Deuterium Isotope Effects and the Mechanism of Kinetic Enolate Formation[1]

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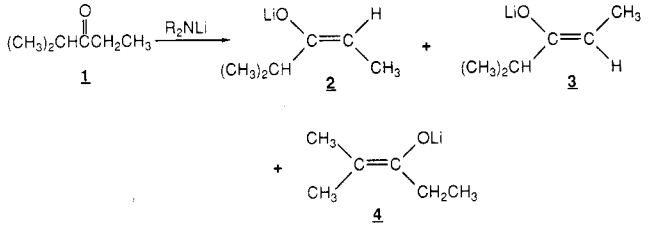
2-Methyl-3-pentanone, 2-methyl-3-pentanone-*2-d*, 2-methyl-3-pentanone-*4,4-d*$_2$, 3-methyl-2-butanone, and 3-methyl-2-butanone-*1,1,1-d*$_3$ have been treated with lithium dialkylamide bases (LDA, LDEA, and LTMP) in the dipolar aprotic solvents THF and DME, with and without added HMPA. Ratios of the product enolates were determined by quenching with trimethylsilyl chloride followed by GC analysis. Isotope effects calculated from these product ratios are all appreciable, k_H/k_D = 2.3–5.9 at 0 °C, but below the "maximum" of ca. 8.4 expected at this temperature. A reactant-like transition state is proposed. The temperature dependences of the isotope effects are abnormal (A_{aH}/A_{aD} = 1.6–3.2) without, but normal with, HMPA (A_{aH}/A_{aD} = 0.35–1.0). It is suggested that two or more different base species are active in proton removal and that the concentrations of these base species depend on temperature and solvent. Variations in the E/Z and regioisomer ratios are discussed in terms of models previously advanced by Ireland, Narula, and Dauben. It is concluded that different factors govern the E/Z and regioisomer ratios and that none of the models accounts satisfactorily for all of the observed variations.

When enolates are formed from ketones possessing two or more different α-hydrogens, the mixture formed under conditions of kinetic control often differs markedly in composition from the equilibrium mixture, usually in the direction of predominance of the thermodynamically less (or least) stable enolate. The synthetic utility of contrathermodynamic enolates was first demonstrated by Stork.[3] House showed that stable kinetically controlled mixtures of enolates could be produced by reaction of a ketone with a very strong base in a dipolar aprotic solvent such as tetrahydrofuran (THF) or dimethoxyethane (DME).[4-6] The most widely used bases have been lithium dialkylamides, especially lithium diisopropylamide (LDA). In spite of the synthetic importance of kinetic enolates,[7] there are few careful, quantitative studies in the literature of the reactions that produce them.

Our aims in studying these reactions were to provide extensive quantitative data on simple systems and to explore the mechanistic details of the reaction. We set out to determine deuterium isotope effects so as to establish whether, as has been widely assumed, kinetic enolate formation involves a simple, rate-determining attack of the base on an α-hydrogen of the ketone. For this purpose we chose a substrate that had been studied by House,[5] 2-methyl-3-pentanone (1), which yields the enolates **2**–**4**.



Direct kinetic studies were not feasible because the UV absorbance of the base obscures the weak absorbances of the ketone and the enolates, so a competitive method was adopted. The regiospecifically deuterated ketones, 1-*4,4-d*$_2$ and 1-*2-d*, were prepared as described in the Experimental Section. The ketones 3-methyl-2-butanone and 3-methyl-2-butanone-*1,1,1-d*$_3$ were also prepared, and their reactions to form enolates were briefly examined. The product ratio from **1** can be determined by treating the enolates with trimethylsilyl chloride and analyzing the resulting mixture of trimethylsilyl enol ethers by GC.[5] This process was repeated for 1-*2-d* and 1-*4,4-d*$_2$. The isotope effects were then calculated simply from the ratios of the appropriate product ratios for the unlabeled and labeled ketones. It was assumed that deprotonation of the unlabeled α-positions in 1-*2-d* and 1-*4,4-d*$_2$ occurs at the same rate as at the corresponding positions of **1**, an assumption that is probably good to within a few percent.

Appropriate control experiments were carried out. The total yield of enolates, determined by an internal standard, was almost always above 90% and dropped below 85% only in two instances. The deuterated ketones showed no protium in the labeled positions by NMR, and the trimethylsilyl enol ethers were shown by NMR to have suffered no exchange. To suppress any possible equilibration, the base concentration was always at least 3 times the ketone concentration. Under these conditions, the product ratios were the same whether the enolates were quenched immediately after reaction or up to 15 min later. The enol ether composition and yield remained constant for at least 24 h.

Some further comment on the importance of using excess base is desirable, for synthetic applications have frequently used little or no excess. Fataftah, Kopka, and Rathke, however, have reported $E \rightleftharpoons Z$ equilibration to be rapid in the presence of hexamethylphosphoric triamide (HMPA) and tetramethylethylenediamine (TMEDA) unless at least a 2-fold excess of base is used.[8] They proposed that the equilibration occurred via a reversible aldol condensation between enolate and unreacted ketone. The work of Corey and Gross on enolate formation in the presence and absence of trimethylsilyl chloride confirms the danger of equilibration.[9] We believe our control experiments demonstrate the absence of equilibration in any of our reactions, but this possibility should be kept in mind when interpreting literature data.

(1) This work was supported by the National Science Foundation.
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Table I. Trimethylsilyl Enol Ether Product Ratios and Isotope Effects for Enolate Formation from 3-Methyl-2-butanone at 0 °C

ketone[a]	base/solvent[b]	$P/T^{c,d}$	$(k_H/k_D)^d$
H	LDA/THF	132.0 ± 11.4	
1,1,1-d$_3$	LDA/THF	42.2 ± 0.4	3.29 ± 0.44
H	LDEA/THF	191.9 ± 14.1	
1,1,1-d$_3$	LDEA/THF	58.3 ± 3.5	3.13 ± 0.30
H	LDA/DME	254.9 ± 18.8	
1,1,1-d$_3$	LDA/DME	38.7 ± 0.7	5.87 ± 1.12

[a] H = 3-methyl-2-butanone, *1,1,1-d*$_3$ = 3-methyl-2-butanone-*1,1,1-d*$_3$. [b] LDA = lithium diisopropylamide, LDEA = lithium diethylamide, THF = tetrahydrofuran, DME = dimethoxyethane. [c] Product from reaction at primary vs tertiary α-hydrogen. Mean values of two to five runs, each run analyzed four to six times. [d] Deviations are standard deviations of the mean.

