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Origin of stereochemistry in Meyers enolate alkylations. Importance of major enolate structure and population in tetrahydrofuran

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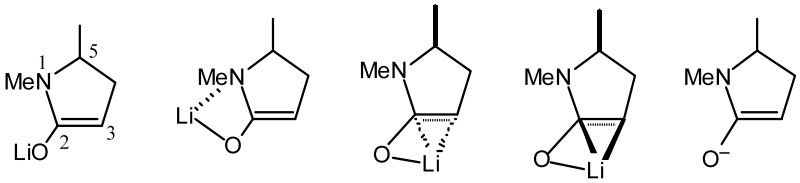
Abstract—It was found that in tetrahydrofuran solution, predominance (99.2%) of the highly stabilized Meyers enolate (1,5-dimethylpyrrolidin-2-one lithium enolate (**1**)) isomer with intramolecular Li-$\pi_{C=C}$ coordination from the *endo*-face (**C***t*-*endo*) may be responsible for exceedingly high *endo*-selectivity in Meyers enolate alkylation.

The origin of π-facial stereoselection remains a controversial issue in organic chemistry.[1] Particularly intriguing is the behaviors of Meyers' bicyclic lactam enolates.[2] Recently, Meyers and co-workers reported a study on π-facial diastereoselection in the alkylation of the simple cyclic lactam enolate (**1**) derived from 1,5-dimethylpyrrolidin-2-one.[3] Exceedingly high *endo*-selectivity (99%) using alkyl halide as an electrophile was interpreted in terms of frontier orbital theory. On the other hand, Houk et al. have recently reported that torsional and steric effects might be responsible for unusually high diastereoselection.[4] Reported herein is a simple explanation for the stereoselectivity of **1** based on the EFOE Model.[5]

Elaborate experiments have shown that monomeric enolate(s) would be reactive species[6] and that virtually no solvent effects were detected on diastereoselectivity in Meyers enolate alkylations.[2] In principle, monomer enolate **1** can exist in five forms: the free Li enolate (**E**), the intramolecular Li–N complex (**N**), the intramolecular Li-$\pi_{C=C}$ complexes (**C**-*endo* and **C**-*exo*) and Li-free anion (**A**). Each form of these species has two stereoisomers with respect to the spatial configuration of the two methyl groups at N1 and C5 (*cis* (**X***c*) and *trans* (**X***t*); **X** = **E**, **N**, **C** or **A**).

Table 1 shows the relative stability of all these monomer enolate species except for anions (**A***t* and **A***c*) and **C***c*-*endo* conformer[7] in gas phase and in tetrahydrofuran (THF) solution.[8,10] It is clear that *trans*-conformations are uniformly more stable by 0.2–3 kcal mol^{-1} than the corresponding *cis* forms in both phases. Minor differences in the composition of enolate species between gas phase and THF solution are seen from Table 1. In both phases, the most populated species (over 98%) is the $\pi_{C=C}$-coordinated stereoisomer (**C***t*-*endo*), in which Li cation interacts with the enolate C=C π-bond from the *endo*-face. In gas phase, enolate species would be the three isomers of **C** (**C***t*-*endo* (98.3%), **C***t*-*exo* (1.0%) and **C***c*-*exo* (0.7%)). In each enolate, considerable pyramidalization at the α-carbon (C3) is observed due to coordination of Li at the C=C bond.[9] In THF solution, however, in addition to these gas-phase species (**C***t*-*endo* (99.2%), **C***t*-*exo* (0.1%) and **C***c*-*exo* (0.3%)), a small amount of free lithium enolate **E***t* shows up (0.4%). Figure 1 displays these structures.



