

Intermolecular Michael Reactions: A Computational Investigation

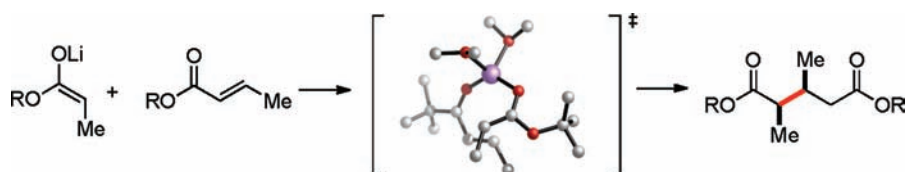
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ABSTRACT

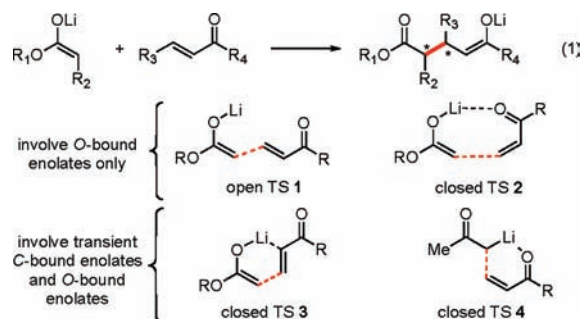


Computational studies have suggested that η^3 -lithium enolates in which the cation is partially bound to both carbon and oxygen may be important reactive intermediates. DFT calculations are used to demonstrate that explicitly solvated acetone enolates are largely *O*-bound. With this premise in mind, the stereochemical course of intermolecular Michael additions is examined. The results are generally consistent with what is observed experimentally and the model advanced by Heathcock and co-workers.

Since the pioneering work of Arthur Michael in the late nineteenth century,¹ the conjugate addition of stabilized carbanions to activated olefins has become a valued method for the construction of C–C bonds.² In particular, the union of lithium enolates with α,β -unsaturated carbonyl derivatives is a reliable process for the diastereoselective formation of vicinal stereocenters (Scheme 1).³ Here, computations are used to probe the nature of the intermediates involved (*O*-bound vs *C*-bound enolates) and the origin of stereoselectivity (6- vs 8-membered transition states).

From a thermodynamic standpoint, Michael reactions are exothermic by ~ 21 kcal/mol, the energetic benefit of replacing a C=C bond with a C–C bond.⁴ In contrast, the kinetic details of how the C–C bond is formed and the lithium ion is transferred from enolate to enolate are unknown. Canonically, lithium enolates are represented as *O*-bound structures, which can react with Michael acceptors through either open (1) or closed (2) transition states (TSs).

Scheme 1. Michael Reactions via *O*- vs *C*-Bound Enolates



Alternatively, if *C*-bound lithium enolates are viable, even if only as transient entities, then one can also imagine closed, six-membered TSs 3 and 4. Because such closed, six-membered TSs are known to relay stereochemical information with high fidelity, they are attractive motifs for understanding the origin of diastereoselectivity in intermolecular Michael reactions.

Although non-*O*-bound lithium enolates may seem exotic, they have been examined before. It has been found that η^3 - and *O*-bound lithioacetophenone are similar in energy.⁴ A more recent study found that the η^3 form of lithioacetone is

(1) (a) Michael, A. *J. Prakt. Chem.* **1887**, 3, 349–356. (b) Michael, A. *Am. J. Chem.* **1887**, 9, 112–114.

(2) Perlmutter, P. *Conjugate Additions in Organic Synthesis*; Tetrahedron Organic Chemistry Series; Pergamon Press: Oxford, 1992; Vol. 9.

(3) Oare, D. A.; Heathcock, C. H. *Stereochemistry of the Base-Promoted Michael Addition Reaction*. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1989; Vol. 19, pp 227–408.

(4) Rosi, M.; Sgamellotti, A.; Floriani, C. *J. Mol. Struct.* **1997**, 431, 33–46.

