

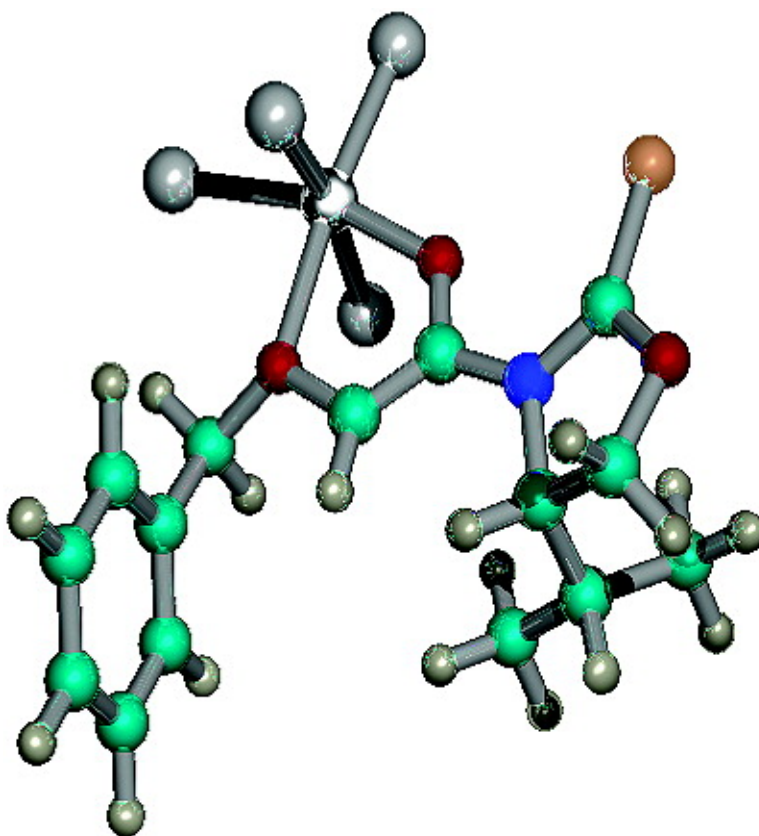
Communication

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Determining the Solution State Orientation of a Ti Enolate via Stable Isotope Labeling, NMR Spectroscopy, and Modeling Studies

David B. Kimball,[‡] Ryszard Michalczyk,^{*†} Eddie Moody,[‡] Morgane Ollivault-Shiflett,[‡]
Karl De Jesus,[‡] and Louis A. "Pete" Silks, III^{*†}

*NIH Stable Isotope Resource, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, and
Department of Chemistry, Campus Box 8023, Idaho State University, Pocatello, Idaho 83209*

Received May 29, 2003; E-mail: pete-silks@lanl.gov

The aldol reaction is one of the most widely known reactions in organic chemistry.^{1–7} When used in conjunction with a chiral promoter, aldols give high stereoselectivities for a variety of metal acid and base combinations.^{1–7} Although many aldol reactions have been reported, few accounts propose a geometry for the enolate intermediate, and fewer still are the result of direct observation. Of those that propose a structure, evidence is in the form of product ratios or modeling calculations.⁸ NMR observation of the enolate itself is rare,⁹ understandably due to the low temperatures necessary for its synthesis as well as the lack of suitably NMR active reporter groups within the substrate.

The oxazolidineselone⁴ is useful both to promote chirality in aldol reactions as well as to report on the ratios of each isomer produced in the reaction using ⁷⁷Se NMR spectroscopy. In an effort to determine the solution state geometry of the Ti enolate of a glycolate selone, we have synthesized compounds **1a–c** (Figure 1) enriched in ¹³C and ⁷⁷Se and studied their enolates using low-temperature NMR spectroscopy.

Selones **1a–c** (1.0 equiv) dissolved in CD₂Cl₂ were first combined with TiCl₄ (1.1 equiv) at –10 °C, and the ¹H, ¹³C, and ⁷⁷Se NMR spectra of an aliquot were measured at that temperature. ¹H–¹H NOESY was measured only for compound **1a**. Previous work^{4a} indicated that the lowest energy configuration for **1** was one where the dihedral angle between the amide carbonyl and the selenocarbonyl was close to 180° (pseudo trans). This was consistent with our NOESY results for the Ti complex of **1a**, as there were no cross-peaks between H α of the amide and H *iPr* of the oxazolidineselone. This would suggest a distance greater than 4 Å. Ab initio theory predicts a minimum distance of 4.64 Å, a maximum distance of 6.76 Å, and an average distance of 5.73 Å between H α of the amide and H *iPr* of the oxazolidineselone. Model A (Figure 2), where the dihedral angle between the two carbonyls is close to 0° (11.7°, pseudo cis), is higher in energy by 12.2 kcal/mol than model B, where the dihedral angle is 162°.