Table II. Trimethylsilyl Enol Ether Product Ratios for Enolate Formation from 2-Methyl-3-pentanone at 0 °C

ketone[a]	base/solvent[b]	$E/Z^{c,d}$	$(E + Z)/T^{d,e}$	% yield[d,f]
H	LDA/THF	1.595 ± 0.033	10.37 ± 0.17	92.6 ± 0.4
2-d		1.544 ± 0.024	39.92 ± 2.75	91.7 ± 0.5
4,4-d$_2$		2.076 ± 0.015	3.086 ± 0.013	95.5 ± 1.6
H	LDA/THF-HMPA	1.325 ± 0.027	10.01 ± 0.40	89.0 ± 2.4
2-d		1.336 ± 0.019	41.66 ± 0.92	94.4 ± 0.3
4,4-d$_2$		1.946 ± 0.013	2.531 ± 0.022	93.7 ± 2.5
H	LDA/DME	1.885 ± 0.015	9.18 ± 0.43	93.0 ± 2.5
2-d		1.930 ± 0.017	39.56 ± 4.36	94.3 ± 1.4
4,4-d$_2$		2.327 ± 0.008	2.656 ± 0.009	94.8 ± 2.5
H	LDA/DME-HMPA	1.405 ± 0.006	11.37 ± 0.15	93.2 ± 0.7
2-d		1.464 ± 0.005	49.80 ± 1.65	97.3 ± 0.1
4,4-d$_2$		1.907 ± 0.039	2.577 ± 0.026	94.8 ± 0.8
H	LDEA/THF	0.257 ± 0.001	11.25 ± 0.15	83.4 ± 1.1
2-d		0.268 ± 0.001	34.13 ± 0.55	85.4 ± 0.3
4,4-d$_2$		0.230 ± 0.002	4.830 ± 0.020	76.9 ± 2.1
H	LTMP/THF	3.952 ± 0.052	17.33 ± 0.23	93.8 ± 1.2
2-d		3.757 ± 0.018	62.92 ± 1.13	95.2 ± 1.5
4,4-d$_2$		5.829 ± 0.060	5.393 ± 0.031	95.8 ± 1.4

[a] H = 2-methyl-3-pentanone, *2-d* = 3-methyl-2-pentanone-*2-d*, *4,4-d*$_2$ = 2-methyl-3-pentanone-*4,4-d*$_2$. [b] LDA = lithium diisopropylamide, LDEA = lithium diethylamide, LTMP = lithium tetramethylpiperidide, THF = tetrahydrofuran, DME = dimethoxyethane, HMPA = hexamethylphosphoric triamide. [c] *E* enol ether/*Z* enol ether from reaction at secondary α-hydrogen. [d] Mean values of two to three runs, each run analyzed three to four times. Deviation is standard deviation of the mean. [e] Product from reaction at secondary vs tertiary α-hydrogen. [f] Determined by GC with a *m*-xylene internal standard.

Previous work on the deprotonation of **1** by LDA in DME (dimethoxyethane) at 0 °C gave 53% **2**, 42% **3**, and 5% **4**, in marked contrast to the results obtained by equilibrating the trimethylsilyl enol ethers with triethylammonium chloride in DMF at 130 °C (6% **2**, 31% **3**, 63% **4**).[5] Other equilibration procedures gave qualitatively similar results. Our product ratios for a variety of solvent-base systems and temperatures are reported in Tables II, IV, and V. We will discuss them in more detail below. At the present we simply compare our findings with the earlier results[5] on the reaction of **1** with LDA in DME at 0 °C. Our results, expressed in percentages, are 58.9% **2**, 31.3% **3**, and 9.8% **4**. The qualitative agreement is not bad, but the *E*/*Z* ratios differ considerably (1.9 in our case, 1.3 in theirs). The earlier workers used only a 0.2% excess of base,[5] raising the possibility of partial $E \rightleftharpoons Z$ equilibration.

We turn now to the isotope effects for 2-methyl-3-pentanone and 3-methyl-2-butanone, Tables I, III, and VI, which serve to establish a crucial mechanistic point. Collectively they show that for both ketones, all the solvent/base combinations, and all the temperatures we have studied, proton transfer is at least mainly (and probably entirely) rate controlling. We had previously reported that the formation of **2** and **3** in the reaction of **1** with LDA in THF occurred with a negligibly small isotope effect.[10] Inability to repeat this finding, both by the present (H. P.B., L.X.) and earlier (D.J.M.) workers, have convinced us that it is in error.[11] All workers now agree that the true

Table III. Isotope Effects for Enolate Formation from 2-Methyl-3-pentanone at 0 °C

base/solvent[a]	$(k_H/k_D)_{E+Z}^{b,c}$	$(k_H/k_D)_E^{c,d}$	$(k_H/k_D)_Z^{c,e}$	$(k_H/k_D)_T^{c,f}$
LDA/THF	3.36 ± 0.06	3.06 ± 0.07	3.98 ± 0.07	3.85 ± 0.27
LDA/THF-HMPA	3.96 ± 0.16	3.41 ± 0.12	5.02 ± 0.25	4.16 ± 0.19
LDA/DME	3.46 ± 0.16	3.23 ± 0.16	3.98 ± 0.17	4.31 ± 0.52
LDA/DME-HMPA	4.41 ± 0.07	3.95 ± 0.06	5.33 ± 0.15	4.38 ± 0.16
LDEA/THF	2.33 ± 0.03	2.54 ± 0.04	2.27 ± 0.03	3.03 ± 0.06
LTMP/THF	3.21 ± 0.05	3.00 ± 0.05	4.43 ± 0.03	3.63 ± 0.08

[a] See footnote *a*, Table II. [b] Weighted average for reaction at CH_2 group (4-position). [c] Deviation calculated from standard deviations of the mean for the product ratios. [d] For formation of *E* enolate. [e] For formation of *Z* enolate. [f] For reaction at CH group (2-position).

Table IV. Trimethylsilyl Enol Ether Product Ratios for Enolate Formation from 2-Methyl-3-pentanone and LDA in THF

ketone[a]	*T*, °C[b]	$E/Z^{c,d}$	$(E + Z)/T^{d,e}$	% yield[d,f]
H	0.00	1.431 ± 0.014	9.814 ± 0.179	93.0 ± 1.1
2-d		1.567 ± 0.019	41.02 ± 1.30	94.1 ± 2.0
4,4-d$_2$		1.992 ± 0.007	3.291 ± 0.025	89.9 ± 1.1
H	−12.50	1.470 ± 0.037	9.976 ± 0.190	91.0 ± 1.9
4,4-d$_2$		2.087 ± 0.103	3.277 ± 0.041	88.8 ± 1.0
H	−25.00	1.528 ± 0.177	10.03 ± 0.39	92.2 ± 2.0
2-d		1.716 ± 0.007	44.15 ± 1.15	95.3 ± 0.4
4,4-d$_2$		2.150 ± 0.144	3.276 ± 0.050	86.2 ± 2.0
H	−37.50	1.579 ± 0.044	9.788 ± 0.133	89.8 ± 1.1
2-d		1.820 ± 0.018	46.78 ± 2.74	92.1 ± 2.3
4,4-d$_2$		2.239 ± 0.056	3.073 ± 0.013	89.7 ± 1.8
H	−50.0	1.677 ± 0.023	9.719 ± 0.087	91.7 ± 2.1
2-d		1.862 ± 0.033	49.74 ± 2.61	94.1 ± 1.5
4,4-d$_2$		2.222 ± 0.057	2.970 ± 0.020	90.7 ± 1.3
H	−79.0	1.733 ± 0.030	9.248 ± 0.168	93.9 ± 0.8
2-d		1.701 ± 0.040	48.33 ± 1.68	96.1 ± 1.2
4,4-d$_2$		2.094 ± 0.069	2.667 ± 0.012	92.0 ± 1.2