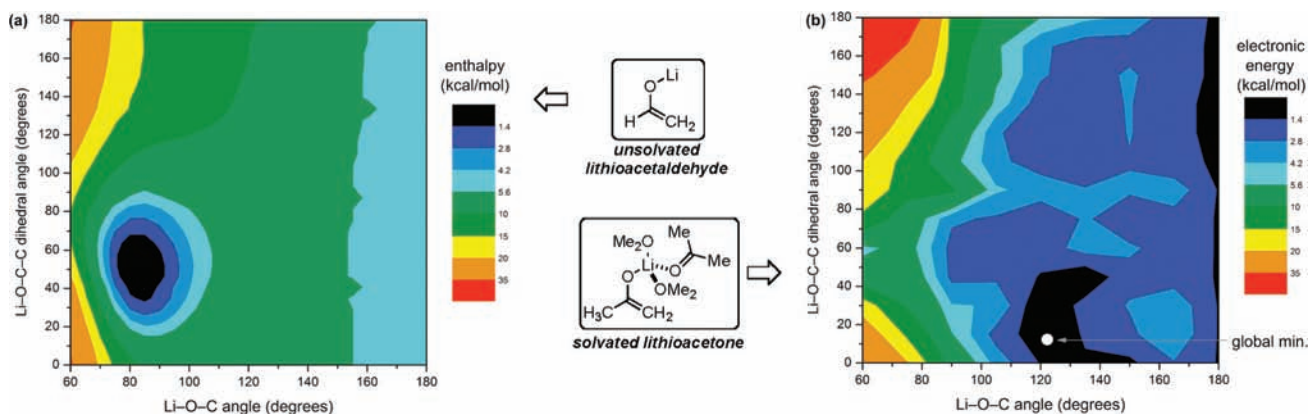


Figure 1. (a) Potential energy surface of unsolvated lithioacetaldehyde (enthalpy, MP2/6-31 g(d)); data plotted from ref 5. (b) Potential energy surface of trisolvated lithioacetone (electronic energy, M05-2X/6-31 g(d), two Me₂O ligands, one acetone ligand). Both plots are to the same scale; notice that solvation flattens the potential energy surface considerably.

its sole global energy minimum (Figure 1a).⁵ However, these gas-phase computations did not account for solvation, which can have a powerful effect. For example, η^3 -lithioimines are predicted to be global energy minima when lithium is doubly solvated by Me₂O, but canonical *N*-bound lithioimines are the global energy minima when lithium is triply solvated.⁶

To determine if non-*O*-bound lithium enolates are merely an artifact of incomplete solvation or are, in fact, chemically relevant, the explicitly trisolvated lithium enolate of acetone was examined by DFT.⁷ Two Me₂O ligands and one acetone ligand were chosen to approximate an enolate that is poised to undergo a Michael addition. The CH₂-C-O-Li dihedral angle and C-O-Li angle were systematically varied, while all of the other geometric parameters were allowed to relax. Since many different solvation configurations can have similar energies, at least three configurations were tried for each point (the energy of the most stable configuration is shown in Figure 1b). The M05-2X/6-31 g(d) method⁸ was chosen as an acceptable compromise between accuracy and computational cost.

The behavior of solvated lithioacetone is compared with that reported for unsolvated lithioacetaldehyde⁵ in Figure 1. While unsolvated lithioacetaldehyde has a relatively deep global energy minimum (its η^3 isomer), solvated lithioacetone has a relatively flat potential energy surface in which a continuum of geometries (blue) between the global minima (black) are feasible. Bent and linear *O*-bound structures correspond to global minima (Figure 2), while *C*-bound enolates are very high in energy (red). η^3 enolates (blue) are accessible but are not local minima. (NBO analyses

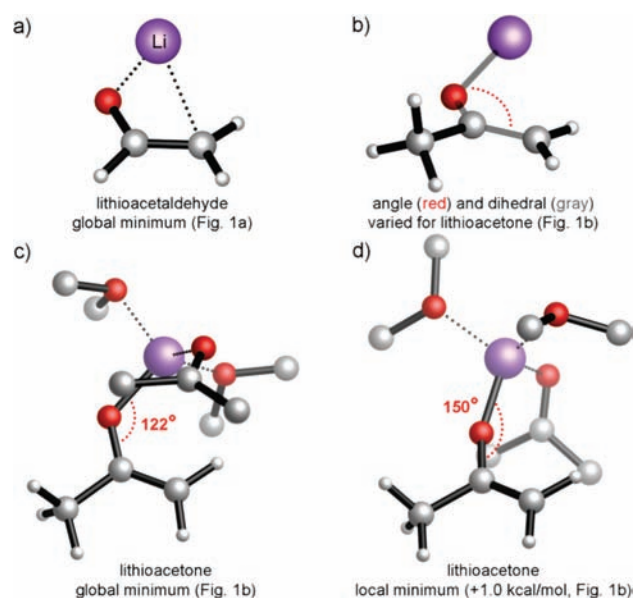


Figure 2. (a) η^3 global minimum⁵ of unsolvated lithioacetaldehyde in Figure 1a. (b) C-O-Li and CH₂-C-O-Li that were varied for solvated lithioacetone (Figure 1b, solvents hidden). (c) *O*-bound global minimum (white dot) in Figure 1b. (d) Another *O*-bound minimum in Figure 1b (black region on right-hand side) is similar in energy (+1.0 kcal/mol).

