(14) C. C. Costain, *J. Chem. Phys.*, **29**, 864 (1958).
(15) The C—H bond length is 1.104 Å and the H–C–H bond angle is 117.0°.
(16) The C_β—C_α bonds were set at 1.54 Å, C_β—H bonds at 1.10 Å, and H–C_β–H angles at 109° 28′. The C_β–C_α–H angle (**3**) and C_β–C_α–C_β (**4**) angles were set at 120°. The similar C–C–C angle in $(CH_3)_2C^+OCH_3$ has been optimized giving 120.5°: D. A. Dixon and P. A. Charlier, unpublished results.
(17) The H–C_α–H angle was set at 109° 28′. The optimized results for C_α—C_β, C_α–C_β–C_N, and H–C_β–H are 1.475 Å, 103.3°, and 116.2°, respectively.
(18) The geometry for **5** was taken from that of **4** with the geometry parameters for the additional methyl groups on C_β as in note 16. The geometry for **7** was taken from **6** with all hydrogens substituted with methyl groups with the parameters given in note 16.
(19) J. A. Pople and M. Gordon, *J. Am. Chem. Soc.*, **89**, 4253 (1967).
(20) (a) W. N. Lipscomb, *Acc. Chem. Res.*, **6**, 257 (1973); (b) D. A. Dixon, D. A. Kleier, and W- N. Lipscomb, *J. Am. Chem. Soc.*, **100**, 5681 (1978).
(21) This description is for one of two symmetric equivalent sets of LMOs for **4**. The equivalent sets are due to the presence of a molecular mirror plane.
(22) (a) D. A. Kleier, D. A. Dixon, and W. N. Lipscomb, *Theoret. Chim. Acta (Berlin)*, **40**, 33 (1975); (b) D. A. Dixon, D. A. Kleier, T. A. Halgren, J. H. Hall, and W. N. Lipscomb, *J. Am. Chem. Soc.*, **99**, 6226 (1977).
(23) The basis set is of the form (9,5,1/4,1)/[3,2,1/2,1] with exponents and contraction coefficients from T. H. Dunning, Jr., and P. J. Hay, in "Modern Theoretical Chemistry. Methods of Electronic Structure Theory", Vol. 3, H. F. Schaeffer, III, Ed., Plenum, New York, 1977, Chapter 1.
(24) (a) M. Dupuis, J. Rys, and H. F. King, Jr., *J. Chem. Phys.*, **65**, 111 (1976); (b) M. Dupuis, private communication.
(25) The optimized full ab initio parameters (within 0.01 Å) are $R(C_\alpha—C_N)$ = 1.384, R(C—N) = 1.165, $R(C_\alpha—H)$ = 1.088 Å; $\theta(HC_\alpha H)$ = 118.6°. The optimized PRDDO parameters are $R(C_\alpha—C_N)$ = 1.366, R(C—N) = 1.197, $R(C_\alpha—H)$ = 1.104 Å; $\theta(HC_\alpha H)$ = 117.0°.
(26) The bond orders evaluated from PRDDO wave functions at the optimum full ab initio geometry are 1.36 and 2.60 for the C_α—C_N and C—N bonds, respectively.
(27) Calculations were carried out using $R(C_\alpha—C_N)$ = 1.456 and R(C—N) = 1.16 Å for the ions and also with $R(C_\alpha—C_N)$ scaled by the ratio $R(C_\alpha—C_N)_{ab\ initio}/R(C_\alpha—C_N)_{PRDDO}$ obtained for **2**.
(28) (a) A. P. Sloan Fellow, 1977–1979; (b) Camille and Henry Dreyfus Teacher-Scholar, 1978–1983; (c) Du Pont Young Faculty Grantee, 1978; (d) Lando Fellow, summer 1979.
(29) NOTE ADDED IN PROOF. Preliminary data indicated that full geometry optimization of **7** and **5** may result in a change in the order of stability such that **7** may be slightly more stable than **5**. This would reflect the difference of an H/α-CN ratio for **6** and **3** vs. a CH_3/α-CN ratio for **7** and **5**.