E **N** **C**-*endo* **C**-*exo* **A**

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Table 1. Thermodynamic stability of possible enolate isomers (**1**) in gas phase and in tetrahydrofuran (THF)

Enolates (**1**)[a]	Gas phase[b]		THF[c]	
	Rel. E[d] (kcal mol^{-1})	Population[e] (%)	Rel. E[d] (kcal mol^{-1})	Population[e] (%)
C*t*-*endo*	0.00	98.3	0.00	99.2
C*t*-*exo*	1.78	1.0	2.61	0.1
C*c*-*endo*[f]	–	–	–	–
C*c*-*exo*	1.98	0.7	2.29	0.3
E*t*	7.60	0.0	2.15	0.4
E*c*	10.42	0.0	4.90	0.0
N*t*	4.57	0.0	3.49	0.0
N*c*	6.50	0.0	4.68	0.0

[a] See also the text and Figure 1 for enolate structures and notations.
[b] B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d).
[c] THF = tetrahydrofuran (dielectric constant = 7.58); B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) using the PCM method.[8,10]
[d] ZPE-corrected energy relative to the most stable enolate species (**C***t*-*endo*).
[e] Relative abundance calculated at 195.15 K (−78°C).
[f] Converted into **C***t*-*endo* upon geometry optimization.[7]

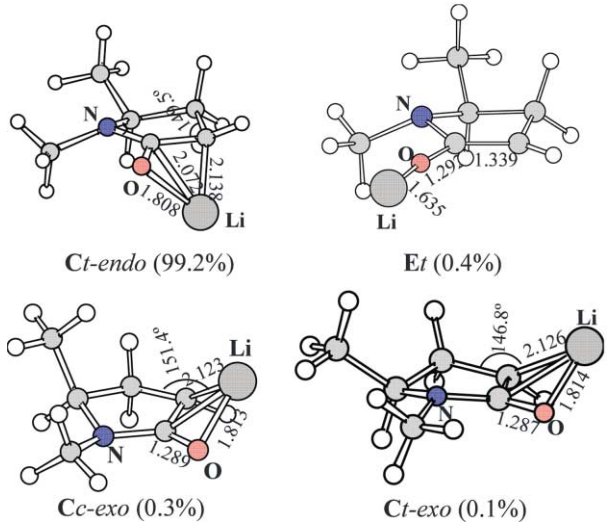


Figure 1. Structures and relative stability (%) of Meyers' enolate (**1**) in THF solution (PCM method;[10] B3LYP/6-311+G(d,p)//B3LYP/6-31G(d); bond lengths are in Å and angles in degrees).

It was suspected that this isomer ratio in THF solution (**C***t*-*endo* (99.2%), **C***t*-*exo* (0.1%), **C***c*-*exo* (0.3%) and **E***t* (0.4%)) might reflect the high diastereoselection (*endo*:*exo* = 99:1) in the S_N2 process involving **1**. Since π-facial diastereoselectivity should depend on the facial difference in the reaction rates (rate constant times concentration) between two π-faces, it is highly likely that preferred diastereoselectivity in Meyers' enolate alkylation should depend mainly on π-facial environment in the most stable enolate species (**C***t*-*endo*) in THF solution. To this end, the exterior frontier orbital extension model (the EFOE model)[5] was employed to delineate whether or not **C***t*-*endo* species truly predicts observed overwhelming *endo* stereochemistry. The results, obtained using the HOMOs of the enolates, are collected in Table 2 along with those of other species including the free anions (**A***t*, **A***c*) for comparison (HF/6-31G(d)//B3LYP/6-31G(d)).[10]