indicate that the bonding to lithium is mostly ionic in all cases.) Thus, *C*-bound lithium enolates are probably unimportant in Michael reactions. This is likely to be true whether the enolates are coordinatively saturated monomers (ethereal solvents as ligands) or oligomers (other enolates as ligands).

How is stereochemical information transferred in intermolecular Michael additions? In the Heathcock model,³ one considers the possible approaches of a lithium enolate to a Michael acceptor by making several assumptions: a monomeric *O*-bound enolate; an *s*-cis acceptor; a closed transition state; and a staggered conformation about the forming C-C bond. To examine this model computationally, the prototypi-

(5) Houk, R. J. T.; Anslyn, E. V.; Stanton, J. F. *Org. Lett.* **2006**, *8*, 3461–3463.

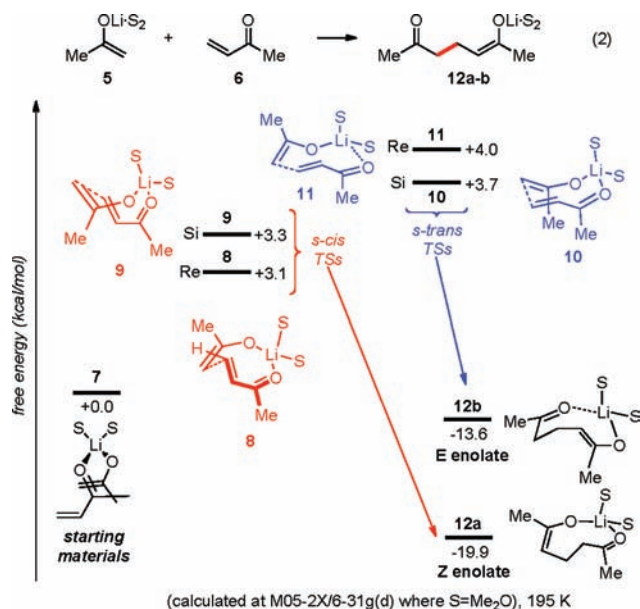
(6) Doubly solvated structures were the overall minimum (triply solvated structures, while enthalpically favored are entropically disfavored. Zuend, S. J.; Ramirez, A.; Lobkovsky, E.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 6939–6948.

(7) In contrast to the behavior of lithioimines (ref 6), serial solvation studies indicated that the triply solvated form of lithioacetone is the overall minimum.

(8) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157–167.

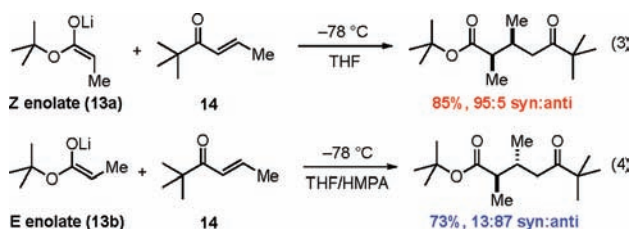
cal Michael reaction between solvated lithioacetone and methyl vinyl ketone (MVK) was chosen for analysis. Four transition states were located at the M05-2X/6-31g(d) level (8–11, Scheme 3).⁹ These correspond to closed, eight-

Scheme 3. Reaction between Lithioacetone and MVK



membered structures in which either the *Re* or *Si* face of lithioacetone is combined with *s-cis* or *s-trans* MVK. (No six-membered structures could be located.) Note that *s-cis* conformations lead to *Z*-enolates, while *s-trans* conformations lead to *E*-enolates.

