Unusual Induced Isotope Effects in the Reaction of 2-Pentanone with Dialkylamide Bases. Evidence on the Nature of the Reactive Base Species[1]

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Abstract: The treatment of 2-pentanone and 2-pentanone-*1,1,1*-d_3 with various bases (3 mol/mol of ketone) in tetrahydrofuran (THF) or THF-hexamethylphosphoric triamide (HMPA) (3 mol/mol of base) gave enolate mixtures which were treated with trimethylsilyl chloride (TMSCl) to give trimethylsilyl enol ethers (80-100% yields, mostly >90%) for analysis by GC. The bases were lithium diisopropylamide (LDA), lithium hexamethyldisilazide (LHMDS), and lithium tetramethylpiperidide (LTMP). Isotope effects for attack at methyl, calculated from product ratios, showed a variety of temperature dependences: normal (A_{aH}/A_{aD} = 0.6-0.8, all reactions in THF-HMPA) to temperature independent (k_H/k_D and A_{aH}/A_{aD} = 2.8-2.9, LDA in THF) to inverse (A_{aH}/A_{aD} = 12.3, LTMP in THF). The Z/E ratios for (2-pentenyl-2-oxy)trimethylsilane ranged from 0.062 (LTMP in THF, -40 °C) to 67 (LHMDS in THF-HMPA, -60 °C). The enolates equilibrated in the presence of excess ketone at 0 °C to give Z/E ratios near 3.0, and [1(2)-pentenyl-2-oxy]trimethylsilane ratios near 1.0 in THF and 0.7 in THF-HMPA. Surprisingly, the kinetic Z/E ratios from the unlabeled and methyl-labeled ketones differed by as much as a factor of 3 (LTMP in THF-HMPA, -62 °C). The differences were also substantial for LDA in THF-HMPA and LHMDS in THF and THF-HMPA, but not beyond experimental error for LDA or LTMP in THF. A model is proposed in which two or more base species (probably differently solvated monomers) are active in deprotonation, so that overall rates of deprotonation are composite. This model can explain the unusual temperature dependences of k_H/k_D. If the base species interconvert slowly on the time scale of the deprotonation, it can also explain the unexpected isotopic sensitivities of the Z/E ratios as *induced isotope effects*.

Introduction

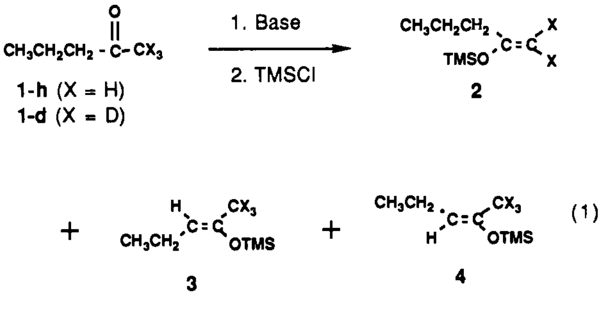
Lithium dialkylamide bases, to the best of our knowledge, first appeared in organic synthesis nearly 60 years ago[3] and have been widely used over the past 25-30 years.[4-7] Their ability to produce selectively the less thermodynamically stable enolates from unsymmetrical ketones has been especially valuable. We undertook some time ago a careful investigation of isotope effects and mechanisms in the kinetic deprotonation of ketones by lithium dialkylamides.[8,9] The present investigation is a continuation of that effort.

Our first experiments centered on 2-methyl-3-pentanone (ethyl isopropyl ketone) and its reactions with LDA, LDEA, and LTMP in THF and DME, with and without added HMPA,[10] all under conditions where the product ratios could be shown to be kinetically controlled. In agreement with earlier workers,[5] we found that base attack at the methylene is much faster than at the methinyl group and that the *E* enolate is usually preferred over the *Z*. Deuterium isotope effects are less than maximum at both the methylene and methinyl positions, a fact we took to indicate a relatively reactant-like transition state. The regio- and stereoselectivities appear to arise from different causes, for they can vary independently, and show quite different temperature dependences. These observations are not easily accommodated by any of the transition-state models currently in the literature.[11-13]

The unusual temperature dependences of the deuterium isotope effects suggest strongly that the reaction is not a simple proton transfer. The ratio of apparent Arrhenius preexponential factors, A_{aH}/A_{aD}, is 1.55-3.25 in the absence and 0.35-1.02 in the presence of HMPA.

Results and Discussion

2-Pentanone (**1h**) and 2-pentanone-*1,1,1*-d_3 (**1d**) were chosen for further exploration because they gave less unbalanced regioisomer ratios than 2-methyl-3-pentanone (which gave no detectable attack at the methinyl proton with LHMDS). The products are shown in eq 1. As before, isotope effects were



(1)

determined from the **2**/(**3** + **4**) ratio from **1h** divided by the corresponding ratio from **1d**. Some of these isotope effects have been previously reported[9] and are summarized with those from the present work in Table I. A sample set of product ratio data is given in Table II. Tables of product ratio data under other conditions are available as supplementary material (see end of paper).

The isotope effects cover a wide range of magnitudes, the most striking differences being between LDA and LTMP on the one hand and LHMDS on the other. LHMDS is reported to be weaker than LDA by nearly 10 pK_a units.[14,15] While the pos-

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[10] Abbreviations: LDA, lithium diisopropylamide; LDEA, lithium diethylamide; LTMP, lithium tetramethylpiperidide; LHMDS, lithium hexamethyldisilazide; THF, tetrahydrofuran; DME, dimethoxyethane; HMPA, hexamethylphosphoric triamide; TMSCl, trimethylsilyl chloride.

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Table I. Temperature Dependence of Isotope Effects in Enolate Formation by Dialkylamide Bases from 2-Pentanone-*1,1,1*-d_3

conditions[a]	k_H/k_D[d] (°C)	k_H/k_D[d] (°C)	A_{aH}/A_{aD}[d]	$E_{aD} - E_{aH}$[d,e]
LDA/THF[b]	2.84 ± 0.05 (0)	2.87 ± 0.03 (−60)	2.78 ± 0.08	0.015 ± 0.014
LDA/THF-HMPA[b]	4.45 ± 0.09 (0)	7.93 ± 0.14 (−62)	0.61 ± 0.03	1.07 ± 0.02
LHMDS/THF[b]	12.27 ± 0.33 (0)	20.90 ± 0.65 (−70)	2.53 ± 0.29	0.85 ± 0.06
LHMDS/THF-HMPA[b]	13.29 ± 0.12 (0)	32.66 ± 0.43 (−60)	0.60 ± 0.18	1.66 ± 0.14
LTMP/THF[c]	3.38 ± 0.12 (−10)	2.56 ± 0.18 (−53)	12.3 ± 5.2	−0.70 ± 0.20
LTMP/THF-HMPA[c]	4.10 ± 0.08 (−10)	6.07 ± 0.12 (−52)	0.79 ± 0.18	0.88 ± 0.10

[a] All reactions were carried out in tetrahydrofuran (THF) solutions ca. 0.08 M in ketone and 0.25 M in base. Bases were lithium diisopropylamide (LDA), lithium hexamethyldisilazide (LHMDS), and lithium tetramethylpiperidide (LTMP). The cosolvent was 0.75 M hexamethylphosphoric triamide (HMPA) where indicated. [b] Reference 9. [c] Present work. [d] All deviations are standard deviations. [e] kcal mol^{-1}.