[a] See footnote *a*, Table II. [b] Maintained by a refrigerated ethanol bath, except for −79.0 °C, which was maintained by dry ice–acetone. Kept within ±0.05 °C, except ±0.2 °C for −50.0 and −79.0 °C. [c–f] See corresponding footnotes, Table II.

Table V. Trimethylsilyl Enol Ether Product Ratios for Enolate Formation from 2-Methyl-3-pentanone and LDA in THF-HMPA[g]

ketone[a]	*T*, °C[b]	$E/Z^{c,d}$	$(E + Z)/T^{d,e}$	% yield[d,f]
H	0.00	1.262 ± 0.040	9.412 ± 0.260	89.8 ± 0.5
4,4-d$_2$		1.821 ± 0.104	2.887 ± 0.069	89.4 ± 2.1
H	−12.50	1.098 ± 0.043	10.13 ± 0.34	85.9 ± 1.7
4,4-d$_2$		1.598 ± 0.064	2.788 ± 0.130	87.9 ± 1.2
H	−25.00	0.850 ± 0.014	11.34 ± 0.45	92.0 ± 1.4
4,4-d$_2$		1.438 ± 0.001	2.786 ± 0.008	87.9 ± 0.3
H	−37.00	0.662 ± 0.010	14.61 ± 0.72	90.3 ± 1.3
4,4-d$_2$		1.211 ± 0.065	3.064 ± 0.096	85.8 ± 2.2
H	−47.0	0.550 ± 0.016	16.52 ± 0.85	91.3 ± 4.7
4,4-d$_2$		1.031 ± 0.044	3.305 ± 0.164	86.9 ± 2.6
H	−80.0	0.364 ± 0.004	11.42 ± 0.41	87.6 ± 0.4
4,4-d$_2$		0.659 ± 0.027	3.158 ± 0.060	88.1 ± 1.3

[a–f] See corresponding footnotes, Table IV. [g] Molar ratio of LDA to ketone 3:1; molar ratio of HMPA to LDA 1:1.

(10) Miller, D. J.; Saunders, W. H., Jr. *J. Org. Chem.* **1982**, *47*, 5039–5041.

Table VI. Isotope Effects for Enolate Formation from 2-Methyl-3-pentanone and LDA in THF and THF-HMPA[g]

HMPA	T, °C[a]	$(k_H/k_D)_{E+Z}$[b,c]	$(k_H/k_D)_E$[c,d]	$(k_H/k_D)_Z$[c,e]	$(k_H/k_D)_T$[c,f]
no	0.0	2.98 ± 0.06	2.64 ± 0.05	3.67 ± 0.08	4.18 ± 0.15
no	−12.5	3.04 ± 0.07	2.68 ± 0.07	3.80 ± 0.18	–
no	−25.0	3.06 ± 0.13	2.71 ± 0.23	3.82 ± 0.26	4.40 ± 0.21
no	−37.5	3.18 ± 0.04	2.81 ± 0.05	4.02 ± 0.12	4.77 ± 0.29
no	−50.0	3.27 ± 0.04	2.98 ± 0.05	3.94 ± 0.08	5.11 ± 0.27
no	−79.0	3.47 ± 0.06	3.25 ± 0.08	3.92 ± 0.11	5.22 ± 0.20
yes	0.0	3.26 ± 0.12	2.82 ± 0.05	4.06 ± 0.30	–
yes	−12.5	3.63 ± 0.21	3.09 ± 0.18	4.50 ± 0.32	–
yes	−25.0	4.07 ± 0.16	3.17 ± 0.12	5.37 ± 0.24	–
yes	−37.0	4.77 ± 0.28	3.47 ± 0.17	6.33 ± 0.50	–
yes	−47.0	5.00 ± 0.24	3.50 ± 0.16	6.54 ± 0.62	–
yes	−80.0	3.62 ± 0.15	2.42 ± 0.12	4.40 ± 0.18	–

[a] See footnote *b*, Table V. [b–f] See corresponding footnotes, Table III. [g] See footnote *g*, Table V.

k_H/k_D for formation of **2** + **3** is near 3.3 at 0 °C.

To test the possibility that the discrepancy arises from differences in experimental conditions, we varied the ratio diisopropylamine:BuLi over the range 1:1 to 3:1, and the ratio LDA:ketone over the range 3:1 to 5:1. Neither of these factors causes k_H/k_D to vary by more than experimental error. We are not sure of the cause of the error. One possibility lies in the GC procedure for analyzing the mixture of enol ethers. The earlier analysis used a packed 12 ft × 0.125 in. column of 5% SF-96 on Chromosorb P, while the present analysis used a J & W Scientific Model DB-1 30 m × 0.53 mm i.d. capillary column with a nonpolar methyl silicone stationary phase. The superior resolving power of the capillary column revealed minor impurities that were not resolved from the enol ethers by the packed column. In addition, the broader and less symmetrical peak shapes of chromatograms from the packed column could be expected to affect adversely the accuracy with which the HP 3380A recorder performed integrations.

The isotope effects in Table III are all substantial, but there are no striking trends. Somewhat larger k_H/k_D values are found for attack at the methinyl (T) hydrogen than for attack at the methylene (E + Z) hydrogens, and for formation of the Z isomer than for the E. The differences could arise from small variations in zero-point energy or tunneling effects and are scarcely large enough to merit further attempts at interpretation.