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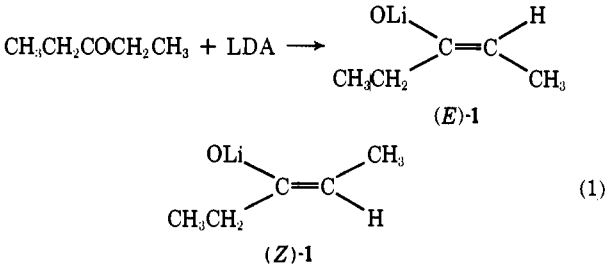
Role of HMPT and TMEDA in Control of Enolate Stereochemistry for Reactions of Lithium Amides with 3-Pentanone

Sir:

In his pioneering study of the stereochemistry of enolate formation, Ireland reported a remarkable solvent effect of HMPT (hexamethylphosphoric triamide).[1] Deprotonation of 3-pentanone with LDA (lithium diisopropylamide) in THF (tetrahydrofuran) solution gave chiefly the *E* enolate [77% (*E*)-**1**, 23% (*Z*)-**1**; eq 1]. The same sequence in a THF/HMPT

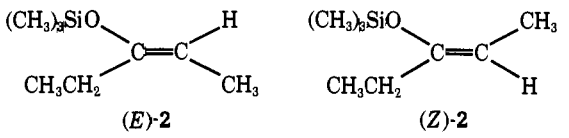


(1)

solvent mixture gave predominantly *Z* enolate [5% (*E*)-**1**, 95% (*Z*)-**1**]. Ireland suggested that the observed stereoselectivity arises in either case by a kinetically controlled process and that the increased *Z* stereoselectivity is a consequence of the lesser coordinating ability of lithium for carbonyl oxygen in a solvent mixture containing HMPT. Similar effects of HMPT on anion stereochemistry have been reported by Ireland and by other workers for deprotonation reactions of a variety of ketones,[2] esters,[1] hydrazones,[3] and oxazolines.[4]

Because control of enolate stereochemistry is vital to the stereochemical outcome of the aldol reaction,[2,5-6] we have begun a study of the factors which determine the stereoselectivity of enolate formation. We now report evidence that, for deprotonation reactions of 3-pentanone with lithium amide bases, predominant *Z* stereoselectivity is a consequence of thermodynamic control. Under conditions where kinetic control is ensured, predominant *E* stereoselectivity is observed in the presence or absence of HMPT or the related solvent additive, TMEDA (*N,N,N,N*-tetramethylethylenediamine).

Standard solutions of enolates (*E*)-**1** and (*Z*)-**1** were prepared by addition of 3-pentanone to a slight excess (1.1 equiv) of a 1.0 M solution of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF at 0 °C. The enolate content of the solutions was determined by quenching aliquots with trimethylchlorosilane followed by GlC analysis for the corresponding trimethylsilyl ethers, (*E*)-**2** and (*Z*)-**2**. The total yield of enolate



was thus established to be 90–100% with an (*E*)-**1**:(*Z*)-**1** ratio of 87:13. The stability of these standard solutions was studied under a variety of conditions. Both enolate total yield and (*E*)-**1**:(*Z*)-**1** ratio did not change over a period of 24 h at 25 °C in the absence of any additive or in the presence of 1.0–4.0 equiv of HMPT or TMEDA. However, addition of 0.2 equiv of 3-pentanone caused a rapid isomerization (complete in 30 min at 0 °C) to an equilibrium mixture of enolates with an (*E*)-**1**:(*Z*)-**1** ratio of 16:84. The rate of this isomerization was appreciably faster (complete in <10 min at 0 °C) in the presence of HMPT or TMEDA. We observed a modest effect of both HMPT and TMEDA on the position of enolate equilibrium at 0 °C: (*E*)-1:(*Z*)-**1** ratio of 10:90 (1.0 equiv of HMPT); 6:94 (4.0 equiv of HMPT); 16:84 (1.0 equiv of TMEDA); 11:89 (4.0 equov of TMEDA).

Although α hydrogen exchange[7] between ketone and enolate would provide a mechanism for enolate isomerization, such a process is probably too slow to account for the rapid isomerization observed at 0 °C. Furthermore, we observe that benzophenone, a ketone without α hydrogens, promotes enolate isomerization about as efficiently as 3-pentanone. We suggest that the most likely isomerization mechanism is reversible aldol condensation:

$$(E)\text{-}\mathbf{1} + R_2CO \rightleftharpoons R_2COLiCH(CH_3)COCH_2CH_3 \rightleftharpoons (Z)\text{-}\mathbf{1} + R_2CO \quad (2)$$

We note that, as a consequence of this rapid isomerization, it is possible to control the deprotonation of 3-pentanone in THF solution alone so as to produce predominantly enolate (*E*)-**1** [87% (*E*)-**1**, by addition of the ketone to 10% excess LiTMP at 0 °C] or predomiantly enolate (*Z*)-**1** [84% (*Z*)-**1**, either by addition of the ketone to a slight deficiency of LiTMP or by addition of a stoichiometric amount of LiTMP dropwise to a solution of the ketone at 0 °C].