Table II. Products from the Reaction of 2-Pentanone-*1,1,1*-X_3 with LDA in THF-HMPA[a,b]

temp, °C	X	**2**/(**3** + **4**)[c]	**3**/**4**[c]	yield,[c] %
0.0	H	8.02 ± 0.16	0.99 ± 0.02	91.0 ± 5.0
	D	1.80 ± 0.01	1.08 ± 0.01	93.9 ± 2.8
−15.0	H	7.64 ± 0.02	1.18 ± 0.03	96.5 ± 2.0
	D	1.55 ± 0.06	1.67 ± 0.13	91.0 ± 3.4
−30.0	H	7.33 ± 0.02	1.60 ± 0.08	91.9 ± 4.6
	D	1.32 ± 0.001	2.66 ± 0.001	92.6 ± 2.1
−45.0	H	6.75 ± 0.08	2.11 ± 0.06	93.9 ± 5.7
	D	1.04 ± 0.01	4.61 ± 0.17	92.2 ± 1.8
−62.0	H	5.61 ± 0.09	3.08 ± 0.08	80.7 ± 0.9
	D	0.707 ± 0.004	8.55 ± 0.31	81.8 ± 3.0

[a] See footnotes to Table I for abbreviations. [b] Products were determined by treating enolate mixture with trimethylsilyl chloride (TMSCl) followed by GC analysis of the trimethylsilyl enol ethers. Yields by internal standard. [c] Each result is the average of two or three independent runs and two or three injections of each sample. Deviations are standard deviations.

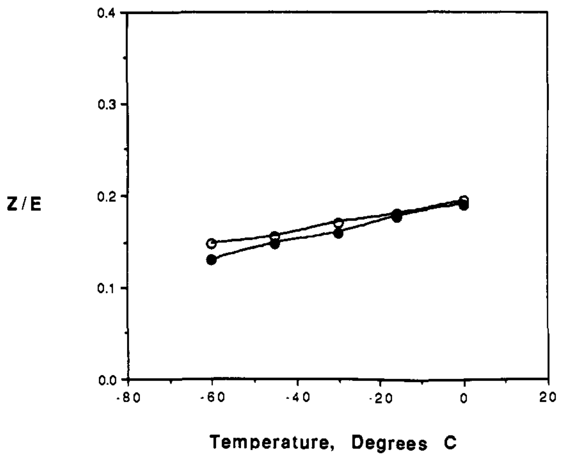

Figure 1. Z/E ratios for (2-pentenyl-2-oxy)trimethylsilane from 2-pentanone (open circles) and 2-pentanone-*1,1,1*-d_3 (solid circles) with LDA in THF. Lines are drawn to connect points smoothly.

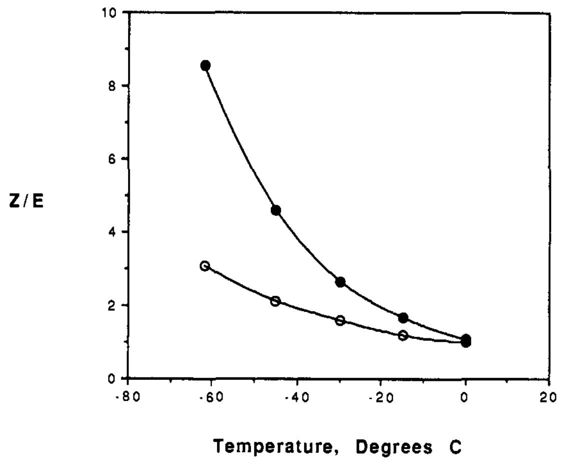

Figure 2. Z/E ratios for (2-pentenyl-2-oxy)trimethylsilane from 2-pentanone (open circles) and 2-pentanone-*1,1,1*-d_3 (solid circles) with LDA in THF-HMPA. Lines are drawn to connect points smoothly.

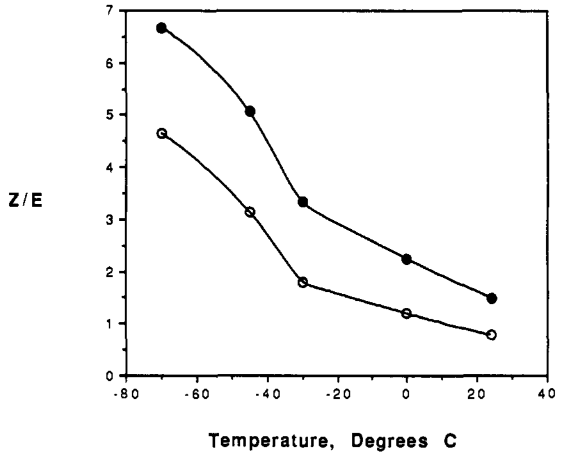

Figure 3. Z/E ratios for (2-pentenyl-2-oxy)trimethylsilane from 2-pentanone (open circles) and 2-pentanone-*1,1,1*-d_3 (solid circles) with LHMDS in THF. Lines are drawn to connect points smoothly.

sibility of multiple reactive base species in solutions of dialkylamide bases (see below) complicates comparisons, it is probably reasonable to suppose that LTMP and LDA give relatively reactant-like, and LHMDS relatively central, transition states with respect to the extent of proton transfer.

The data in Table I reveal strikingly different variations of the isotope effects with temperature under different conditions. The temperature dependences range from normal in the presence of HMPA to temperature independent with LDA in THF to inverse with LTMP in THF.

The ratio A_{aH}/A_{aD} is expected to remain close to unity at temperatures near ambient, though tunneling can give values substantially *below* unity.[16-19] In no case does theory allow a value *above* 1.4, and values close to 1.4 should be found only at elevated temperatures. A fundamental violation of theory seemed unlikely, so we concluded that mechanistic complexity was responsible for the abnormal behavior.

Solutions of LDA and related bases in aprotic solvents are known to contain monomeric ion pairs in equilibrium with dimers and possibly with higher aggregates.[20-23] Differently solvated

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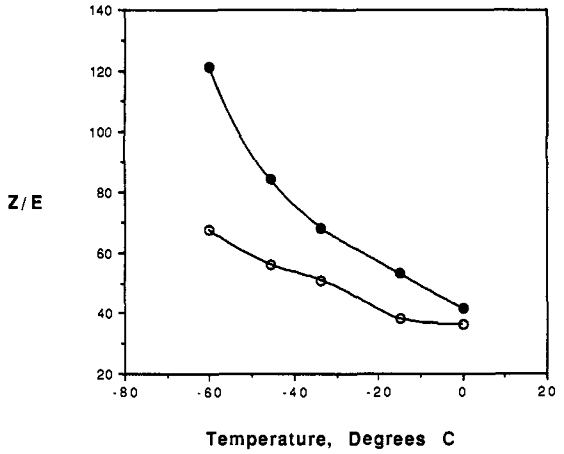

Figure 4. *Z*/*E* ratios for (2-pentenyl-2-oxy)trimethylsilane from 2-pentanone (open circles) and 2-pentanone-*1,1,1*-d_3 (solid circles) with LHMDS in THF–HMPA. Lines are drawn to connect points smoothly.