Hunig's base (1.15 equiv) was added, and another aliquot was taken for NMR analysis. Identical conditions were used and spectra were taken as with the Ti complex. For the enolate, however, we observed cross-peaks between the enolate proton and both the H1 oxazolidineselone as well as H *iPr* (Figure 3). Consecutive NOESY experiments with different mixing times allowed us to calculate a distance between the enolate proton and H1 of the oxazolidineselone of 2.33 Å (Table 1). We further determined the distance between H enolate and H *iPr* to be 2.89 Å. The H enolate–H1 distance calculated from NMR data is about 0.2 Å longer and the H enolate–H *iPr* distance is about 0.5 Å shorter than those in the model structures. This is due to the efficient spin diffusion pathway formed by H enolate, H1, H *iPr*, and the methyl protons.¹⁰

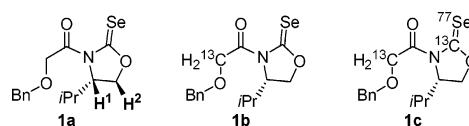


Figure 1.

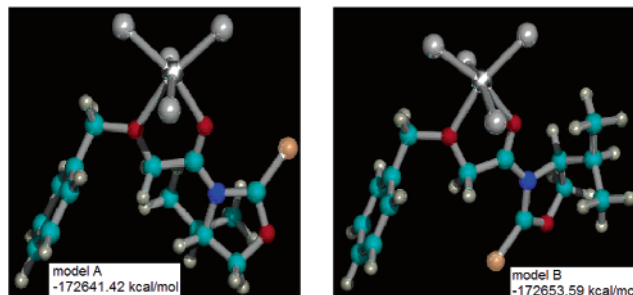


Figure 2. Lowest energy configurations and calculated energies of models A and B.

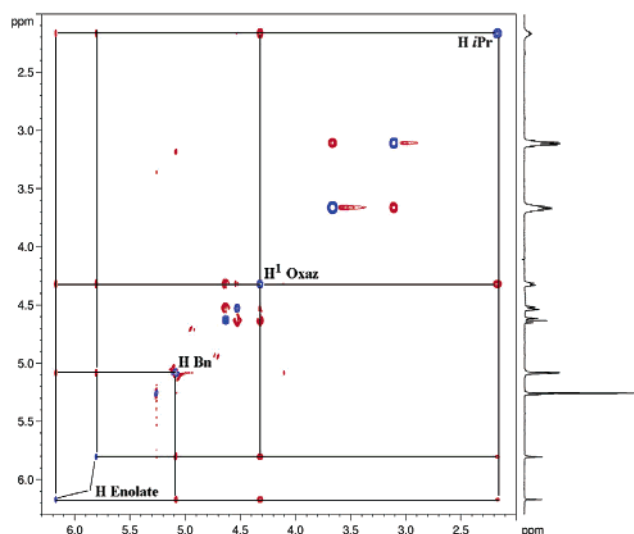


Figure 3. ¹H–¹H NOESY spectrum of the enolate of **1b** (750 ms mixing time).

These distances confirm that the enolate oxygens are cis to each other and strongly suggest that the selenocarbonyl is cis to the enolate. Thus, the orientation of this enolate should promote a strong facial preference upon subsequent reaction with an aldehyde or ketone. Indeed, product ratios confirm this tendency.^{1,4a} Modeling also indicated one side of the Ti enolate complex is less sterically hindered than the other side (vide infra).

It is important to note how unexpected this orientation for the enolate is, with respect to the selenocarbonyl. Although depending on the conditions used both *cis*^{8e,11,12} and *trans*^{2a,8e,14} enolate transition states have been proposed, little discussion is found on why the starting amides, precomplexed amides, and products seldom exist in a *cis* orientation relative to the auxiliary carbonyl and the

[†] Los Alamos National Laboratory.

[‡] Idaho State University.

Table 1. ^1H – ^1H Distances within the Enolate of **1b** Calculated from NOESY Spectra as Compared to Calculated Models C, D, and E¹²

spin transfer systems	NOE buildup rate	NMR distance (Å)	calculated distances (Å)		
			C	D	E
H enolate–H Bn	0.0123 ± 0.00075	2.96	2.58	3.36	3.27
H enolate–H ¹ Oxaz	0.0517 ± 0.005	2.33	2.14	2.13	4.27
H ¹ Oxaz–H <i>i</i> Pr	0.0376 ± 0.0007	2.45	2.42	2.43	2.51
H ² Oxaz–Me <i>i</i> Pr	0.0170 ± 0.0053	2.8			
H ¹ Oxaz–Me <i>i</i> Pr	0.00888 ± 0.00034	3.12			
Me/ <i>i</i> Pr–H <i>i</i> Pr	0.02429 ± 0.0013	2.64			
H enolate–H <i>i</i> Pr	0.0141 ± 0.00002	2.89	3.39	3.47	5.67

side chain carbonyl. Because both calculations and NOESY data indicate a trans orientation of the selenocarbonyl relative to the glycolate carbonyl in the Ti complex, there must be a strong driving force for rotation about the amide bond to form the enolate observed. The halfway point between models A and B, which should give a rough idea of the barrier to rotation between the two, was calculated to be 19.0 kcal/mol¹⁵ higher in energy than A.

