transition states for the deprotonation reactions must exist under these different deprotonation conditions.

Scheme I



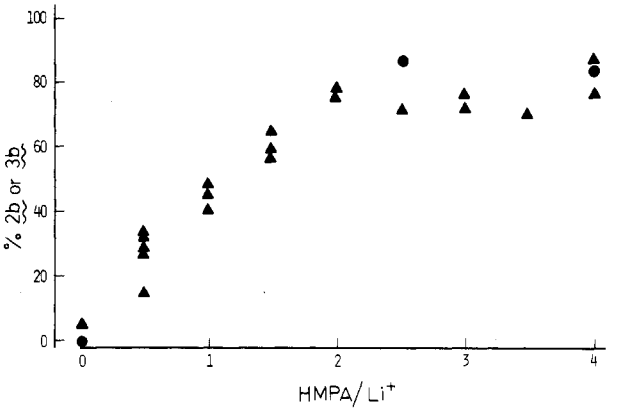
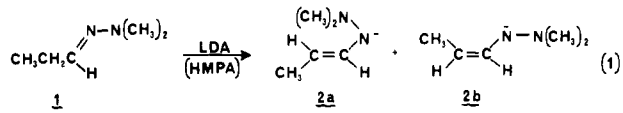


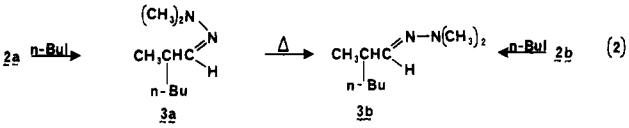
Figure 1. Percentage of **2b** (●) or **3b** (▲) formed from LDA deprotonation of **1** in the presence of increasing equivalents of HMPA per lithium ion.

As reported, propionaldehyde DMH (**1**) is deprotonated by LDA or LDA/HMPA to give the E_{C-C},Z_{C-N} (**2a**) and Z_{C-C},E_{C-N} (**2b**) azaallyllithium reagents as the only products detectable by ^{1}H NMR spectroscopy.[2d] The C–C



(1)

bond stereochemistry of **2a** and **2b** was determined by ^{1}H NMR spectroscopy of the azaallyllithium reagents; **2a** shows a trans coupling (J = 12.5 Hz) and **2b** a cis coupling (J = 7.7 Hz) to the formyl protons. The C–N stereochemistry was determined by alkylation of **2a** and **2b**, which gave the butylated products **3a** and **3b**, respectively



(2)

(this froze out the C–N stereochemistry), and subsequent ^{1}H NMR analysis. The formyl proton of **3a** gave a signal at δ 6.7 and that of **3b** gave a signal at δ 6.4; on standing at 25 °C **3a** slowly isomerized to **3b**. When **1** was treated with LDA containing 0.0 to 4.0 equiv of HMPA per lithium ion, the ratio of **2a**:**2b** changed smoothly from >95:<5 (0.0 equiv of HMPA) to ca. 20:80 (>2.0 equiv of HMPA) as shown in Figure 1. The **2a**:**2b** ratio either was obtained by integration of the proton signals at δ 6.2 and 6.6, re-

(1) Camille and Henry Dreyfus Teacher-Scholar, 1980–1985.

(2) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. (b) Hoobler, M. A.; Bergbreiter, D. E.; Newcomb, M. *Ibid.* **1978**, *100*, 8182–8185. (c) Meyers, A. I.; Snyder, E. S.; Ackerman, J. J. H. *Ibid.* **1978**, *100*, 8186–8189. (d) Davenport, K. G.; Eichenauer, H.; Enders, D.; Newcomb, M.; Bergbreiter, D. E. *Ibid.* **1979**, *101*, 5654–5659. (e) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081. (f) Houk, K. N.; Strozier, R. W.; Rondan, N. G.; Fraser, R. R.; Chuaqui-Offermanns, N. *J. Am. Chem. Soc.* **1980**, *102*, 1426–1429. (g) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, 4233–4236. (h) Kuwajima, I.; Kato, M.; Mori, A. *Ibid.* **1980**, 2745–2748.