It should be noted, however, that none of the k_H/k_D values is as large as the normally expected maximum. An often-quoted figure is k_H/k_D = 7 at 25 °C. This figure is rather elastic, for it can be raised by loosened bending vibrations or by tunneling and lowered by an unsymmetrically located proton in the transition state, a nonlinear proton transfer, or heavy-atom motion in the reaction coordinate.[12] It can, of course, also be lowered when proton transfer is not wholly rate controlling. Nonetheless, k_H/k_D = 7 near room temperature is in a commonly observed range (ca. 6–8) for isotope effects, and it corresponds (assuming exponential temperature dependence) to k_H/k_D = 8.4 at 0 °C. That our values are all well below this figure suggests the consistent operation of some lowering effect. Incomplete rate control by proton transfer seems unlikely, for our isotope effects remain in a relatively narrow range over wide variations in conditions and temperatures. A likely possibility is an unsymmetrically located proton in the transition state. Maxima in k_H/k_D due to a symmetrically located proton in the transition state are expected when the pK_a's of the proton donor and the conjugate acid of the acceptor are approximately equal.[12,13] But diisopropylamine is a substantially weaker acid (pK_a 35.7 in THF)[14,16] than simple ketones (pK_a ~27 in DMSO).[15,16] Consequently, the proton is expected to be less than half transferred in the transition state. A relatively reactant-like transition state would also be consistent with the fact that product ratios are not usually determined by product stabilities.

Table VII. Arrhenius Parameter for the Isotope Effects for Enolate Formation for 2-Methyl-3-pentanone and LDA in THF and THF-HMPA[a]

HMPA[b]	k_H/k_D for[c]	A_{aH}/A_{aD}	$E_{aD} - E_{aH}$[d]
no	E + Z	2.04 ± 0.06	0.207 ± 0.013
no	E	1.55 ± 0.07	0.292 ± 0.020
no	Z	3.25 ± 0.32	0.080 ± 0.045
no	T	1.66 ± 0.25[e]	0.492 ± 0.072[e]
yes	E + Z	0.38 ± 0.07[f]	1.166 ± 0.086[f]
yes	E	1.02 ± 0.18[f]	0.562 ± 0.085[f]
yes	Z	0.35 ± 0.10[f]	1.341 ± 0.140[f]

[a] The results of least-squares fits of data from Table VI to the Arrhenius equation. Deviations are standard deviations. [b] See footnote *g*, Table V. [c] See footnotes *b*, *d*, *e*, and *f*, Table III. [d] In kcal mol^{-1}. [e] Isotope effect at −79 °C omitted. [f] Isotope effect at −80 °C omitted.

Although it is clear that proton transfer is part of the rate-determining step, examination of the temperature dependences of the isotope effects reveals interesting anomalies. Isotope effects from 0 to −80 °C for reactions with LDA–THF and LDA–THF/HMPA are recorded in Table VI, and the results of fitting these data to the Arrhenius equation are given in Table VII. In some cases the points below −50 °C fell distinctly off the line defined by the other points and were omitted in the least-squares fits. If we focus attention first on the reactions without added HMPA, it is clear that all of the A_{aH}/A_{aD} values are well above unity.

The transition-state theory of isotope effects predicts that A_{aH}/A_{aD} should usually be close to unity in the absence of tunneling.[19] Values below 0.7–0.9 are ascribable

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(16) Although these figures refer to two different solvents, the difference is unlikely to affect ΔpK by more than 1–2 pK units.[17] The figures are in any event only semiquantitatively correct. Ion-pair acidities involving aggregated species such as enolates or dialkylamides are concentration dependent.[18]

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(18) Kaufman, M.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 6092–6097.

(19) Reference 12, pp 24–28, 73–74, 144–147.

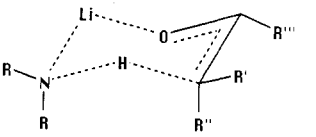
to tunneling. The absolute upper limit is 1.4, and values approaching this figure are expected only at very high temperatures. The first four entries in Table VII are thus all decidedly abnormal. The only circumstance under which such anomalies can be consistent with transition-state theory is when A_{aH}/A_{aD} is a composite value reflecting two or more competing processes.[20]

Evidence that the anomalies do arise from mechanistic complexities is afforded by the last three entries of Table VII. All of these values are in the normal range if there is a moderate contribution from tunneling. Dipolar aprotic additives such as HMPA appear to act by breaking up ion-pair aggregates.[21] The difference between the reactions without and with HMPA, then, probably lies in the nature of the base species responsible for proton abstraction.

Cryoscopic measurements show that LDA exists as a mixture of monomer and dimer in THF at −108 °C.[22] Evidence on its state of aggregation at higher temperatures is lacking, but lithium hexamethyldisilazide in THF is also a mixture of monomer and dimer, and the proportion of dimer increases with increasing temperature.[23] It seems reasonable to suppose that the dimer of LDA, and perhaps higher aggregates, might become predominant species in THF solutions as the temperature is raised. Sterically bulkier bases tend to give larger k_H/k_D values with a given substrate. 2,6-Disubstituted pyridines, for example, give much larger k_H/k_D values than other alkylpyridines in the deprotonation of 2-nitropropane.[24]

If in our reactions the isotope effect is larger the higher the state of aggregation of the base, and if the state of aggregation of the base increases with increasing temperature, the normal tendency of the isotope effect to decrease as the temperature rises will be partly counteracted, and an attenuated temperature dependence will be observed. The isotope effects without HMPA in Table VI do change more gradually with temperature than predicted for the usual exponential temperature dependence, and thus lead to the abnormally large A_{aH}/A_{aD} values of Table VII. Note that two or more base species must be contributing in changing proportions to the overall reaction as the temperature changes. Normal temperature dependence should result if only a single base species is reactive, regardless of how many are present in the reaction mixture. In this picture, then, HMPA shifts the aggregation equilibrium of the base such that a single species (probably monomer) predominates over the entire temperature range. The failure of the point at −80 °C to fall on the Arrhenius plot (compare last two lines of Table VI) may indicate that the situation becomes more complex at very low temperatures.

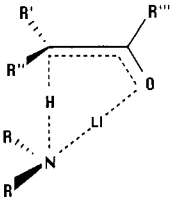
The picture of the reaction that emerges from these considerations is of a rate-determining proton transfer that may involve more than a single base species, the exact nature of the base species in any given case depending on base, solvent, solvent additives, and temperature. There is no need to postulate a discrete intermediate,[10] but it is still quite possible that the rate-determining transition state involves interaction of the substrate with both positive and negative regions of the base. The model proposed by Ireland involved such interactions and has been widely used to predict and explain product compositions.[25,26] For reaction between R_2NLi and R′R″CHCOR‴, it may be depicted as **5**. In this model both E/Z and regioisomer



5

ratios can be rationalized as resulting from a balance of steric interactions between R and R″ (or R′) on the one hand, and R‴ and R′ (or R″) on the other, where R′ and R″ can be H, alkyl, or aryl. Because there is $E \rightleftharpoons Z$ equilibration in the presence of HMPA,[8] Ireland's explanation of the results under these conditions is not applicable. The kinds of steric interactions he postulates for the absence of HMPA, however, are still reasonable. The model does have the unrealistic features of a nonlinear proton transfer, and a less-than-optimum alignment of the breaking C–H bond and the π-orbital of the carbonyl group.