Modeling studies do not agree with our NOESY results for the enolate and predict a different state as being the lowest in energy.¹⁶ Similar to the Ti complex, the orientation in which the selenocarbonyl is trans to the enolate oxygen, model E,¹⁶ is predicted to be lower in energy by 11.8 kcal/mol relative to molecule D.¹⁶ Since the ammonium group was left out of the calculations, it is possible this leads to inaccuracy in the resulting model.

Once the enolate has reacted with an aldehyde, crystal structure analysis of the product again confirms the trans orientation of the selenocarbonyl relative to the glycolate carbonyl.^{4a} This orientation suggests a stabilizing interaction through H-bonding between the selenocarbonyl and H α of the glycolate. This type of interaction has also been suggested from crystal structures of products based on oxazolindione,¹⁷ thiazolidinethione,¹⁸ and imidazolidone¹⁹ auxiliaries.

Comparing the NMR spectra of the starting material, Ti complex, and enolate of **1b,c** shows an important trend in the coupling within the selenocarbonyl that might shed light on the above discrepancy. The $J_{\text{C-Se}}$ value is essentially the same between the starting material and the Ti complex (~240 Hz), but drops significantly after formation of the enolate (222 Hz). The ⁷⁷Se NMR shift of the selenocarbonyl moiety is quite sensitive to subtle intramolecular electronic changes,²⁰ but the $J_{\text{C-Se}}$ should be relatively constant unless there is a dramatic change in the electronic character of the selenocarbonyl double bond. It is likely that this decrease in $J_{\text{C-Se}}$ could indicate a drop in the s orbital contribution to the Se=C bond. Considering the proximity of the Ti to the Se as indicated by the NOESY data, this effect could be the result of an interaction between Ti and Se. The ⁷⁷Se NMR spectrum of the enolates of **1a–c**, however, showed only a very broad resonance centered at 558.7 ppm, possibly indicating a dynamic association with Ti, the ammonium group, or both. Other groups using similar enolates have reported low deuterium incorporation in cases where the base used to generate the enolate is capable of returning a proton.²¹ This may be the result of tight association of the enolate with the protonated base, which can act as a proton “shuttle” once the reaction is quenched with an H⁺/D⁺ source.

Our results show that Ti-mediated enolate formation from **1** gives a Z enolate with the dihedral angle between the enolate oxygen and the selenocarbonyl close to 0°. We are currently modeling these structures with experimentally determined distance constraints, as well as using DFT calculations to determine the lowest energy position for the protonated amine base. Efforts are also underway to obtain ¹H, ¹³C, ⁷⁷Se, and ¹H–¹H NOESY data during subsequent reaction of the enolate with an aldehyde.