Since enolate equilibration occurs only by reaction of enolate with starting ketone, a true kinetically controlled deprotonation of 3-pentanone should be favored by high base/ketone ratios. Accordingly the relative amounts of (*E*)-**1** and (*Z*)-**1** enolates formed by deprotonation of varying amounts of 3-pentanone with fixed amounts of LiTMP[8] in THF solutions containing HMPT or TMEDA was determined and the results are presented in Table I. Addition of 0.9 equiv of 3-pentanone to THF

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Table I. Deprotonation of 3-Pentanone with LiTMP (1.0 mmol) in THF Solution at 0 °C in the Presence of Solvent Additives[a]

3-pentanone + LiTMP → (*E*)-**1** + (*Z*)-**1**

entry	3-pentanone, mmol	additive, mmol	(*E*)-**1**:(*Z*)-**1**	overall yield, %[b]
1	0.9		86:14	100
2	0.45		86:14	90
3	0.9	HMPT, 1.0	8:92	89
4	0.45	HMPT, 1.0	65:35	75
5	0.25	HMPT, 1.0	66:34	80
6	0.45	HMPT, 2.0	54:46	70
7	0.45	HMPT, 4.7	52:48	89
8	0.9	TMEDA, 1.0	17:83	70
9	0.45	TMEDA, 1.0	91:9	90
10	0.25	TMEDA, 1.0	95:5	70
11	0.45	TMEDA, 2.0	88:12	77
12	0.45	TMEDA, 4.7	86:14	90

[a] 3-Pentanone was added dropwise to a solution of LiTMP in 1.0 mL of THF containing the indicated amount of solvent additive. After 15 min, 1.2 mmol of trimethylchlorosilane was added, followed, after an additional 30 min, by 2.5 mL of saturated aqueous $NaHCO_3$. Aliquots were analyzed by GLC (⅛ in. × 40 ft stainless steel column packed with 20% Se-30 on Chromosorb W, 100 °C) for the silyl ethers, (*E*)-**2** and (*Z*)-**2**. Pure samples of (*E*)-**2** and (*Z*)-**2** were isolated by preparative GlC and exhibited spectral properties in agreement with published values.[9] [b] Overall yields obtained by internal GLC standard, based on 3-pentanone.

solutions at 0 °C containing LiTMP and either HMPT (entry 3) or TMEDA (entry 8) produces mainly enolate (*Z*)-**1**. However, addition of only 0.45 equiv of 3-pentanone to the same solutions produces mainly enolate (*E*)-**1** (entry 4, HMPT; entry 9, TMEDA). Furthermore, the absolute amount of (*E*)-**1** obtained from 0.45 equiv of 3-pentanone is greater than the absolute amount of (*E*)-**1** obtained from 0.9 equiv of 3-pentanone (compare entries 3 and 4 and entries 8 and 9). Clearly, isomerization of (*E*)-**1** to (*Z*)-**1** must occur in the reactions with 0.9 equiv of ketone. When even smaller amounts of 3-pentanone are added to the fixed amount of LiTMP, slightly greater *E* selectively is observed until a maximum value is reached where the (*E*)-**1**:(*Z*)-**1** ratio is 66:34 (HMPT, entry 5) or 95:5 (TMEDA, entry 10). We believe that these latter ratios are the results of a true kinetically controlled deprotonation and we note that under such conditions deprotonation actually occurs with slightly greater *E* selectivity in the presence of TMEDA (a well-known chelate for lithium) than in THF alone (entires 1 and 2). Kinetically controlled deprotonation of 3-pentanone in the presence of HMPT does give increased *Z* selectivity, but the major enolate formed under these conditions is still the *E* isomer (entries 5–7).