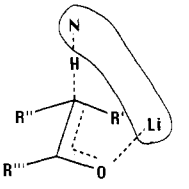
A variant proposed by Narula remedies these deficiencies.[27] It may be pictured as **6** (a slight modification of Narula's formulation to emphasize the common features of **5** and **6**). Narula postulates that the Li coordinates



6

either with a nonbonding orbital on oxygen or the π-orbital of the carbonyl group, depending on the bulk of R‴. Actually the lithium–oxygen interaction is probably so ionic that the lithium can adopt whatever position is necessary to give the best balance of repulsive and attractive interactions with other atoms.

A still more recent model by Moreland and Dauben recognizes the aggregated nature of the base and utilizes molecular mechanics to calculate the energies of transition states.[28] It may be pictured as **7**, where the region enclosed



7

by a solid line represents the base aggregate. Again, both E/Z and regioisomer ratios can be interpreted as arising from steric interactions of the different R groups with each other, on the one hand, and with the aggregate on the other. A common feature of all of the models is that the same kinds of steric interactions control both E/Z and regioisomer ratios.

An examination of our product ratios (Table II) reveals trends not adequately accommodated by any of these models. For the first five solvent-base systems in the table,

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Table VIII. Arrhenius Parameters for the Product Ratios for Enolate Formation from 2-Methyl-3-pentanone and LDA in THF and THF-HMPA[a]

HMPA[b]	A_{aE}/A_{aZ}	$E_{aZ} - E_{aA}$[c]	A_{aS}/A_{aT}[d]	E_{aT}/E_{aS}[c,d]
no	0.71 ± 0.03	0.37 ± 0.02	10.72 ± 0.89	−0.04 ± 0.04
yes	81.0 ± 14.9	−2.25 ± 0.09	0.52 ± 0.17	1.55 ± 0.16

[a] The results of least-squares fits of data from Tables IV and V to the Arrhenius equation (0 to −50 °C without HMPA, 0 to −47 °C with HMPA). Deviations are standard deviations. [b] See footnote *g*, Table V. [c] In kcal mol^{-1}. [d] *S* refers to reaction at the CH_2 group (4-position) and *T* to attack at the CH group (2-position).

the E/Z ratio ranges from 0.257 to 1.885 with the unlabeled ketone, while the $(E + Z)/T$ ratio remains almost constant (9.18–11.37). Only when the base is changed to LTMP do E/Z and $(E + Z)/T$ both show substantial increases. The temperature dependences of the product ratios for reaction with LDA in THF further support the idea that E/Z and $(E + Z)/T$ are not determined by the same mix of factors. Without HMPA (Table IV), the E/Z ratio increases with decreasing temperature, while the $(E + Z)/T$ ratio is essentially independent of temperature. Thus, the former is controlled by activation energy differences and the latter by activation entropy differences (Table VIII). With HMPA (Table V) E/Z *decreases* markedly with decreasing temperature, while $(E + Z)/T$ *increases* (but note the reversal from −47 to −80 °C). In both of these cases, there is a sizable difference in activation energies. It should be kept in mind that apparent activation energies and entropies may be composite values if our postulate that two or more base species contribute to proton abstraction is correct. Thus, detailed interpretation will require a better understanding of the systems than we now have. The results do suggest consideration of temperature as a variable in efforts to achieve improved selectivity in synthetic applications.

We also explored briefly the reaction of 3-methyl-2-butanone with LDA and LDEA (Table I). All three of the reactions give isotope effects comparable to those found with 2-methyl-3-pentanone. There is a strong preference for attack at methyl (*P*) over methinyl (*T*). Steric effects are not dominant, as shown by a greater P/T ratio for LDEA/THF than for LDA/THF. The solvent change alone, from LDA/THF to LDA/DME, causes a still greater change in P/T.

We are unable, with the information now available, to propose explanations that account for all of the effects on product ratios. Models **5–7**, while useful in rationalizing major changes in steric requirements of the base and ketone, obviously ignore other factors that are important in determining product ratios. We are continuing our investigations in the hope of sorting out the more important of these factors.

Experimental Section

General. Glassware, syringes, and needles were dried at 140 °C and allowed to cool under dry nitrogen. All manipulations involving moisture-sensitive reagents and solvents were carried out under a positive pressure of prepurified nitrogen with standard syringe–septum and anaerobic techniques.[29,30] Analytical and preparative gas chromatography were performed on Hewlett-Packard 5730A (flame ionization detector) and 5700A (thermal conductivity detector) instruments, respectively. Quantitative analyses utilized a Hewlett-Packard 3380A computing digital integrator. UV–visible spectra were recorded on a Varian DMS-200 spectrophotometer. ^{1}H NMR spectra were recorded on Varian EM-390, Nicolet QE-300, or Bruker WH-400 instruments. Mass spectra were obtained on a VG 7035 instrument. Low-temperature reactions (0 to −50 °C) utilized a heavily insulated 4.5-L bath filled with 99% ethanol and equipped with a Braun Thermomix Model 1450 thermoregulator and a Neslab Model CC-60 Cryocool unit with a flexible immersion cooling probe. The bath was magnetically stirred. A dry ice–acetone bath was used for −79 °C.

Solvents and Reagents. Diethylene glycol dibutyl ether was dried over lithium aluminum hydride and distilled from lithium aluminum hydride under vacuum (bp 93 °C (1 mm)) immediately prior to use.[31] 1,2-Dimethoxyethane (Baker reagent grade) was refluxed over and distilled from lithium aluminum hydride. It was then refluxed over sodium–potassium alloy and benzophenone in a solvent still,[32] and the desired amount of dry solvent distilled from the deep purple solution immediately prior to use. Dimethylformamide (Baker reagent grade) was dried over 3A molecular sieves immediately prior to use. Hexamethylphosphoramide was dried over calcium hydride, distilled under vacuum (bp 89 °C (1 mm)), and stored over 3A molecular sieves under a nitrogen atmosphere. Tetrahydrofuran (Baker reagent grade) was dried over 3A molecular sieves and then refluxed over sodium–potassium alloy and benzophenone,[32] and the desired amount of solvent was distilled from the deep purple solution immediately prior to use. Acetone was dried over potassium carbonate immediately prior to use. *n*-Butyllithium (Aldrich) was titrated against diphenylacetic acid.[33] At least two titrations were performed on each bottle, and the results were averaged. Diethylamine (Aldrich) was refluxed over calcium hydride, and the desired amount was distilled immediately prior to use. Diisopropylamine (Aldrich) and triethylamine (Aldrich) were purified in the same way. 2,2,6,6-Tetramethylpiperidine (Aldrich) was dried over calcium hydride, distilled under reduced pressure (bp 52 °C (25 mm)), and stored over potassium hydroxide under nitrogen. Isoamyl acetate (Baker reagent grade) was distilled under reduced pressure (bp 45 °C (25 mm)) and dried over potassium carbonate immediately prior to use. 2-Methyl-2-butanone (Aldrich) was fractionated on a spinning-band column, dried over calcium sulfate, and stored over 3A molecular sieves under nitrogen. 2-Methyl-3-pentanone was purified by preparative gas chromatography on a 10 ft × 0.25 in. column packed with 30% SF-96 on Chromosorb W-NAW, 40–60 mesh, column and reference flow rates 60 and 30 mL min^{-1}, respectively, at 60 psi of helium. Column, injector, and detector temperatures were 75, 150, and 150 °C, respectively, and 0.1-mL samples were injected each time. The collected ketone was dried and stored over 3A molecular sieves. 2-Methylpropionaldehyde was fractionated and dried over calcium sulfate immediately prior to use. Propionaldehyde was purified in the same way. Trimethylsilyl chloride was dried over calcium hydride and distilled from calcium hydride immediately prior to use.