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Supporting Information Available: Detailed experimental procedures for the NMR experiments, modeling calculations, as well as ¹H, ¹³C, ⁷⁷Se, and ¹H–¹H NOESY spectra of **1a–c**, their Ti complexes, and their enolates (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
- Ti enolates: (a) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894–902. (b) Koch, G.; Loiseleur, O.; Fuentes, D.; Jantsch, A.; Altmann, K.-H. *Org. Lett.* **2002**, *4*, 3811–3814.
- Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613–2621.
- (a) Li, Z.; Wu, R.; Michalczyk, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A., III. *J. Am. Chem. Soc.* **2000**, *122*, 386–387. (b) Michalczyk, R.; Schmidt, J. G.; Moody, E.; Li, Z.; Wu, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A., III. *Angew. Chem., Int. Ed.* **2000**, *39*, 3067–3070.
- Representative boron enolates: (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586–2587. (b) Abiko, A.; Liu, J.-F. *J. Org. Chem.* **1996**, *61*, 2590–2591. (c) Inoue, T.; Liu, J.-F.; Buske, D. C.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5250–5256.
- Representative Si enol ethers: (a) Shirakawa, S.; Maruoka, K. *Tetrahedron Lett.* **2003**, *44*, 281–284. (b) Honda, M.; Oguchi, W.; Segi, M.; Nakajima, T. *Tetrahedron* **2002**, *58*, 6815–6823. (c) Braga, A. L.; Dornelles, L.; Silveira, C. C.; Wessjohann, L. A. *Synthesis* **1999**, 562–564. (d) Tanabe, Y.; Ohno, N. *J. Org. Chem.* **1988**, *53*, 1560–1563.
- Selected metal enolates: (a) Wang, Y.; Zhao, C.; Romo, D. *Org. Lett.* **1999**, *1*, 1197–1199. (b) Yasuda, M.; Tsuji, S.; Shigeyoshi, Y.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 7740–7747. (c) Knopff, O.; Alexakis, A. *Org. Lett.* **2002**, *4*, 3835–3837. (d) Ruiz, M.; Ojea, V.; Ruanova, T. M.; Quintela, J. M. *Tetrahedron: Asymmetry* **2002**, *13*, 795–799. (e) Kamimura, A.; Mitsudera, H.; Omata, Y.; Matsuura, K.; Shirai, M.; Kakehi, A. *Tetrahedron* **2002**, *58*, 9817–9826.
- Proposed transition states: (a) Evans, D. A.; Masse, C. E.; Wu, J. *Org. Lett.* **2002**, *4*, 3375–3378. (b) Ireland, R. E.; Wipf, P.; Xiang, J.-N. *J. Org. Chem.* **1991**, *56*, 3572–3582. (c) Xie, L.; Isenberger, K. M.; Held, G.; Dahl, L. M. *J. Am. Chem. Soc.* **1997**, *119*, 7516–7519. (d) Murga, J.; Falomir, E.; González, F.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 9697–9707. (e) Crimmins, M. T.; McDougall, P. *J. Org. Lett.* **2003**, *5*, 591–594.
- Selected enolate NMR studies: (a) Veya, P.; Cozzi, P. G.; Floriani, C.; Rotzinger, F. P.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1995**, *14*, 4101–4108. (b) Bernardi, A.; Cavicchioli, M.; Marchionni, C.; Potenza, D.; Scolastico, C. *J. Org. Chem.* **1994**, *59*, 3690–3694. (c) Baringhaus, K.-H.; Matter, H.; Kurz, M. *J. Org. Chem.* **2000**, *65*, 5031–5033. (d) Yasuda, M.; Hayashi, K.; Katoh, Y.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **1998**, *120*, 715–721. (e) Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7829–7830.
- The magnetization exchanged between H enolate and H1 at a distance of 2.1 Å is efficiently transferred further to H *i*Pr at a distance of 2.4 Å, thus reducing the intensity of the H enolate–H1 cross-peak, indicating a longer distance. Moreover, this diffusion increases the intensity of the H enolate–H *i*Pr cross-peak, thus leading to the underestimate of this distance.
- Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747–5750.
- (a) Cozzi, P. G.; Solari, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Chem. Ber.* **1996**, *129*, 1361–1368 and references therein. (b) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673–4675.
- For a graphical depiction of calculated models C, D, and E, see Supporting Information.
- Hsiao, C.-N.; Liu, L.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 2201–2206.
- To compare this energy barrier to other amides, see: Neuman, R. C.; Young, L. B. *J. Phys. Chem.* **1965**, *69*, 2570–2576.
- See Supporting Information.
- Breit, B.; Dauber, M.; Harms, K. *Chem.-Eur. J.* **1999**, *5*, 2819–2827.
- Cosp, A.; Larrosa, I.; Anglada, J. M.; Bofill, J. M.; Romea, P.; Urpi, F. *Org. Lett.* **2003**, *5*, 2809–2812.
- Davies, S. G.; Edwards, A. J.; Evans, G. B.; Mortlock, A. A. *Tetrahedron* **1994**, *50*, 6621–6642.
- Reference with Se as a sensitive reporter: (a) Menezes, P. H.; Gonçalves, S. M. C.; Hallwass, F.; Silva, R. O.; Bieber, L. W.; Simas, A. M. *Org. Lett.* **2003**, *5*, 1601–1604. (b) Silks, L. A.; Dunlap, R. B.; Odom, J. D. *J. Am. Chem. Soc.* **1990**, *112*, 4979–4982. (c) Smith, A. B.; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Duan, J. J. W.; Hull, K. G.; Iwashima, M.; Qiu, Y. P.; Spoor, P. G.; Salvatore, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 10478–10486. (d) Hedenstrom, E.; Nguyen, B. V.; Silks, L. A. *Tetrahedron: Asymmetry* **2002**, *13*, 835–844.
- Internal proton return: (a) Coumbarides, G. S.; Eames, J.; Weerasooriya, N. *J. Labelled Compd. Radiopharm.* **2001**, *44*, 871–879. (b) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1995**, *117*, 891–900 and references therein.

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