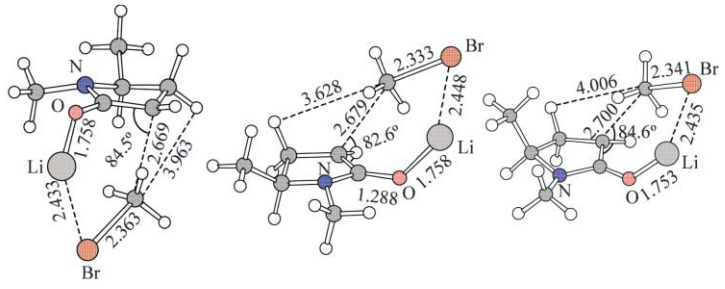
The following points are evident from Table 2. First, none of the two nitrogen-coordinated species (**N***t* and **N***c*) predicts distinct *endo*-selectivity: their EFOE densities fall between 1.2–1.4%. Secondly, other *cis*-species (**C***c*-*exo*, **E***c* and **A***c*) and **C***t*-*exo* predict preferential *exo* stereochemistry: both EFOE densities and PDAS values are much larger over the *exo*-faces (1.540–2.055%; 58.4–120.8 au^3) than those over the *endo*-faces (0.575–1.156%; 17.9–83.6 au^3). Consequently, they (**N***t*, **N***c*, **C***c*-*exo*, **C***t*-*exo*, **E***c* and **A***c*) should not be responsible for the observed high *endo*-selectivity. The remaining three species (**C***t*-*endo*, **E***t*, and **A***t*) all predict *endo*-selectivity. Among these, **C***t*-*endo* is the most populated species both in gas phase (98.3%) and in THF (99.2%). As clearly seen in Table 2, **C***t*-*endo* shows much higher EFOE density and PDAS values in the *endo*-face (1.780%, 58.1 au^3) than in the *exo*-face (0.587%, 19.7 au^3). Since a PDAS value around 20 au^3 is generally considered as highly sterically hindered for alkylation,[12] its *exo*-face, having only 19.7 au^3 of reagent accessible space (PDAS), must be extremely sterically hindered for an alkylation process to take place owing to a high degree of pyramidalization at the α-carbon (C3) toward Li.[9] Moreover, the HOMO of **C***t*-*endo* is much less extended over the *exo*-face (EFOE density = 0.587%) than that over the *endo*-face (1.780%) at C3. Accordingly, in THF solution, EFOE analysis predicts at least 99.2% *endo*-selectivity due to **C***t*-*endo* (abundance: 99.2%) and at least 0.4% *exo*-selectivity due to **C***t*-*exo* (0.1%) and **C***c*-*exo* (0.3%) in excellent agreement with experiment.[2,4] The observation that high *endo*-selectivity was unaffected by solvent polarity[2] could be rationalized in terms of the predominance of the *endo*-selective enolate species (**C***t*-*endo*) in common organic solvents.

In agreement with the above results, three transition states (TS) of alkylation were located using MeBr as an electrophile (Fig. 2).[8] In consonant with experimental stereoselectivity, the two conformers of *exo*-TS are less stable than the *endo*-TS (*trans*) in both phases. These TS show the following unique structural features. The angle of electrophile approach to C3 (∠MeBr–C3–C2)

Table 2. EFOE analysis of possible enolate isomers (**1**)[a]

Enolates (**1**)[b]	EFOE density[c] (%)		PDAS[d] (au^3)		Predicted stereochemistry
	endo	*exo*	*endo*	*exo*	
C*t*-*endo*	1.780	0.587	58.1	19.7	*endo*
C*t*-*exo*	0.866	1.540	23.4	61.6	*exo*
C*c*-*exo*	0.575	1.743	17.9	58.4	*exo*
E*t*	1.767	1.008	147.1	81.5	*endo>exo*
E*c*	1.035	1.618	83.6	105.7	*exo>endo*
N*t*	1.269	1.253	111.0	67.6	*endo>exo*
N*c*	1.420	1.243	102.0	108.4	*endo<>exo*
A*t*	2.125	1.220	159.7	72.7	*endo>exo*
A*c*	1.156	2.055	64.8	120.8	*exo>endo*

[a] HF/6-31G(d)//B3LYP/6-31G(d). See Ref. 11 for the conditions of EFOE analysis.
[b] Refer to the text and Figure 1 for enolate structures and notations.
[c] Exterior frontier orbital electron density of HOMO at C3 expressed in %.[5]
[d] π-Plane-divided accessible space at C3 in au^3.[5b]



	endo-TS (*trans*)	*exo*-TS (*trans*)	*exo*-TS (*cis*)
Gas Phase	0.00 (98%)	9.30 (0%)	1.43 (2%)
THF	0.00 (96%)	1.29 (3%)	1.82 (1%)

