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AN ANALYSIS OF THE DIASTEREOMERIC TRANSITION STATE INTERACTIONS FOR THE KINETIC DEPROTONATION OF ACYCLIC CARBONYL DERIVATIVES WITH LITHIUM DIISOPROPYLAMIDE*

Acharan S. Narula
Research School of Chemistry, Australian National University
P.O. Box 4, Canberra, A.C.T. 2600, AUSTRALIA

SUMMARY: Consideration of $A^{(1,2)}$ and $A^{(1,3)}$-strain in the transition states for the deprotonation of carbonyl compounds using LDA as a base has powerful predictive value.

Since Stork's highly original and fundamental observation that the kinetically derived less stable lithium enolates can often be alkylated without equilibration, and House's pioneering demonstration that lithium enolates can be readily prepared under kinetic or thermodynamic control from ketones with lithium diisopropylamide (LDA), their use in synthesis has grown enormously.[1] Current interest[2] in the synthesis of polyketide-derived natural products such as macrolide, ansamycin and polyether antibiotics has demonstrated[3] that the elusive goal of stereo-[4] and enantioselective[5,6] construction of carbon-carbon bonds can be successfully achieved through the use of an appropriate metal enolate (Metal = Li, B, Zr, etc.). This has resulted because of the availability of the diastereomerically pure E- and Z-metal enolates,[4,5,6] and the experimental realization that a high kinetic selection can be achieved in aldol and related processes.[4,5,6]

Although, a few recent reports[7] on erythro-selective aldol condensations have appeared, which are independent of the enolate geometry, nonetheless it is of fundamental importance to underline the factors which control the stereoselective formation[8] of metal enolates. This letter is an attempt to evaluate the diastereomeric transition state (TS) interactions involved in the kinetic deprotonation of acyclic carbonyl derivatives, employing LDA as a hindered base.[9] Table 1, provides a reflection of the observed kinetic enolate ratios from several ethyl carbonyl derivatives and although substrates such as R = H, Me, C=C or $-(CH_2)_n$ are not included, the discussion to follow is general in scope, and may be relevant to a consideration of the derivatives of imines, oxazolines, thioamides, N,N-dimethylhydrazones, N-pyrrolidylpropionamide and N-acyloxazolidones, etc.

Transition-State Model: In the pioneering study on the kinetic deprotonation of esters and ketones (Table 1, "entries 1a,e,n,p) Ireland and Coworkers[10] "imagined" transition states (4) and (5) for the selective formation of trans(E)-enolates in THF and cis(Z)-enolates in 23% HMPA-THF. Although, Ireland's model has an enormous aesthetic appeal in being a chair six-membered ring and has been extended by others to include derivatives of oxazolines,[16]

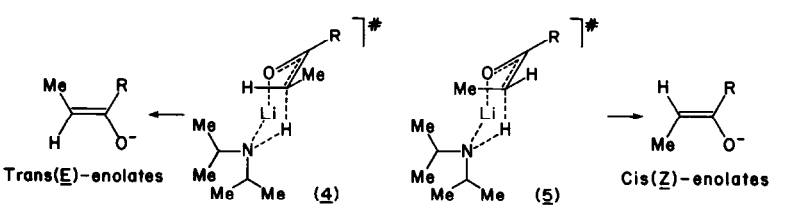

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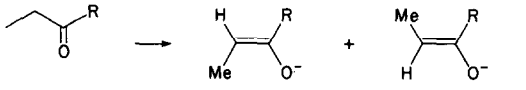
Table 1. Kinetic Enolate Ratios in the Deprotonation of Various Ethyl Carbonyl Derivatives (1a-p)



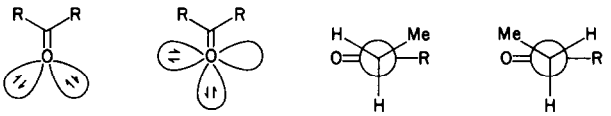
(1a-p) Cis(Z)-enolates (2a-p) Trans(E)-enolates (3a-p)

Entry	R	Base, Solvent, Temp.	(Z : E ratio) ref.
1a	C_2H_5	LDA, THF, -78°	(23:77)[10]
1b	C_2H_5	LTMP, THF, 0°	(16:84)[11]
1c	$SiMe_3$	LDA, THF, -70°	(38:62)[4]
1d	mesityl	LDA, THF, -70°	(5:95)[4]
1e	OMe	LDA, THF, -78°	(5:95)[10]
1f	OCH_2OMe	LDA, THF, -78°	(2:98)[12]
1g	$S.^{t-}C_4H_9$	LDA, THF, -78°	(10:90)[13]
1h	phenyl	LDA, THF, -70°	(98:2)[4]
1i	$t\text{-}C_4H_9$	LDA, THF, -70°	(98:2)[4]
1j	pyrrolidyl	LDA, THF, -78°	(95:5)[13]
1k	1-admantyl	LDA, THF, -70°	(98:2)[4]
1ℓ	C_2H_5	ETSA-TBAF, -78°	(99.5:0.5)[11]
1m	C_2H_5	$(i\text{-}C_3H_7)_2NEt$, ether, -78°	(99:1)[14]
1n	C_2H_5	LDA, THF-HMPA (23%), -78°	(95:5)[10]
1o*	C_2H_5	LTMP, THF-TMEDA or THF-HMPA, 0°	(83:17),[15] (92:8)[15]
1p	OMe	LDA, THF-HMPA (23%), -78°	(95:5)[10]