2-Alkyl-1,3-dithianes were prepared according to the procedure of Corey and Seebach.[34] 2-Methylpropionaldehyde (0.36 mol) and 1,3-propanedithiol (0.36 mol) gave 76% of 2-(2-propyl)-1,3-dithiane, bp 63–67 °C (1 mm) (lit.[37] bp 134 °C (35 mm)). ^{1}H NMR ($CDCl_3$): δ 1.1 (6 H, d), 1.7–2.3 (3 H, m), 2.85 (4 H m), 4.0 (1 H, d). Propionaldehyde (0.36 mol) and 1,3-propanedithiol (0.36 mol) gave 72% of 2-ethyl-1,3-dithiane, bp 56–60 °C (1 mm) (lit.[34] bp 91 °C (10 mm)). ^{1}H NMR ($CDCl_3$): δ 1.1 (3 H, t), 1.8–2.3 (4 H, m), 2.8 (4 H, m), 4.05 (1 H, t).

α-Deuterated alcohols were obtained by the reduction of the appropriate substrates with lithium aluminum deuteride (Aldrich 98%) according to the procedure of Friedman and Jurewicz.[31] Isoamyl acetate (0.12 mol) and lithium aluminum deuteride (0.12 mol) gave 88% of ethanol-*1,1*-d_2, bp 78–79 °C. ^{1}H NMR ($CDCl_3$):

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δ 1.22 (3 H, s), 2.1 (1 H, s). MS: *m/e* 48 (20), 46 (28), 33 (100). Acetone (0.24 mol) and lithium aluminum deuteride (0.12 mol) gave 69% of 2-propanol-*2-d*, bp 81–82 °C. ^{1}H NMR ($CDCl_3$): δ 1.15 (6 H, s), 1.62 (1 H, s). MS: *m/e* 61 (2), 59 (23), 46 (100).

α-Deuterated alkyl iodides were prepared by the procedure of Landauer and Rydon.[35] The reaction was followed by periodic removal of small samples. Then ^{1}H NMR spectra were examined for the peaks due to the disappearing alcohol and the forming iodide. The product was distilled from the reaction mixture by progressively reducing the pressure from 25 to 0.5 mm and collecting the distillate in a receiver cooled by liquid nitrogen. The distillate was washed once with water, twice with aqueous sodium thiosulfate, and once more with water and dried over potassium carbonate. It was then filtered, dried over 3A molecular sieves, and stored over 3A molecular sieves and copper wire under nitrogen. Ethanol-*1,1-*d_2 (0.094 mol) and methyltriphenoxyphosphonium iodide (0.095 mol) reacted in 1 h at 25 °C to give 54% of ethyl-*1,1-*d_2 iodide. ^{1}H NMR ($CDCl_3$): δ 1.79 (3 H, s). 2-Propanol-*2-d* (0.041 mol) and methyltriphenoxyphosphonium iodide (0.042 mol) reacted in 5 h at 30 °C to give 47% of 2-propyl-*2-d* iodide. ^{1}H NMR: δ 1.85 (6 H, s).

Alkylation of 2-alkyl-1,3-dithianes followed the procedure of Corey and Seebach.[34] The extent of deprotonation by butyllithium of the dithiane was checked at 2-h intervals by removing a 2-mL aliquot of the reaction mixture and quenching with 2 mL of 99.8% D_2O. The solution was extracted with 15 mL of chloroform, the extract was dried over potassium carbonate and filtered, and the solvent was removed under reduced pressure on a rotary evaporator. The residue was taken up in $CDCl_3$, and residual protium in the 2-position was determined by comparison of its NMR absorption with that of any other well defined peak(s). When the dithiane was >95% deprotonated, the mixture was cooled to −78 °C, the desired deuterated alkyl iodide was added slowly, and the mixture was left standing at −78 °C for 1 h. It was then warmed to room temperature, poured into three volumes of water, and extracted three times with $CHCl_3$. The organic layers were combined and washed twice with 10% potassium hydroxide, once with water, and once with saturated sodium chloride and dried over potassium carbonate. The solution was filtered, concentrated on a rotary evaporator to remove solvent, and distilled under vacuum. 2-(2-Propyl)-1,3-dithiane (0.031 mol) and *n*-butyllithium (.032 mol) gave an anion, which was alkylated with methyl-*1,1,1-*d_3 iodide (Aldrich 99%) to give 92% of 2-(2-propyl)-2-methyl-*1,1,1-*d_3-1,3-dithiane, bp 80–85 °C (1 mm) (lit.[34] bp 60 °C (0.3 mm)). ^{1}H NMR ($CDCl_3$): δ 1.1 (6 H, d), 1.8–2.4 (3 H, m), 2.85 (4 H, m). MS: *m/e* 179 (10), 136 (100). 2-(2-Propyl)-1,3-dithiane (0.045 mol) and *n*-butyllithium (0.049 mol) gave an anion, which was alkylated with ethyl-*1,1-*d_2 iodide (0.049 mol) to give 88% of 2-(2-propyl)-2-ethyl-*1,1-*d_2-1,3-dithiane, bp 67–70 °C (0.3 mm) (lit.[38] bp 58 °C (0.3 mm)). ^{1}H NMR ($CDCl_3$): δ 0.92 (3 H, s), 1.05 (6 H, d), 1.7–2.0 (2 H, m), 2.1 (1 H, m), 2.8 (4 H, m). MS: *m/e* 192 (6), 161 (14), 149 (100). 2-Ethyl-1,3-dithiane (0.015 mol) and *n*-butyllithium (0.018 mol) gave an anion, which was alkylated with 2-propyl-2-d iodide (0.018 mol) to give 2-ethyl-2-(2-propyl-*2-d*)-1,3-dithiane in 75% yield, bp 78–82 °C (0.6 mm) (lit.[38] bp 58 °C (0.3 mm)). ^{1}H NMR ($CDCl_3$): δ 0.97 (3 H, t), 1.07 (6 H, s), 1.8–2.0 (2 H, m), 2.1 (2 H, q), 2.8 (4 H, m). MS: *m/e* 191 (4), 162 (10), 147 (100).