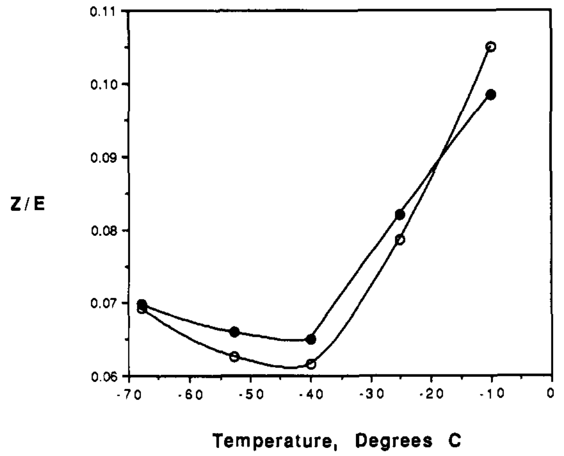

Figure 5. *Z*/*E* ratios for (2-pentenyl-2-oxy)trimethylsilane from 2-pentanone (open circles) and 2-pentanone-*1,1,1*-d_3 (solid circles) with LTMP in THF. Lines are drawn to connect points smoothly.

monomers are also possible; e.g., contact and solvent-separated ion pairs. If one assumes that two or more different base species are active in deprotonation, the apparent Arrhenius parameters are composites, and no a priori limits can be set on the values they can assume. A plausible situation, for example, is one in which the base species giving the larger isotope effect accounts for a higher and higher proportion of the overall reaction as the temperature increases. This would tend to attenuate or even reverse the normal tendency of primary deuterium isotope effects to decrease with increasing temperature.

This hypothesis also offered an attractive explanation for the normal temperature dependences observed in the presence of HMPA. If HMPA breaks up aggregates[24] to produce a single effective deprotonating agent (though not necessarily the only base species in solution), the normal temperature dependences observed under these conditions would be expected. It quickly became apparent, however, that the reactions in the presence of HMPA were still decidedly unusual in other respects, the most dramatic of which was the observation of substantial deuterium kinetic isotope effects on *Z*/*E* ratios.

Figures 1–6 depict *Z*/*E* ratios as functions of temperature. The rate of attack of base on the *methylene* position should at most show a small secondary kinetic isotope effect when the *methyl* position is deuterated, and there is no reason that this effect should be significantly different for the formation of the *Z* and *E* isomers. This expectation is fulfilled by LDA and LTMP in THF (Figures 1 and 5), where *Z*/*E* ratios are the same within experimental error

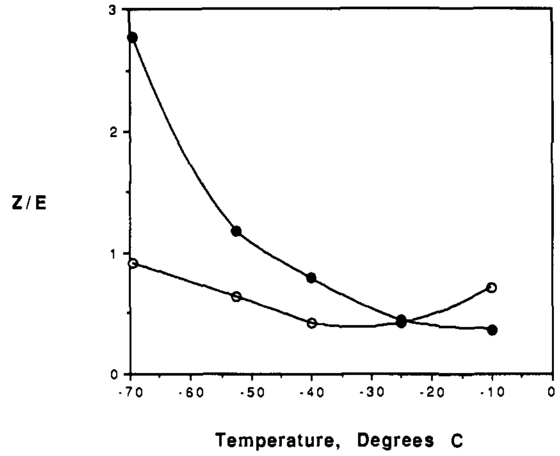

Figure 6. *Z*/*E* ratios for (2-pentenyl-2-oxy)trimethylsilane from 2-pentanone (open circles) and 2-pentanone-*1,1,1*-d_3 (solid circles) with LTMP in THF–HMPA. Lines are drawn to connect points smoothly.

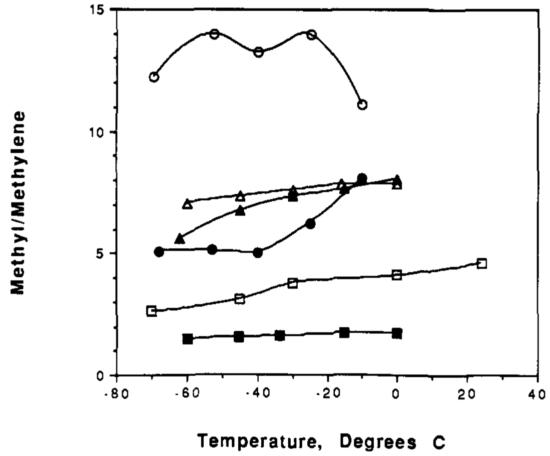

Figure 7. Ratios of methyl/methylene attack for the reaction of dialkylamide bases with 2-pentanone: (open circles) LTMP in THF–HMPA; (solid circles) LTMP in THF; (open triangles) LDA in THF; (solid triangles) LDA in THF–HMPA; (open squares) LHMDS in THF; (solid squares) LHMDS in THF–HMPA. Lines are drawn to connect points smoothly.

for the deuterated and undeuterated species. In the presence of HMPA, however, the *Z*/*E* ratios can differ by as much as a factor of 3 at low temperatures (Figures 2, 4, and 6). Even in the absence of HMPA, LHMDS shows significant isotope effects on the *Z*/*E* ratio (Figure 3).

Another noteworthy feature of the results is the strong dependence of the *Z*/*E* ratios on the reaction conditions. The ratios for the unlabeled ketone range from 0.062 (LTMP in THF, −40 °C) to 67 (LHMDS in THF–HMPA at −60 °C), a variation of 3 orders of magnitude. The ratios run higher in the presence of HMPA with any given base and often are strongly dependent on temperature. That with LTMP in THF is particularly interesting because it goes through a minimum between −40 and −50 °C. The proportions of regioisomers show much less variation (Figure 7). They cover a range of barely 1 order of magnitude and in most cases are not very temperature dependent. This contrasting behavior of regio- and stereoisomer ratios further supports our conclusion that they arise from different causes.[8]

To compare these kinetically controlled product ratios with the thermodynamic values, we set about finding conditions under which the product enolates would equilibrate. In the presence of a 25% excess of ketone over base the *Z*/*E* and methyl/methylene ratios changed with time (Figures 8 and 9). Equilibration at 0 °C appeared to be complete in a few minutes in the presence of HMPA but took several hours in THF alone. The equilibrium *Z*/*E* ratio was about 3 in both the presence and absence of HMPA and with three different bases. The ratio in the presence of HMPA

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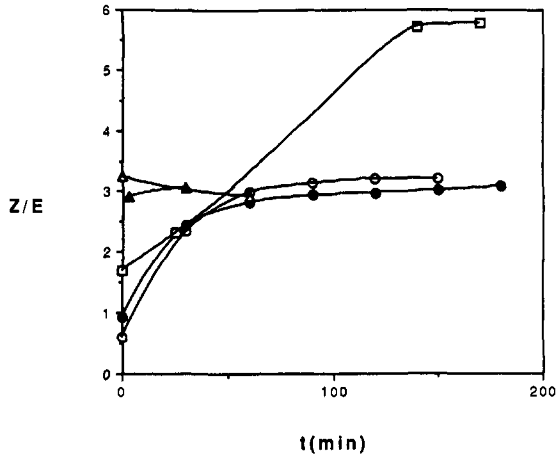

Figure 8. Equilibration of 2-pentanone enolates. Z/E ratios from excess ketone (25%) with (open circles) LDA in THF, (solid circles) LTMP in THF, (open triangles) LHMDS in THF-HMPA, (solid triangles) LDA in THF-HMPA, and (open squares) LDA in THF-HMPA at -40 °C. Lines are drawn to connect points smoothly.