(3) Exceptions include ketones[2e] and thioamides.[4a] The stereochemistry originally assigned to thioamide lithium anions[4b] appears to have been in error.

(4) (a) Tamaru, Y.; Harada, T.; Nishi, S.; Mizutani, M.; Hioki, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1980**, *102*, 7806–7808. (b) Tamaru, Y.; Harada, T.; Yoshida, Z. *Ibid.* **1978**, *100*, 1923–1925.

(5) Typically, these different transition states proposed involved coordination of lithium of the base to the heteroatom in the absence of HMPA and less or no coordination in the presence of HMPA.[2a,d,e]

(6) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959–3960.

0022-3263/81/1946-3143$01.25/0

Table I. Equilibrium Ratios of 2a:2b and 3a:3b (after Butylation)[a]

LDA, mequiv	HMPA, equiv/Li$^+$	additive (mmol)	relative yield, %[b] 2a	2b	3a	3b
1.6	0	none	66	34	63	37
1.6	2.0	none	64	36	64	36
2.2	0	benzophenone (0.4)			66	34
2.2	2.0	benzophenone (0.4)			65	35
2.2	0	diphenylamine (0.4)			69	31
2.2	2.0	diphenylamine (0.4)			70	30

[a] Deprotonation of 2.0 mmol of 1 in THF as described in the text. [b] Determined by ^{1}H NMR spectroscopy, ± 5%.

spectively, of the azaallyllithium reagents or was deduced from the **3a:3b** ratio after butylation (formyl proton signals at δ 6.7 and 6.4, respectively); the results were the same in cases where both methods were used at a specific HMPA:Li$^+$ ratio. In cases where less than 2.0 equiv of HMPA per lithium ion was used for the deprotonation reactions, additional HMPA was added *after* the deprotonation to provide solutions which were suitable for ^{1}H NMR spectroscopy. Typical yields of **3** after butylation were ca. 84%.

Experiments which apparently led to equilibration of **2a** and **2b** showed that the stereoisomeric azaallyllithium reagents formed above had not been equilibrated. These experiments included either use of insufficient base (0.8 equiv) or addition of diphenylamine (0.2 equiv) or benzophenone (0.2 equiv) to the reaction mixtures. In the first two cases, equilibration of **2** by a protonation–deprotonation sequence could occur. Benzophenone could act as an electrophile, permitting equilibration by a reversible aldol condensation as suggested by Rathke[6] for equilibration of 3-pentanone enolates, or could permit electron-transfer reactions. Each of these deprotonations was run in the absence of HMPA and in the presence of 2.0 equiv of HMPA per lithium ion. The results given in Table I show that the equilibrium ratio of **2a:2b** is approximately 65:35.

Thus, deprotonation of **1** in the absence of and in the presence of >2.0 equiv of HMPA gave ratios of **2a:2b** which are far removed from the equilibrium ratio and, further, which are, respectively, greater and less than the equilibrium ratio. In both cases, kinetic products were formed, and the interpretation that distinct transition states for deprotonation exist is supported.[5] Although HMPA may affect the ratio of ketone enolate isomers by activating the system for a reversible aldol condensation leading to equilibration,[6] similar equilibration schemes are less likely for less electrophilic ketone equivalents.

Experimental Section

General Methods. Tetrahydrofuran (THF) was distilled from sodium–benzophenone, diisopropylamine was distilled from calcium hydride, and HMPA was distilled from sodium in vacuo. Reactions were run under nitrogen and syringe transfers were employed.[7] ^{1}H NMR spectra of mixtures of **2** or **3** used for the data in Figure 1 were recorded on a Varian T-60 spectrometer; the formyl protons resonated at the following positions: **2a**, δ 6.2; **2b**, δ 6.6; **3a**, δ 6.7; **3b**, δ 6.4. Spectra of **2** were recorded at ca. 0 °C. In the experiments reported in Table I, the ^{1}H NMR signals of **1** overlapped with those of **2** and **3** at 60 MHz but were resolved at 200 MHz (Varian XL-200, FT with a benzene-d_6 lock).