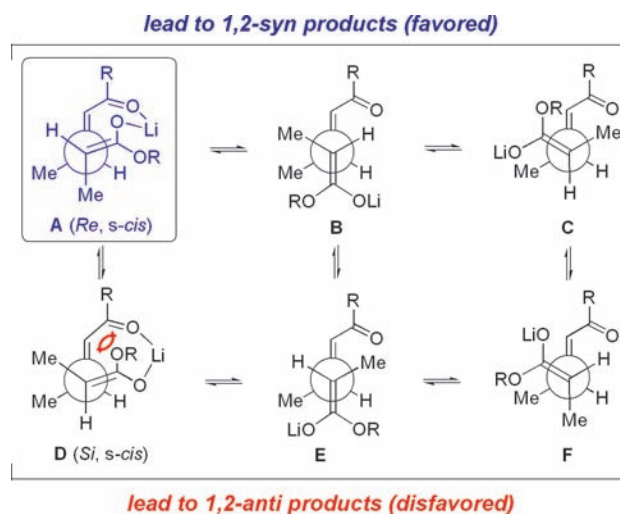
Interestingly, this revealed only a slight preference for *s-cis* over *s-trans* TSs. In contrast, Bernardi and co-workers found a substantial *s-cis* preference in the addition of lithioacetaldehyde to acrolein (HF/3-21g/MNDO).¹⁰ One explanation for this lack of preference for *s-cis* conformers is that neither lithioacetone nor MVK are sterically demanding reagents. To investigate this, and to allow a comparison between theory and experiment, reactions 3 and 4 were examined.¹¹



Here, the *Z*-enolate of *tert*-butyl propionate (13a) reacts with enoate 14 to give predominantly 1,2-*syn* product, while the corresponding *E*-enolate (13b) gives predominantly 1,2-*anti* product. The stereodivergent but highly selective nature of these reactions made them an attractive benchmark for these calculations.

How does the Heathcock model apply to reaction 3? One considers six staggered transition state conformers (A–F,

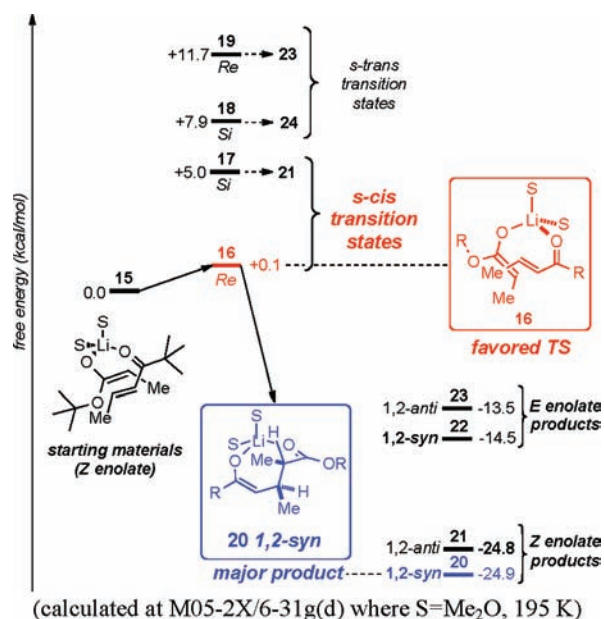
Scheme 4. Heathcock Model Applied to Reaction 3



Scheme 4), of which **A** and **D** are considered “closed” and, therefore, viable. The unfavorable OR/C(O)R interaction in **D** suggests that TS **A** should be favored. Therefore, *Z*-ester enolates should lead to 1,2-*syn* products; similarly, *E*-enolates should lead to 1,2-*anti* products. Both predictions agree with experiment (calculated at M05-2X/6-31g(d) where R = Me₂O, 195 K).

When reaction 3 was computed, four TSs were located (16–19, Scheme 5). This time, the *s-cis* TSs (16 and 17)

Scheme 5. Free Energy Profile for Reaction 3

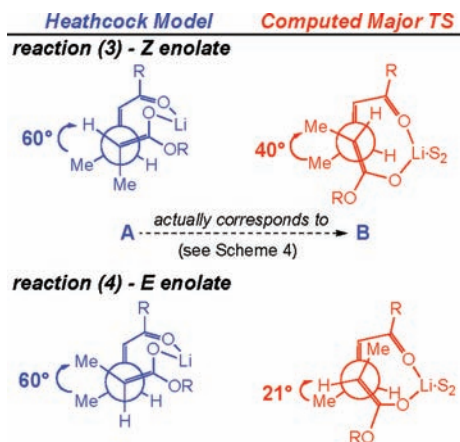


were much lower in energy than the *s-trans* ones (18 and 19). Additionally, the correct 1,2-*syn* product was predicted.