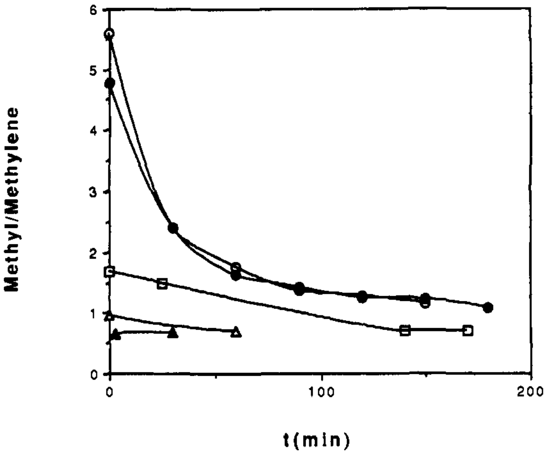

Figure 9. Equilibration of 2-pentanone enolates. Regioisomer ratios from excess ketone (25%) with (open circles) LDA in THF, (solid circles) LTMP in THF, (open triangles) LHMDS in THF-HMPA, (solid triangles) LDA in THF-HMPA, and (open squares) LDA in THF-HMPA at -40 °C. Lines are drawn to connect points smoothly.

at -40 °C rose to 5.8. Equilibration was too slow to determine reliable ratios at lower temperatures, but reasonable extrapolation suggests a value of about 9 at -60 °C. The methyl/methylene ratio approached 1.0-1.2 in the absence of HMPA and 0.7 in its presence. The equilibrium value at -40 °C in the presence of HMPA was unchanged (0.7) within experimental error. Thus, the kinetic Z/E ratios range from contrathermodynamic to suprathermodynamic, while the methyl/methylene ratios are all contrathermodynamic.

Closer examination of the curves of Figures 8 and 9 shows that the stereo- and regioisomer equilibrations are occurring at similar rates, which strongly suggests that they are occurring by the same mechanism. The most reasonable assumption would be that proton transfer from ketone to enolate is responsible for the interconversion of isomers. Fataftah et al.[25] observed stereoisomer equilibration of the enolates from 3-pentanone and proposed that the interconversion occurred via an aldol condensation between enolate and unreacted ketone, followed by bond rotation and reversal of the aldol reaction. This mechanism is incapable of explaining our regioisomer equilibration.[26] It appears likely that a proton-transfer mechanism is responsible for equilibration of the enolates from both 2- and 3-pentanone.

We now return to the unexpected isotope effects on the Z/E ratios. It is extremely improbable that these could be any kind of normal secondary isotope effect, because of both their magnitudes and their strong dependence on reaction conditions and temperature. Note, for example, that $(Z/E)_D/(Z/E)_H$ with LDA in THF-HMPA goes from 1.1 at 0 °C to 2.8 at -62 °C. We thus conclude that we are observing an *induced isotope effect*, i.e., an isotope effect resulting from competition between deprotonation of the unlabeled methylene group and the labeled methyl group.

Such an effect would clearly not be expected if deprotonation in the presence of HMPA resulted from a single active base species. It is necessary to assume that there are at least two active base species. Furthermore, these species cannot equilibrate rapidly with each other. If they are two rapidly equilibrating species of the same state of aggregation, they will remain in a constant ratio to each other throughout the reaction and the Curtin-Hammett principle[27] will apply. The proportions of reaction via the two bases will depend only on the free energies of the respective transition states, which cannot show any significant sensitivity to isotopic substitution in a nonreacting position.

The Curtin-Hammett principle is not strictly applicable when the proportions of the reactive bases change during the course of the reaction, as they would if one were a monomer and the other a dimer. Nonetheless, rapid equilibration would still mean that each isotopic substrate reacts with the same mix of bases at any given fraction of reaction, so there is still no way that major differences in rates of methylene attack to give Z vs methylene attack to give E from the deuterated and undeuterated substrates could occur.

If, however, the bases do not interconvert rapidly on the time scale of the deprotonation, then the more reactive base would be depleted as the reaction progressed, and the composition of the base mixture at the end of the reaction could be very different from that at the beginning. In addition, deuteration slows the rate of methyl attack sufficiently that there is substantially more product of methylene attack from the deuterated than from the undeuterated ketone. Given these two conditions, it is possible that the two products of methylene attack on the deuterated ketone result from a different mix of bases than is the case for the corresponding products from the unlabeled ketone. If the different bases give different Z/E ratios, the observed induced isotope effects would result.

To avoid the risk of self-deception by a plausible but perhaps flawed "hand-waving" explanation, a computer model of the above hypothesis was undertaken. Two bases that do not interconvert at all were assumed for the sake of simplicity, and six rate constants (three for each base, one each for methyl attack, methylene attack to form Z product, and methylene attack to form E product) were arbitrarily assigned. Only those for attack at methyl were changed for the deuterated ketone ($k_H/k_D = 10$). An initial total base concentration of 3 M was assumed, and numerical integrations to obtain the accumulated product compositions at ketone concentrations from 0.1 to 2.0 M were performed. As expected, $(Z/E)_D$ and $(Z/E)_H$ diverge at higher substrate concentrations (greater consumption of base), reaching a ratio of 1.5 at 2 M ketone (Figure 10), similar in magnitude to the observed ratios. If the base mixture is assumed to consist of monomer and dimer in rapid equilibrium, $(Z/E)_D$ and $(Z/E)_H$ remain the same over the entire range of the integration (Figure 11).