*Rathke and Coworkers have recently shown[15] that the selective formation of Z-enolates under these conditions is a consequence of the thermodynamic control, which is in contrast to Ireland's original suggestion,[10] where kinetic control was considered operative (Entry 1n,1p).

dimethyl-hydrazones[17] etc., unfortunately, it fails to satisfy the stereoelectronic requirements[18] of enolization (notice that the base does not approach along the axis of the correctly aligned α C-H bond being broken), and that by increasing the bulk of the base (maximizing 1,3-diaxial interaction), selectivity does not improve markedly (Table 1, entry 1b). More recently, Heathcock and Coworkers[4] have rationalized their results in terms of the preferred conformation of the starting ketone. Such an analysis however, could not explain the selective formation of E-enolates (Table 1, entries 1a-g), and in order to accommodate the observed results, the stereoelectronic constraints had to be sacrificed.

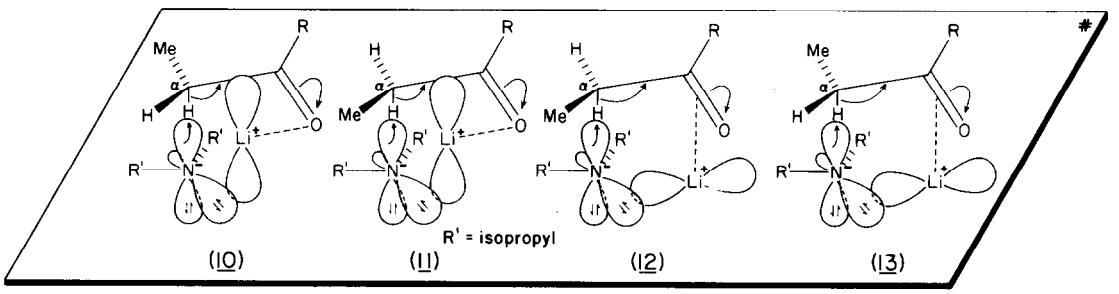
Before we present our transition state model, we note that (i) contrary to the conventional representation (6) of equivalent lone pairs on oxygen of the carbonyl group, the two lone pairs are non-equivalent both in terms of their energy and orientation (cf. 7), (ii) the non-bonding lone pair in an MO of π-symmetry is the HOMO, and π CO the next HOMO,[19] (iii) stereoelectronic considerations require conformations (8) and (9) to be vital at the transition state, when strong bases are employed for deprotonations, although partial carbanionic character has developed at the α-carbon,[18] and (iv) in solvents of low dielectric constant such as THF (ε = 7.6), solvation of LDA leading to ion-pairing, must be quite important.



(6) (7) (8) (9)

Thus kinetically, chelation of Li^+ along the non-bonding HOMO of the C=O group would be a favourable process,[20] and in an event such an approach is sterically demanding, chelation of the lithium cation along the next HOMO (π-CO) would be the preferred pathway.

With the above considerations in mind, transition states such as (10, 11, 12, and 13) emerge as possible candidates for the "kinetic" deprotonation of carbonyl derivatives.



(10) (11) (12) (13)

Notice that the Coulombic attraction between the amide anion and lithium cation provides compactness to all of the above competing diastereomeric transition states. Clearly, such transition states can however be expected to be highly sensitive to the presence of strongly coordinating ligands (inter- and intramolecular type), since they would themselves effectively compete with the amide anion for chelation with lithium cation.

Evaluation of the Diastereomeric-Transition State Interactions for the Kinetic Deprotonation of Acyclic Carbonyl Compounds: A careful inspection of the transition states (10-13) reveals that allylic strain ($A^{1,2}$- and $A^{1,3}$-) arguments[21,22] can shed light, as to which transition state would dominate, as the steric and electronic character of R is varied. When R is sterically not very demanding[23] (Table 1, entries 1a-g), chelation of Li^+ along the C=O HOMO would project transition states (10 and 11) to be significant. Clearly, transition state (10) leading to E-enolates is energetically more favourable, since transition state (11) experiences a severe $A^{(1,3)}$-strain between the solvated bulky -OLi and methyl group at the α-carbon. As R becomes bulky (Table 1, 1h-k), chelation of Li^+ along the next HOMO of the carbonyl group (π-CO) would be favoured, which leaves transition states (12 and 13) to choose from. Since transition state (13) is destabilized as a consequence of $A^{(1,2)}$-strain between the Me at C-α and R group, ($A^{(1,2)}$-strain operates best when group R is sterically demanding and/or can effectively conjugate with the unsaturated carbon), transition state (12) leading to Z-enolates is favoured. For entry 1j, it is worth noting that transition states (12 and 13) represent chelation of Li^+ along the HOMO, and thus formation of Z-enolates from amides is favoured on both kinetic and thermodynamic grounds.

To substantiate further our analysis which relies heavily upon the compact nature of the transition states, made possible by using LDA as a base, we note that the kinetic deprotonations (Table 1, entries 1ℓ,m) employing ethyl trimethylsilyl acetate-tetrabutyl-

ammonium fluoride (catalyst) and diisopropyl ethyl amine, reverses the product ratio and leads to the selective formation of Z-enolates. Such results can be best interpreted in terms of an open transition state in line with Heathcock's arguments.[4] Discussion for entries 1,o,n (and possibly 1p) is inconsequential, since the product ratio reflects equilibration.[15]

In conclusion, the discussion presented above, provides yet another demonstration of the value of frontier orbitals to the understanding of chemical reactivity.

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