It is possible that the explanation presented here for the role of HMPT in controlling the stereochemistry of a ketone enolate may apply to the previously reported[1-4] deprotonation reactions of other carbon acids. If this is true, efficient anion equilibration mechanisms[10] must be available to such systems. We are actively exploring these possibilities.

Acknowledgment is made to the National Science Foundation and to the Alfred P. Sloan Foundation for partial support of this research.

References and Notes

(1) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(2) Klebshick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247.
(3) Davenport, K. G.; Eichenauer, H.; Enders, D.; Newcomb, M.; Bergbreiter, D. E. *J. Am. Chem. Soc.* **1979**, *101*, 5654.
(4) Hoobler, M. A.; Bergbreiter, D. E.; Newcomb, M. *J. Am. Chem. Soc.* **1978**, *100*, 8182. Meyers, A. I.; Snyder, E. S.; Ackerman, J. J. H. *Ibid.* **1978**, *100*, 8186.
(5) Dubois, J. E.; Fellman, P. *Tetrahedron Lett.* **1975**, 1225.
(6) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120.
(7) House, H. O. "Modern Synthetic Reactions," 2nd ed.; W. A. Benjamin: New York, 1972; pp 492–510.
(8) Similar results were obtained with LDA in place of LiTMP except (*E*)-**1**:(*Z*)-**1** ratios were slightly greater with LiTMP under conditions of kinetic control, as reported by Kuwajima.[9]
(9) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Tetrahedron Lett.* **1978**, 2079.
(10) Simple aldol-type equilibrations of the type shown in, e.g., **2** are probably too slow (or are irreversible) to account for the results with other carbon acids.

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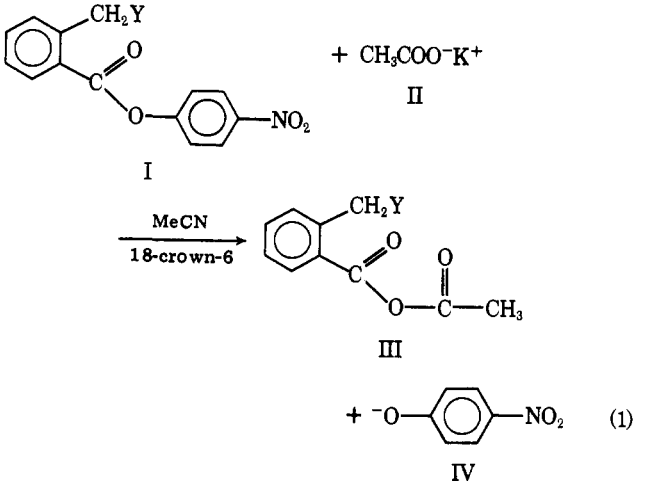
Catalytic Mechanisms of Acyl Transfer Reactions in Dipolar Aprotic Media. 1. Desolvated Carboxylate Ion as Acyl Acceptor[1]

Sir:

Elucidation of the mechanism of acyl transfer reactions in nonprotic media has become a timely and important problem since it was discovered that the active site of hydrolytic enzymes contains hydrophobic regions.[2] Nonenzymic model reactions are of potential value in this context as they can provide important insights and chemical precedents crucial for understanding the mechanism of enzyme catalyzed acyl transfer reactions.

In this communication we report that generating "naked" carboxylate ions in dipolar aprotic environment enhances the nucleophilic reactivity of the anion to the extent that it allows facile interconversion of *p*-nitrophenyl esters into highly reactive mixed anhydrides. Specifically, we have found that addition of potassium acetate to an anhydrous acetonitrile solution of the crown ether 18-crown-6 affords CH_3COO^- ions which readily cleave *p*-nitrophenyl *o*-toluates (eq 1) via direct



(1)

nucleophilic addition at the scissile carbonyl carbon. *o*-Toluyl acetate (III) is produced and 1 equiv of *p*-nitrophenolate is liberated. The reaction represents an example of *intermolecular* conversion of an ester to a highly reactive anhydride by a carboxylate nucleophile. By analogy the reaction also provides a physical organic model for the possible mechanism of enzyme-catalyzed acyl transfer reactions involving the catalytic participation of a "buried" carboxylate residue. Such glutamate and aspartate functions have been found at the active site of metalloproteases[3] as well as other hydrolytic enzymes which contain no catalytic serine residues.[4]

The reaction between desolvated acetate and *p*-nitrophenyl *o*-toluate proceeds at room temperature in quantitative yield

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