While our computer models validate the general assumptions that go into our qualitative model, they oversimplify the factors that must contribute to the experimental observations. The most serious oversimplification is the omission of the effect of temperature. In the presence of HMPA, $(Z/E)_D$ increases much more steeply with decreasing temperature than does $(Z/E)_H$ (Figures 2, 4, and 6). This can be explained in part by the increase in the primary isotope effect with decreasing temperature, which will result in a more rapidly increasing methylene/methyl ratio for the products from **1d** than for those from **1h**. But it also seems

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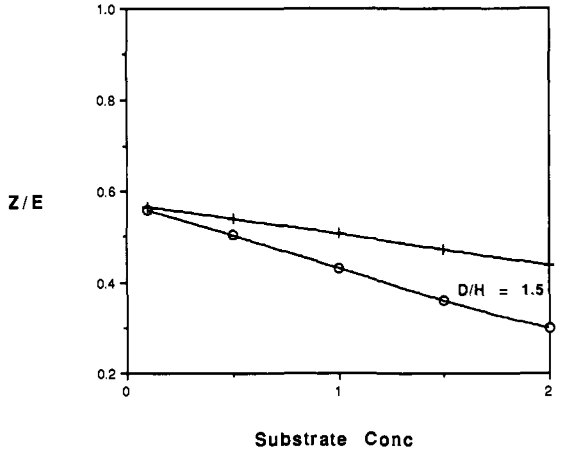

Figure 10. Computer model of 2-pentanone deprotonation by two nonequilibrating bases with total initial base concentration of 3 M and initial substrate concentrations of 0.1–2 M: (open circles) 2-pentanone; (plus marks) 2-pentanone-*1,1,1*-d_3. See text for details. Lines are drawn to connect points smoothly.

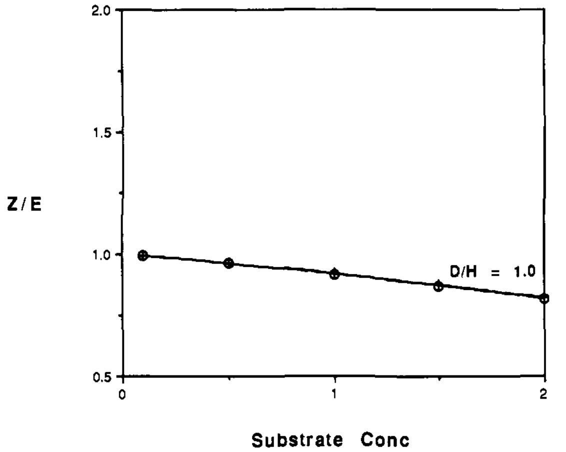

Figure 11. Computer model of 2-pentanone deprotonation by monomeric and dimeric bases in rapid equilibrium, K_{eq} = 1.0, with total initial base concentration of 3 M and initial substrate concentrations of 0.1–2 M: (open circles) 2-pentanone; (plus marks) 2-pentanone-*1,1,1*-d_3. See text for details. Lines are drawn to connect points smoothly.

very likely that the composition of the base mixture and the rate of interconversion of the base species depend on temperature. Our present knowledge of the base–solvent systems gives us no way of incorporating these factors. We can thus not expect to account with our simple models for all of the details of the experimental product ratios. We can nonetheless cite a number of further experiments that support the assumptions behind the models and give some further mechanistic clues.

Direct evidence for slow interconversion of base species is afforded by a comparison of lines 3 and 4 and lines 9 and 10 in Table III. The two sets of experiments differ in that HMPA was added to the base solution and the resulting solution held at the desired temperature for at least 15 min in the first set (lines 3 and 4) before the ketone was added, but in the second set (lines 9 and 10), the ketone was added within 30 s after the HMPA was added. There are significant differences in both regioisomer and stereoisomer ratios, the change in the stereoisomer ratio at −62 °C being especially striking. Evidently reorganization of solvation of the base species is not a rapid process. This conclusion is supported by recent evidence that exchange of HMPA ligands on Li is slow on the NMR time scale in solutions of $PhEt_3B^-Li^+$ and PhLi in THF–HMPA.[28]

Table III. Products from the Reaction of 2-Pentanone with LDA (Miscellaneous Experiments)[a,b]

temp, °C	conditions	**2**/(**3** + **4**)[c]	**3**/**4**[c]	yield,[c] %
0	THF, std[d]	7.85 ± 0.10	0.195 ± 0.005	92.4 ± 2.1
−60	THF, std[d]	7.07 ± 0.05	0.148 ± 0.001	92.4 ± 1.9
0	THF–HMPA, std[d]	8.02 ± 0.16	0.987 ± 0.019	91.0 ± 5.0
−62	THF–HMPA, std[d]	5.61 ± 0.09	3.08 ± 0.08	80.7 ± 0.9
0	THF, dil[e]	8.38 ± 0.15	0.176 ± 0.008	97.4 ± 1.1
−62	THF, dil[e]	8.29 ± 0.06	0.130 ± 0.008	97.3 ± 1.5
0	THF–HMPA, dil[e]	9.97 ± 0.45	0.363 ± 0.012	87.0 ± 3.7
−62	THF–HMPA, dil[e]	7.46 ± 0.14	1.03 ± 0.01	89.4 ± 0.3
0	THF–HMPA, fast[f]	7.14 ± 0.08	0.873 ± 0.038	88.8 ± 3.5
−62	THF–HMPA, fast[f]	5.26 ± 0.10	1.78 ± 0.11	85.8 ± 3.6
0	THF, cp[g]	8.12 ± 0.08	0.241 ± 0.010	89.9 ± 3.6
0	THF–HMPA, cp[g]	7.92 ± 0.31	1.12 ± 0.04	90.2 ± 4.6

[a] See footnote *a*, Table I. [b,c] See corresponding footnotes, Table II. [d] Standard conditions involved adding ketone (0.08 M final concentration) to base (0.25 M final concentration) in THF. When HMPA was cosolvent, it was 0.75 M final concentration and added to the THF at least 20 min prior to addition of ketone. [e] Conditions same as standard, except diluted 10-fold to give final concentrations of ketone of 0.008 M, base 0.025 M, and HMPA (when used) 0.075 M. [f] "Fast" conditions were the same as standard, except that ketone was added within 30 s after addition of HMPA to the base solution. [g] The base solution was treated with 0.33 mol/mol of base of cyclopentanone, allowed to stand 10 min, and then treated with 0.25 mol/mol of base of 2-pentanone.

The data in Table III also cast some light on the state of aggregation of the base species. Lines 1–4 and 5–8 differ in that all reaction mixtures in the latter set are diluted 10-fold: from 0.08 to 0.008 M ketone, from 0.25 to 0.025 M base, and from 0.75 to 0.075 M HMPA (when added). The changes in product ratios in THF alone are a little beyond experimental error but not very large. By contrast, there are substantial changes in product ratios, especially of the stereoisomers, on dilution in the THF–HMPA experiments. The stereoisomer ratios are decidedly smaller in the dilute solutions and closer to the values obtained in THF alone. This is understandable if the effect is simply one of a more THF-like solvent (THF/HMPA increased 10-fold). If dimers as well as monomers were active base species, one would expect the monomer to be more important in the more dilute solution, and a greater change would be expected in product ratios in THF alone. We tentatively conclude that the active base species are differently solvated monomers rather than both monomers and dimers.