Deuterated ketones were prepared according to the procedure of Corey and Erickson.[36] To a well-stirred mixture of $HgCl_2$ and HgO in 90 mL of an aqueous organic solvent was added dropwise over 30 min a solution of the dithiane (0.01–0.03 mol) in 30 mL of the organic solvent. The reaction mixture was refluxed for about 18 h. It was then cooled to room temperature, and the mercury salts were removed by suction filtration and washed with 400 mL of cold pentane/CH_2Cl_2 (1:1 v/v). The combined filtrates were diluted with three volumes of water. The organic layer was removed, washed twice with 5 M ammonium acetate and once with saturated NaCl, and then dried over $MgSO_4$. Most of the solvent was removed by distillation, and the product was isolated by further distillation or by preparative gas chromatography using a 10 ft × 0.25 in. column packed with 30% SF-96 on Chromosorb W-NAW, 40–60 mesh. Column and reference flow rates were 60 mL min^{-1} and 30 mL min^{-1} at 60 psi of He. All injections were 0.1 mL through a glass-lined port. Collections were made with a dry collecting tube immersed in dry ice/acetone and protected by a $CaSO_4$ drying tube.

3-Methyl-2-butanone-*1,1,1-*d_3 was obtained by hydrolyzing 0.028 mol of 2-(2-propyl)-2-methyl-*1,1,1-*d_3-1,3-dithiane in acetone/water (9:1 v/v) with 0.061 mol of $HgCl_2$ and 0.042 mol of HgO. Distillation through a short-path condenser gave 30% of product, bp 93–95 °C. ^{1}H NMR ($CDCl_3$): δ 1.1 (6 H, d), 2.6 (1 H, m).

4-Methyl-3-pentanone-*2,2-*d_2 was obtained by hydrolyzing 0.013 mol of 2-(2-propyl)-2-ethyl-*1,1-*d_2-1,3-dithiane in acetonitrile/water (4:1 v/v) with 0.027 mol of $HgCl_2$ and 0.016 mol of HgO. The product was isolated in 63% yield by preparative gas chromatography with column, injector, and detector temperatures of 75, 150, and 150 °C, respectively. ^{1}H NMR ($CDCl_3$): δ 0.99 (3 H, s), 1.05 (6 H, d), 2.57 (1 H, m).

2-Methyl-3-pentanone-*2-d*was obtained by hydrolyzing 0.0105 mol of 2-ethyl-2-(2-propyl-*2-d*)-1,3-dithiane in acetonitrile/water (4:1 v/v) with 0.022 mol of $HgCl_2$ and 0.013 mol of HgO. The product was isolated in 56% yield by preparative gas chromatography (conditions above). ^{1}H NMR ($CDCl_3$): δ 1.0 (3 H, t), 1.05 (6 H, s), 2.43 (2 H, q).

Trimethylsilyl enol ethers were prepared by the procedures of House et al.[5] The ethers from 2-methyl-3-pentanone have been previously reported by House et al.[5] Those from 3-methyl-2-butanone have been previously reported by Reetz et al.[39] Our NMR spectral data (below) are in agreement with those reported by the previous workers and with the assigned structures.

Method A. Lithium diisopropylamide was prepared by the addition of diisopropylamine to a stirred solution of *n*-butyllithium in THF at 0 °C and allowed to stand for 30 min before adding the ketone dropwise. After 15 min of stirring, trimethylsilyl chloride was added. The reaction mixture was poured into 100 mL of hexane, washed three times with saturated aqueous $NaHCO_3$ and once with saturated aqueous NaCl, and then dried over K_2CO_3. The solvents were removed under reduced pressure on a rotary evaporator, and the residue was purified by vacuum distillation or preparative gas chromatography.

Method B. A stirred solution of the ketone, triethylamine, and trimethylsilyl chloride in DMF was refluxed for 48 h. The mixture was cooled to room temperature, poured into 100 mL of hexane, and washed and dried and the product isolated as in method A.

((3-Methyl-1-buten-2-yl)oxy)trimethylsilane was prepared by method A from LDA (0.0075 mol) and 3-methyl-2-butanone (0.0058 mol) in 75 mL of THF, followed by quenching with trimethylsilyl chloride (0.0058 mol). The product was isolated by preparative gas chromatography with column, injector, and detector temperatures of 50, 100, and 100 °C, respectively (see Deuterated ketones above for other conditions). ^{1}H NMR ($CDCl_3$): δ 0.20 (9 H, s), 1.0 (6 H, d), 2.2 (1 H, m), 3.95 (2 H, d).

((3-Methyl-2-buten-2-yl)oxy)trimethylsilane was prepared by method B from 3-methyl-2-butanone (0.023 mol), triethylamine (0.058 mol), and trimethylsilyl chloride (0.032 mol) in 50 mL of DMF. The products were isolated by preparative gas chromatography (see above). The major product was ((3-methyl-2-buten-2-yl)oxy)trimethylsilane. ^{1}H NMR ($CDCl_3$): δ 0.015 (9 H, s), 1.56 (6 H, s), 1.75 (3 H, s). The minor product was ((3-methyl-1-buten-2-yl)oxy)trimethylsilane, identified by NMR but not collected in useful quantity.

(((*E,Z*)-2-Methyl-3-penten-3-yl)oxy)trimethylsilane was prepared by method A from LDA (0.061 mol) and 2-methyl-3-pentanone in 125 mL of THF, followed by quenching with trimethylsilyl chloride (0.061 mol). The residue was purified by preparative gas chromatography with column, injector, and detector temperatures of 60, 100, and 100 °C, respectively. The two major products were collected. The *E* isomer had ^{1}H NMR (C_6D_6): δ 0.36 (9 H, s), 1.25 (6 H, d), 1.69 (3 H, d), 2.89 (1 H, m), 4.74 (1 H, q). The *Z* isomer had ^{1}H NMR (C_6D_6): δ 0.36 (9 H, s), 1.24 (6 H, d), 1.78 (3 H, d), 2.34 (1 H, m), 4.74 (1 H, q of d). The minor product was identified by NMR as ((2-methyl-2-penten-3-yl)oxy)trimethylsilane.