Deprotonations of 1 in the Absence of HMPA. Deprotonations of **1** followed the general method we have reported.[2] DMH **1** (250 μL, 2.0 mmol) was added dropwise to a THF solution of LDA (2.7 mL, 0.82 N, 2.2 mequiv) at −78 °C. The stirred mixture was warmed to 25 °C for 1 h and then cooled to −78 °C. For ^{1}H NMR analyses, the mixture was cooled to −78 °C, 0.9 mL of HMPA (2.5 equiv per lithium ion) was added, and the mixture was warmed to ca. −23 °C to give a yellow solution. For alkylation reactions, the suspension of **2** at −78 °C was treated with 0.25 mL (2.2 mmol) of 1-iodobutane at −78 °C, and then the mixture was warmed to 25 °C for 0.5 h. The mixture was then cooled to −78 °C and treated with ca. 0.1 mL of water. After warming to 25 °C, the mixtures were analyzed by ^{1}H NMR spectroscopy. GC analysis (SE-30, hexadecane internal standard) indicated that 82–88% yields of **3** were obtained.

Deprotonations of 1 in the Presence of HMPA. The method described above was used with the exceptions that HMPA was added to the LDA solutions before **1** was added and the deprotonation reactions were maintained at ca. −23 °C for 1.5 h. For ^{1}H NMR analyses of the mixtures containing <2.0 equiv of HMPA per lithium ion, the reaction mixtures were cooled to −78 °C, and the total amount of HMPA was brought to 2.5 equiv per lithium ion.

Equilibration Studies. Deprotonation reactions were conducted with 0.0 or 2.0 equiv of HMPA per lithium ion as described above. For the reactions initially containing no HMPA, the mixtures were subsequently cooled to −78 °C and 2.5 equiv of HMPA per lithium ion was added. The mixtures were warmed to ca. −23 °C and, when appropriate, an additive was added. The mixtures were maintained at ca. −23 °C for 2 h, then cooled to −78 °C, and treated with 1-iodobutane as described above.

Acknowledgment. This work was supported by a grant from the National Institutes of Health (GM 26268). The Varian XL-200 NMR spectrometer used in this research was purchased with the aid of a National Science Foundation grant (CHE78-27411) to Texas A&M University.

Registry No. 1, 7422-93-7; 2, 66970-40-9; 3a, 72215-77-1; 3b, 72215-76-0.

(7) Brown, H. C. "Organic Syntheses via Boranes"; Wiley-Interscience: New York, 1975.

Facile Oxetane Formation in a Rigid Bicyclo[2.2.2]octane System[1a]

Scott E. Denmark[1b]

Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, CH-8092 Zürich, Switzerland

Received February 18, 1981

Introduction

In connection with studies on the stereoelectronic preference of heterolytic fragmentations[2] we have prepared the racemic hydroxy sulfate **1** and have investigated its reactions in the presence of nonnucleophilic bases. The fundamental stereoelectronic requirement of this reaction

(1) (a) Taken from the Ph.D. thesis of S.E.D., ETH-Zurich, No. 6665, July 1980. (b) Address correspondence to School of Chemical Sciences, University of Illinois, Urbana, IL 61801.

(2) (a) Eschenmoser, A.; Frey, A. *Helv. Chim. Acta* **1952**, *35*, 166. Reviews: Becker, K. B.; Grob, C. A. In "The Chemistry of Double Bonded Functional Groups"; Patai, S., Ed.; Wiley-Interscience: New York, **1977**; Vol. 2, p 653; (b) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1.

0022-3263/81/1946-3144$01.25/0