Another possibility for a base species that changes over the course of the reaction would be a mixed dimer between base and enolate, which would increase in concentration as the reaction proceeded. Such a species has been isolated in crystalline form and its structure shown by X-ray diffraction to be that of a dimer of the mixed dimer, i.e., $(\text{enolate}\cdot\text{LDA})_2$.[29] To test this possibility, we added $^1/_3$ molar equivalent of cyclopentanone to the base solution, let the mixture stand for 10 min, and then added $^1/_4$ molar equivalent of 2-pentanone. On workup cyclopentanone enolate was found to have formed quantitatively, but the regio- and stereoisomer ratios from 2-pentanone changed little (compare lines 1 and 11 and lines 3 and 12 in Table III). It is possible, of course, that a mixed dimer of LDA and cyclopentanone enolate was an active base and fortuitously gave the same product ratios as the mixed dimers from LDA and 2-pentanone enolates. The more plausible conclusion is that mixed dimers played no significant role.

One prediction of the computer model (Figure 10) is that $(Z/E)_H$ and $(Z/E)_D$ should differ least at high and most at low base/ketone ratios. A greater proportion of the base is consumed in the latter case, producing a greater change in base composition over the course of the reaction. With LDA in THF, where no induced isotope effect is found, Z/E ratios change 4–11% between 6:1 and 1.5:1 base/ketone (Figure 12). This is little beyond the experimental error within a run, which is usually 5% or less.

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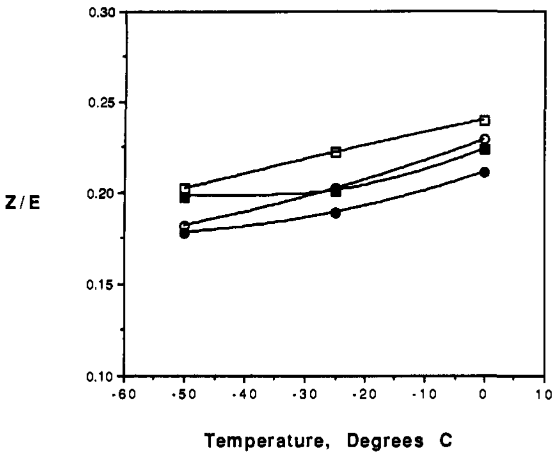

Figure 12. Effect of base/ketone ratio on Z/E at constant base concentration with LDA in THF. (Open symbols) Z/E(H); (solid symbols) Z/E(D); (circles) 6:1 base/ketone; (squares) 1.5:1 base/ketone. Lines are drawn to connect points smoothly.

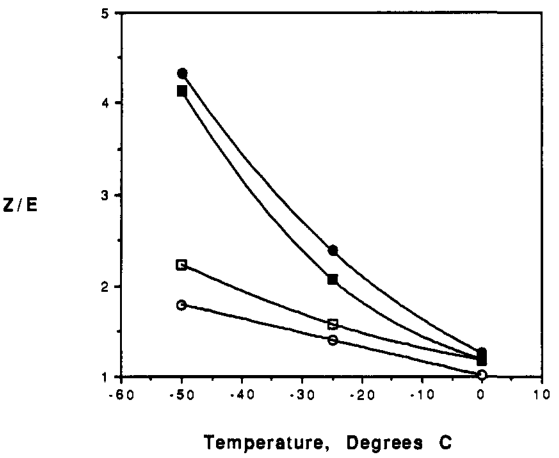

Figure 13. Effect of base/ketone ratio on Z/E at constant base concentration with LDA in THF–HMPA. (Open symbols) Z/E(H); (solid symbols) Z/E(D); (circles) 6:1 base/ketone; (squares) 1.5:1 base/ketone. Lines are drawn to connect points smoothly.

With LDA in THF–HMPA the effect on the Z/E ratio of the same change in the base/ketone ratio is somewhat larger, 4–25%, but only one pair differ by more than 14% (Figure 13). Curiously, the ratio of $(Z/E)_D$ to $(Z/E)_H$ runs closer to unity at 1.5:1 than at 6:1 base/ketone, exactly the reverse of the expected effect, but the differences are only 19–24%. It should be mentioned that the base/ketone ratio was varied by changing the ketone concentration only, so as not to vary the initial composition of the mixture of base species.

Detailed interpretation of these rather small changes is not possible at present. That they did not show the expected pattern further points up the oversimplifications of the model (see above). We can see no alternative, however, to a model which incorporates multiple active base species that slowly interconvert.

Conclusions

The present results demonstrate clearly the mechanistic complexity of kinetic deprotonation by dialkylamide bases. The next logical step is to ask what specific conclusions can be drawn concerning the structures of the reactive base species and the transition states leading to the isomeric products. A candid answer would have to be that few really secure conclusions are possible.

A fundamental problem is that species observable in solution by NMR or other spectroscopic techniques are not necessarily those that are directly involved in reactions. An excellent example is afforded by the work of Galiano-Roth and Collum,[21] who could find NMR evidence only for a dimer of LDA in THF solution but who showed by the kinetics of deprotonation of an *N*,*N*-dimethylhydrazone that a monomeric species was very probably the active base. Numerous aggregates and mixed aggregates have been identified in the solid state or in solutions of lithium dialkylamides,[20–24,29,30] but there is no evidence that they are the active base species in any of our reactions. The most likely candidates under our conditions are two or more monomers such as **5** (contact ion pairs) and **6** (solvent-separated ion pairs) which

$$\underset{\textbf{5}}{R_2N^-Li^+(THF)_{3-n}(HMPA)_n} \qquad \underset{\textbf{6}}{R_2N^-Li^+(THF)_{4-n}(HMPA)_n}$$

interconvert slowly under conditions where induced isotope effects are observed. The structures **5** and **6** both show lithium tetracoordinated, but it is also conceivable that partially desolvated species could be the active bases.

Before proceeding to a discussion of possible transition-state structures, we would like to point out an analogy to another imperfectly understood phenomenon. It has been known for a long time that 2-alkyl halides and tosylates react with ethoxide in ethanol to give the thermodynamically preferred products: 2-ene over 1-ene, and *E*-2-ene over *Z*-2-ene. With *tert*-butoxide in *tert*-butyl alcohol, however, the 2-ene/1-ene and the E/Z ratios are reduced, often below unity.[31] The addition of crown ether or the use of a cation-complexing solvent such as DMSO raises the ratios again to values closer to the thermodynamic ratios.[32] These are all cases where the elimination is predominantly anti, so no change in the gross stereochemistry of the reaction is involved. We thus see two otherwise different reactions that show a similar response to ion-pairing phenomena. Where tight ion pairs can be expected to be involved, product ratios tend toward the contrathermodynamic. Where loose or solvent-separated ion pairing is anticipated, the product ratios are closer to, and sometimes even greater than, the thermodynamic.

Nearly 15 years ago, Ireland[11] proposed a cyclic transition state for reactions giving contrathermodynamic products and a more open transition state for reactions giving the thermodynamic products, although the latter proposal was based on experimental ratios that may not have been entirely kinetic. He was criticized for two features of his model that appeared unrealistic, the nonlinear hydrogen transfer and a dihedral angle between C—H and C=O that was less than 90°.[12,13] Recent evidence suggests that these features are more reasonable than previously supposed. Semiempirical[33] and ab initio[33,34] calculations on the reaction of lithium amide with acetaldehyde give a 160° rather than 180° C---H---N angle and a H—C—C=O dihedral angle of less than 60° rather than the stereoelectronically preferred 90°. The constraints of the cyclic structure seem to outweigh the stereoelectronic preference. Calculations in which the lithium is coordinated to two water molecules do not alter significantly these geometric features, so it seems reasonable to suppose that the structures in THF solution would not be radically different.