Similar results (not shown¹²) were obtained for reaction 4; the correct 1,2-anti product was predicted. Interestingly, these reactions seem to be virtually barrierless, perhaps in part because the computations do not account for enolate desolvation.

Even if the absolute barriers are incorrect, the relative barriers qualitatively agree with Heathcock's model. However, there are some important differences. The TS leading to the major product in reaction 3, **16**, should correspond to **A** but is more similar to **B** (Scheme 6). Note that **B**, labeled

Scheme 6. Major TSs: Heathcock Model vs Computed (DFT)



as an open TS in Scheme 4, is actually closed and, therefore, viable. (The major TS for reaction 4, not shown,¹² does correspond to the predicted one.) Additionally, Heathcock's model predicts fully staggered transition states (60° dihedral angle) with respect to the forming bond, but for both reactions 3 and 4, the computed angle is considerably less: 40° and 21°, respectively.

The diastereoselectivity of these reactions appears to result from the energy difference between **A** and **B**, rather than **A** and **D**. In these eight-membered TSs, the acceptor prefers an *s-cis* conformation to avoid a strained *trans*-cyclooctene-

(9) The M05-2X functional has been found to perform well for conjugate additions. Rokob, T. A.; Hamza, A.; Pápai, I. *Org. Lett.* **2007**, *9*, 4279–482. Frequency analysis confirmed that ground states were true local minima and that transition states had exactly one negative frequency. Single-point energies at M05-2X/6-311+g(d,p)//M05-2X/6-31g(d) gave identical trends (see the Supporting Information).

(10) (a) Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Scolastico, C. *Tetrahedron Lett.* **1991**, *32*, 823–826. (b) Bernardi, A.; Capelli, A. M.; Cassinari, A.; Comotti, A.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1992**, *57*, 7029–7034.

(11) Heathcock, C. H.; Oare, D. A. *J. Org. Chem.* **1985**, *50*, 3022–3024.

(12) See the Supporting Information for full details.

type geometry. This creates a steric interaction between the two *tert*-butyl groups in **B**, causing **A** to be favored (Figure 3). Thus, six-membered TSs are not required to explain stereoselectivity.

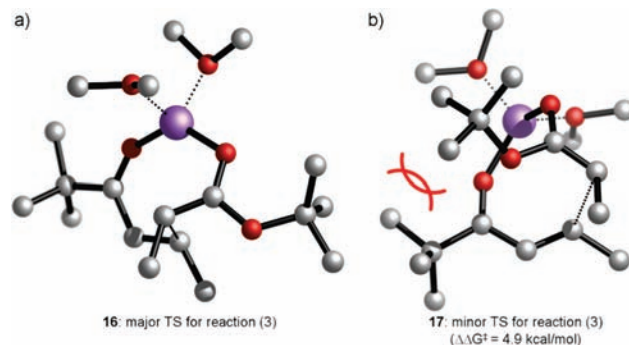


Figure 3. Repulsive interactions give selectivity in reaction 3.

How do the computations fare quantitatively? For both reactions 3 and 4, the predicted selectivity at $-78\text{ }^{\circ}\text{C}$ is apparently too high: $+4.9$ vs $+1.1$ kcal and -4.5 vs -0.7 kcal, respectively (more positive numbers indicate increased 1,2-syn/1,2-anti selectivity). These discrepancies are probably due to incompletely *E/Z*-selective enolizations, rather than poor selectivity in the Michael reactions themselves (leakage through open TSs is also possible). For example, exposure of methyl propionate to LDA/THF and LDA+HMPA/THF gives *E/Z* ratios of only 91:9 and 16:84, respectively.¹³

In conclusion, lithium enolates are most likely *O*-bound in solution. Computations that assume closed TSs for intermolecular Michael reactions correctly rationalize observed trends in diastereoselectivity and generally validate Heathcock's model. These results should provide a precedent for predicting the stereochemical outcomes of a wide range of Michael additions.

Acknowledgment. Support has been provided by the National Institutes of Health (GM081546-04).

Note Added after ASAP Publication. Scheme 4 contained errors in the version published ASAP October 1, 2010; the correct version reposted October 14, 2010.

Supporting Information Available: Coordinates and energies for reactions 2–4. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) As judged by trapping as the silyl enol ether: Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.