Figure 2. Transition structures of the alkylation of Meyers' enolate (**1**) (bond length are in Å and angles in degrees). Numbers indicate relative total energies in kcal mol^{-1} (ZPE-corrected) (top) and relative abundance (bottom; in parenthesis) in gas phase and in THF solution.[8,10]

is less than 90° (82.6–84.6°) owing to the coordination of Br to Li. The distances between the carbon of MeBr and the nearest hydrogen at C4 are greater than 3.5 Å, which is far longer than the sum of the van der Waals radii of carbon (1.70 Å) and hydrogen (1.20 Å). π-Facial difference in the torsional strain[4] caused by eclipsing with the nearest adjacent hydrogens at C4 may therefore be unimportant as a factor of diastereoselection. The *endo*-process is much more preferred than the *exo*-process at −78°C both in THF (96%) and in gas phase (98%) (Fig. 2). This may also explain why the stereochemistry of Meyers' enolate alkylation shows marginal solvent effects.

A high degree of pyramidalization at C3,[9] caused by strong Li-coordination from the *endo*-face of the $\pi_{C=C}$ bond in **C***t*-*endo* enolate, should be responsible for severe steric hindrance and reduced HOMO extension over the *exo*-face. At first glance, intuitive estimation of steric effects in **C***t*-*endo* might predict opposite stereochemistry to be preferred, since the Li atom may exert significant steric hindrance to interfere with reagent access from the *endo*-face. Ingenuity in the design of Meyers' enolate might be found in the key role of the amide nitrogen that may induce substantial pyramidalization at C3 upon Li coordination.[9]

In conclusion, EFOE analysis of possible enolate species of **1** strongly indicates that the single enolate isomer (**C***t*-*endo*) may most probably be responsible for the origin of exceedingly high diastereoselectivity of Meyers' enolates.

Acknowledgements

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7. **C***c-endo* is converted into **C***t-endo* conformer upon geometry optimization.[8] The total energy of anion **A** plus Li^+ is less stable by $\sim$100 kcal mol^{-1} than the lithium enolate **E** (B3LYP/6-31G(d)). The existence of **A** may be less important as a possible candidate of reactive species.
8. All calculations were performed with Gaussian 98 (Rev. A.7) using 6-31G(d) basis for all optimizations except for Br, for which Huzinaga basis with polarization (43321/4321/321*) was used. Solvent effects were calculated in tetrahydrofuran (THF) (dielectric constant = 7.58) using Tomasi's PCM method at the B3LYP/6-311+G(d,p) level.[10]
9. Total angle around the α-carbon (C3) of **1**: 343.4° (**C***t-endo*), 343.7° (**C***t-exo*) and 341.1° (**C***c-exo*). The carbon analog of **1**, *trans*-2,3-dimethylcyclopentanone Li enolate isomers, show only marginal pyramidalization: total angle at α-carbon; 355.6° (**C***t-endo*) and 357.8° (**C***t-exo*) (B3LYP/6-31G(d)).
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11. The EFOE model assumes that FMO extension (exterior frontier orbital electron density = EFOE density) and reagent accessible space (steric effects; π-plane-divided accessible space = PDAS value) outside the molecular surface of the reactant should be major factors of facial stereoselection.[5] EFOE analysis was performed at the HF/6-31G(d) level with a lattice mesh of 0.1 au. Molecular surface was defined by Bondi's van der Waals radii. Integration of EFOE density was performed up to 10 au from the van der Waals surface. PDAS integration was performed up to 5 au from the van der Waals surface according to the original definition.[5]
12. For example, the PDAS value for the axial face of cyclohexanone, which undergoes preferential equatorial methylation with MeLi, is 19.4 au^3. Since an S_N2 reaction is generally sterically more demanding, it may well be expected that a PDAS value around 20 au^3 and an EFOE density less than unity may imply difficult process.