Tightly ion paired cyclic transition states could be pictured on the basis of the calculations as **7** and **8**, where S is THF. In the presence of HMPA the lithium is more effectively solvated and open transition states such as **9** and **10** could be involved, in which S is HMPA or mixtures of HMPA and THF. Such a transition state would be free to adopt the stereoelectronically preferred dihedral angle. So far, these structures look like rather minor modifications of the Ireland models. We would like to suggest, however, that the almost exclusive focus in previous models[11–13] on the steric effect as the reason for stereo- and regiochemical preferences may be wrong or incomplete. The isotope effects suggest that the transition states with LDA and LTMP in THF are reactant-like. Proton transfer seems more advanced with the weaker base LHMDS and with all bases in the THF–HMPA media, but it is likely that rehybridization lags behind proton transfer in the transition state, by analogy to deprotonation of

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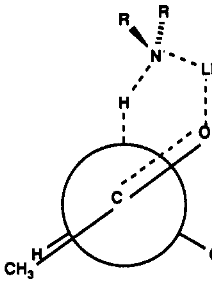

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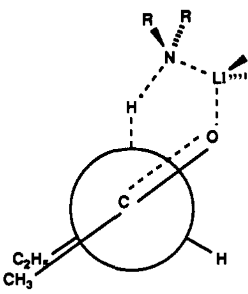

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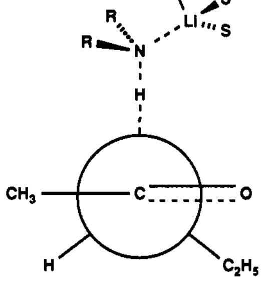

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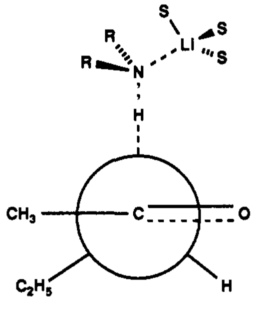

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nitroalkanes, where alkyl substituents slow deprotonation even though they enhance equilibrium acidity.[35] For reactant-like transition states, a more fruitful model might be to consider the electrostatic and conformational effects that come into play as the substrate and reagent approach the transition state. Steric effects in the usual sense are expected to be less important in an early transition state because electrostatic effects operate at longer ranges than steric effects.[36]

The application of these ideas to the regioisomers ratios is relatively straightforward. First, there is a statistical preference of 3:2 for reaction at methyl over reaction at methylene. Second, if rehybridization at the α-carbon lags behind proton removal in the transition state, negative charge will not be delocalized toward oxygen and will be destabilized by alkyl substitution. We submit that the statistical and inductive effects alone suffice to account for the consistently contrathermodynamic regioisomer ratios, although other factors may contribute to their variability.

The stereoisomer ratios present two problems: (1) When the thermodynamic product is favored, it is sometimes obtained in proportions exceeding the thermodynamic, so it does not suffice simply to postulate a product-like transition state. (2) The ratio is often contrathermodynamic. If we continue to pursue the model of a transition state in which little or no rehybridization has occurred, a logical starting point would be to consider the conformational dependence of the energy of the reactant ketone. It should be emphasized that this does *not* amount to assuming ground-state conformational control. Rather, it rests on the assumption that transition-state conformational energies will parallel those of the corresponding ground-state conformations. The energy changes on rotation about the bond between the carbonyl carbon and the α-carbon of 2-pentanone are not known, but they should be close to those for 2-butanone, which has been subjected to 6-31G*/MP2 calculations by Wiberg and Martin,[37] with results that agree with spectroscopic data where comparisons are available.

The suprathermodynamic ratios are found in some of the reactions incorporating HMPA. In such a case, transition states like **9** and **10** should be most favorable. The analogous conformations of 2-butanone differ by 1.5 kcal, enough to account for a substantial fraction of even the largest Z/E ratio (67 at −60 °C, see Figure 4), and exceeding markedly the equilibrium Z/E ratios (Figure 8).

That the same conformational effects do not control the Z/E ratio in THF alone can be ascribed to a transition state in which the base is coordinated to the carbonyl oxygen via the lithium ion (**7** and **8**). The analogous conformations of 2-butanone, however, still differ by 0.9 kcal in favor of **7**, which would predict only a lessened preference for the thermodynamic product, not the contrathermodynamic product as observed. Some effect that more than counterbalances this 0.9 kcal is obviously needed. In previously proposed models,[11-13] this effect has been considered to be a steric interaction between the base (or the alkyl groups on the base nitrogen) and the alkyl substituent on the α-carbon of the ketone. It is not at all clear that the base and the alkyl group are close enough for a significant steric effect, and the complexed carbonyl oxygen and the base associated with it are highly polar, not just a space-filling mass. We suggest that a base–alkyl electrostatic repulsion in **7** is more plausible. It is even possible that an attractive electrostatic effect in **8** also contributes to the net preference for **8**.

Experimental evidence shows that in most cases there must be at least two different transition states in each reaction. A weaker base (LHMDS) or a more effective solvating agent (HMPA) would loosen **7** and **8**, perhaps via structures with S molecules interposed between Li and N or Li and O, the ultimate result of this loosening being open transition states like **9** and **10**. It is also possible that Li could become less than tetracoordinated, especially if R is very large (LTMP) with tightening of the remaining bonds to Li. That the comparably bulky LHMDS gives quite different results from LTMP further emphasizes that a simple steric effect is far from the only factor operating.

Definite identification of specific base species and specific transition states for ketone deprotonation is not possible given the present state of knowledge. We present the above ideas in the hope that they will encourage rethinking of the conventional wisdom on regioselectivity and stereoselectivity in this reaction.

Experimental Section

General. Glassware was dried at 140 °C and cooled under dry nitrogen. Syringes and needles were dried in vacuum (0.5 Torr) for 1 h or more. Ice water was the cooling bath for 0 °C experiments. Lower temperature experiments used a heavily insulated 4.5-L bath filled with 99% ethanol and cooled by a Neslab CC-75W Cryocool unit. Solvents were purified as previously described.[8] Diisopropylamine and 2,2,6,6-tetramethylpiperidine were purified as before.[8] 1,1,1,3,3,3-Hexamethyldisilazane (Aldrich) was dried over calcium hydride and distilled immediately prior to use.