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((2-Methyl-2-penten-3-yl)oxy)trimethylsilane was prepared by method B from 2-methyl-3-pentanone (0.050 mol), triethylamine (0.12 mol), and trimethylsilyl chloride (0.065 mol) in 125 mL of DMF. The products were isolated by preparative gas chromatography (see above). One major product was the desired ((2-methyl-2-penten-3-yl)oxy)trimethylsilane and was collected. ^{1}H NMR (C_6D_6): δ 0.35 (9 H, s), 1.26 (3 H, t), 1.75 (3 H, s), 1.88 (3 H, s), 2.29 (2 H, q). The other two products were identified by NMR as (((*Z*)- and (*E*)-2-methyl-3-penten-3-yl)oxy)trimethylsilane.

Product Ratios in Kinetic Enolate Formation. The base solution was prepared from (8.25–8.70) × 10^{-4} mol of amine and (7.5–8.70) × 10^{-4} mol of butyllithium in 5.0 mL of THF or DME and stirred for 30 min at 0 °C. When HMPA was used, an amount equivalent to the base (7.5 × 10^{-4} mol) was added, and the solution stirred a further 15 min at 0 °C. The ketone solution was prepared by dissolving (2.5–2.9) × 10^{-4} mol of ketone in 1.0 mL of THF or DME. All reactions were carried out in a 25-mL Schlenk tube fitted with a 14-mm rubber septum and equipped with a 6-mm magnetic stirring bar. Nitrogen was introduced by a syringe needle and vented to a mineral oil bubbler by another syringe needle. The base solution was stirred at the desired temperature for at least 15 min, and the ketone solution added dropwise over 5–10 min. The mixture was stirred for up to 15 min and quenched with trimethylsilyl chloride ((8.7–9.0) × 10^{-4} mol). The composition of the trimethylsilyl enol ether mixture was determined by gas chromatography. For the products from 3-methyl-2-butanone a 12 ft × 0.125 in. column of 10% SF-96 on Chromosorb W-AW-DMCS, 60–80 mesh, was used. The flow rate was 30 mL min^{-1} at 65 psi of helium. Column, injector, and detector temperatures were 55, 100, and 100 °C, respectively. Typical elution times were 15.5 min for ((3-methyl-1-buten-2-yl)oxy)trimethylsilane and 25 min for ((3-methyl-2-buten-2-yl)oxy)trimethylsilane. For the products from 2-methyl-3-pentanone a J & W Scientific DB-1 (cross-linked silicone) 30 m × 0.53 mm i.d. fused silica capillary column was used. The column flow rate was 8.0 mL min^{-1} at 60 psi of He, and the detector make-up flow rate was 22 mL min^{-1} at 60 psi of He. The column, injector, and detector temperatures were 35, 100, and 150 °C, respectively. Typical elution times were 28.5 min for ((*E*)-2-methyl-3-penten-3-yl)oxy)trimethylsilane, 35.0 min for the *Z* isomer, and 39.0 min for ((2-methyl-2-penten-3-yl)oxy)trimethylsilane. *m*-Xylene (elution time 17.0 min, response factor 1.409 ± 0.019 by weight) was used as an internal standard.

Control Experiments. That the enolates do not equilibrate was shown by two sets of experiments. First, the product ratios were the same whether the reactions mixtures were quenched just after completion of addition (<1 min) or up to 15 min later. Second, equilibration among regioisomers should introduce protium into the deuterated positions of the enolates and hence into the trimethylsilyl ethers derived from them. None was detected by ^{1}H NMR. The percent yields of trimethylsilyl ethers measured by internal standard are high (90.7 ± 5.9%) and independent of quench time. The compositions and yields of the trimethylsilyl enol ether mixtures remained constant for at least 24 h.

Registry No. 1, 565-69-5; 2 (TMS deriv), 19980-42-8; 3 (TMS deriv), 19980-41-7; 4 (TMS deriv), 19980-40-6; D_2, 7782-39-0; 2-methylpropionaldehyde, 78-84-2; 2-(2-propyl)-1,3-dithiane, 6007-25-6; propionaldehyde, 123-38-6; 2-ethyl-1,3-dithiane, 6007-23-4; isoamyl acetate, 123-92-2; ethanol-*1,1-d*$_2$, 1859-09-2; acetone, 67-64-1; 2-propanol-*2-d*, 3972-26-7; ethyl-*1,1-d*$_2$ iodide, 3652-82-2; 2-propyl-*2-d* iodide, 95927-03-0; methyl-*1,1,1-d*$_3$ iodide, 865-50-9; 2-(2-propyl)-2-(methyl-*1,1,1-d*$_3$)-1,3-dithiane, 119336-34-4; 2-(2-propyl)-2-(ethyl-*1,1-d*$_2$)-1,3-dithiane, 119336-35-5; 2-ethyl-2-(2-propyl-*2-d*)-1,3-dithiane, 119336-36-6; 3-methyl-2-butanone-*1,1,1-d*$_3$, 52809-75-3; 4-methyl-3-pentanone-*2,2-d*$_2$, 83682-04-6; 2-methyl-3-pentanone-*2-d*, 83682-03-5; (3-methyl-1-buten-2-yl-oxy)trimethylsilane, 17510-45-1; 3-methyl-2-butanone, 563-80-4; (3-methyl-2-buten-2-yloxy)trimethylsilane, 17510-44-0.

Conformational Analysis of 1,3,2-Oxazaphospholanes Derived from Ephedrine and Pseudoephedrine[1]

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A series of 1,3,2-oxazaphospholanes has been prepared and studied conformationally by ^{1}H NMR spectroscopy at 200 MHz. The NMR data are best interpreted in terms of conformational equilibria involving twist-envelope and half-chair conformations. The conformational preferences are such that small electronegative substituents (such as phenoxy) on phosphorus prefer a pseudoaxial position, whereas bulky phosphorus substituents prefer pseudoequatorial positions in these equilibria. These stereoelectronic effects generally result in twist-envelope conformations for these five-membered ring heterocycles to be favored over half-chair conformations. X-ray crystallographic analyses have been done on (2*S*,4*R*,5*R*)-2-phenoxy-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane (**3**), (2*S*,4*R*,5*R*)-2-(dimethylamino)-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane (**6**), and (2*S*,4*R*,5*S*)-2-phenoxy-2-oxo-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane (**9**). These X-ray crystal structures confirm our stereochemical assignments for these materials and support the conformational conclusions from the NMR studies.

Introduction

The five-membered ring, the most important ring in chemistry after the six-membered ring, has been extensively studied conformationally. The conformational properties of cyclopentane and substituted cyclopentanes[3] and saturated five-membered ring heterocycles[4] have been reviewed. Conformational analyses of these ring systems are usually discussed in terms of *envelope* (C_s) and *half-chair* (C_2) conformations.

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