2-Pentanone-*1,1,1*-d_3 was prepared by a procedure previously described in detail.[8] 2-(1-Propyl)-1,3-dithiane[38] was deprotonated by butyllithium and treated with methyl-d_3 iodide (Aldrich, 99.5% D) according to the procedure of Corey and Seebach.[39] The resulting 2-(1-propyl)-2-methyl-*1,1,1*-d_3-1,3-dithiane was hydrolyzed according to the procedure of Corey and Erickson[40] to give 2-pentanone-*1,1,1*-d_3, which was purified by preparative GLC 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 were 30 and 60 mL min^{-1}, respectively, at 60 psi; injector, detector, and column temperatures were 150, 150, and 70 °C, respectively. ^{1}H NMR (C_6D_6) δ 0.95 (3 H, t), 1.62 (2 H, m), 2.42 (2 H, t). There was no detectable absorption at δ 2.15 (1-CH_3 in the unlabeled ketone).

Trimethylsilyl enol ethers were prepared according to the methods of House et al.[5,8] and purified by preparative GLC (same conditions as for 2-pentanone above) to yield the following products: (1-pentenyl-2-oxy)trimethylsilane,[41] ^{1}H NMR (C_6D_6) δ 0.15 (9 H, s), 0.85 (3 H, t), 1.50 (2 H, m), 2.01 (2 H, t), 4.10 (1 H, s), 4.17 (1 H, s); [(*Z*)-2-pentenyl-2-oxy]trimethylsilane,[41] ^{1}H NMR (C_6D_6) δ 0.10 (9 H, s), 0.95 (3 H, t), 1.65 (3 H, s), 2.12 (2 H, m), 4.42 (1 H, t); [(*E*)-2-pentenyl-2-

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oxy]trimethylsilane,[9] ^1H NMR (C_6D_6) δ 0.14 (9 H, s), 0.88 (3 H, t), 1.65 (3 H, s), 1.87 (2 H, m), 4.75 (1 H, t).

Reactions of 2-Pentanone and 2-Pentanone-*1,1,1-d*$_3$ with Dialkylamide Bases. The standard procedure for preparation of the base solution involved adding 8.25–8.70 × 10^{-4} mol of amine to 7.5–8.7 × 10^{-4} mol of *n*-butyllithium in 3.0 mL of THF, at 0 °C for diisopropylamine and at −10 °C for tetramethylpiperidine. For hexamethyldisilazane the solution was prepared at room temperature and after 5 min heated to 48 °C and stirred for 15 min. It was then cooled to the temperature of the reaction and left standing for 15 min. This was necessary to ensure high yields and reproducible product ratios in the subsequent deprotonation. When HMPA was used, 3 mol/mol of base was added and the solution kept at the reaction temperature for 15–20 min prior to addition of ketone. To the base solution was added dropwise with stirring 2.5 × 10^{-4} mol of ketone in 0.2 mL of THF (see ref 8 for details of the procedure). The final solution before reaction was thus approximately 0.25 M in base, 0.75 M in HMPA (when added), and 0.08 M in ketone. See the text and Table III for the small number of cases where there were departures from these standard conditions. When the base/ketone ratio was varied (Figures 12 and 13), the base concentration was kept the same as in the standard procedure and the ketone concentration changed appropriately. The enolates were quenched after 10 min by adding 1.2 mol of trimethylsilyl chloride/mol of base. The time of quenching did not affect the results, and the quenched solutions were stable for at least 24 h. See ref 8 for details of other control experiments in a closely related system. The products were analyzed by GLC, using a J&W Scientific DB-1 (cross-linked silicone) 30-m × 0.55-mm i.d. fused silica capillary column. The column, injector, and detector temperatures were 40, 100, and 150 °C, respectively. At 60 psi of helium, 30 psi of hydrogen, and 26 psi of air, approximate retention times were 13 min for (1-pentenyl-2-oxy)-trimethylsilane, 15 min for [(*Z*)-2-pentenyl-2-oxy]trimethylsilane, and 16 min for [(*E*)-2-pentenyl-2-oxy]trimethylsilane. Peaks were cleanly separated. Toluene (retention time 6 min) was the internal standard for yield determinations. The response factor was 2.101 by weight.

Equilibration of Enolates. Solutions of LDA, LTMP, and LHMDS were prepared as above, except 8.25 × 10^{-3} mol of amine was added to 7.5 × 10^{-3} mol of butyllithium in ca. 22 mL of THF at 0 °C. When HMPA was used, 3 mol/mol of base was added. The solution was stirred at 0 °C for 20 min and 1.25 mol of ketone/mol of base (25% excess) added. Aliquots (2 mL) were taken at regular time intervals (usually 30 or 60 min) and quenched with trimethylsilyl chloride. The mixture was worked up and analyzed by GC as above. Aliquots were taken until the product ratios showed no further change.

Supplementary Material Available: Tables S1–S5 containing product ratio data used in Figures 1 and 3–7 and Tables S6 and S7 containing data on enolate equilibration used in Figures 8 and 9 (4 pages). Ordering information is given on any current masthead page.

2,5-Dithiacyclopentylideneketene and Ethenedithione, S=C=C=S, Generated by Flash Vacuum Pyrolysis

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Graham Macfarlane,[1a] Josselin Chuche,[1b] Jean Claude Pommelet,[1b]
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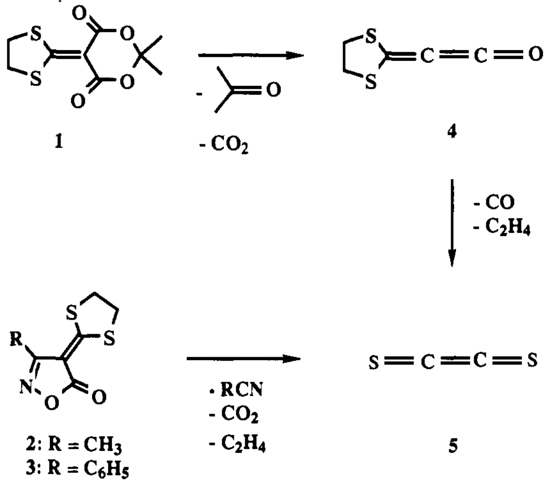
Abstract: 2,5-Dithiacyclopentylideneketene (**4**) is obtained by flash vacuum pyrolysis (FVP) of the Meldrum's acid derivative **1** and characterized by MS, IR, and NMR spectroscopy. **4** is stable in solution at −50 °C. FVP of **4** as well as the isoxazolone derivatives **2** and **3** results in efficient cleavage into ethylene and ethenedithione, S=C=C=S, which is remarkably stable in the gas phase at high temperature, low pressure, and short contact times but extremely unstable in the condensed state or at higher pressures.

Introduction

Methyleneketenes ($R_2C{=}C{=}C{=}O$) are of considerable interest because of their high reactivity, which has led to the discovery of a series of remarkable molecular transformations.[2,3] In this paper we report the preparation of a relatively stable methyleneketene **4** as well as its use, surprising at first sight, in an efficient generation of ethenedithione, S=C=C=S. This molecule, like the other higher oxides and sulfides of carbon, has been the focus of much recent theoretical and experimental activity. Whereas the odd-membered compounds C_3O_2, C_3S_2, C_3OS, and C_5O_2 are relatively stable,[4] even-membered analogues have become known only very recently. Theory[5] predicts C_2O_2 and C_2S_2 to be

Scheme I



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