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EFFECT OF AGGREGATION ON STEREOCHEMISTRY AND MECHANISM OF ASYMMETRIC OXIDATION OF THE LITHIUM ENOLATE OF METHYL 3,3-DIMETHYLBUTANOATE IN THE SOLID STATE AND IN SOLUTION

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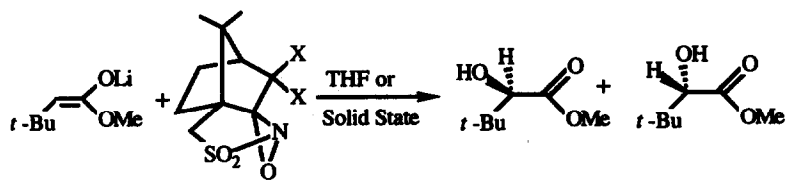
Abstract: Oxidation of the title enolate by enantiopure (camphorylsulfonyl)oxaziridines in THF afforded α-hydroxyester with 53-73% ee, but the product from the solid state reactions was racemic. The results suggest that the enolate exists and reacts as an aggregate in the solid state reactions.

It is well established that lithium enolates in nonpolar and weakly polar solvents usually exist as aggregated species such as dimers, tetramers, hexamers.[1] There is also a growing body of evidence indicating that the aggregate structure of an enolate significantly influences the regio- and stereochemistry of the solution reactions with electrophiles.[2] However, a key question remains unanswered, i. e. what are the structures of the enolates that *actually react* in solution? Recently, we reported the first comparative study of the solid state and solution aldol addition reactions of the lithium enolate of methyl 3,3-dimethylbutanoate (**1**) with various aldehydes.[3] The diastereoselection of the solid state reactions was found to be essentially identical to that of the solution reactions, which suggests that the same reacting species and transition states are involved in both the solid state and the solution aldol reactions.[3] We became interested in investigating the solid state asymmetric oxidation of enolates by enantiopure (camphorylsulfonyl)oxaziridines in view of their value in synthetic organic chemistry.[4] Furthermore, based on theoretical calculations, it has been proposed[5] that a monomeric enolate is involved in the transition state for the asymmetric oxidation. Enolate **1** is known to exist as a tetrameric aggregate in the solid state.[6] We reasoned that the stereochemical outcome from the asymmetric oxidation of **1** in the solid state should be quite different from that in solution media, because in the solid state dissociation of tetramer to lower aggregates and monomer would be severely hindered if not completely suppressed. In this paper, we present our preliminary results on the first solid state oxidation of **1** by enantiopure (+)- and (-)-(camphorylsulfonyl)oxaziridines (**2**). The enantiomeric composition of the product, methyl 2-hydroxy-3,3-dimethylbutanoate (**3**), of the solid state reactions are compared with that of the same reactions performed in solution media.



1 **2a**: X = H, **b**: X = Cl **R-(-)-3** **S-(+)-3**

The lithium ester enolate **1** was prepared as a white solid by treating methyl 3,3-dimethylbutanoate with freshly made LDA in THF at -78 °C followed by evaporation of the solvents at low temperatures (< -20 °C) under vacuum, according to literature procedures.[6] The general procedure for the solid state oxidation reactions are similar to that for the solid state aldol addition reactions.[3] Thus, enolate **1** (1.2 equiv) and the enantiopure (camphorylsulfonyl)oxaziridines (**2**)[7] (1 equiv) were separately ground to a fine powder and mixed at the appropriate temperature with agitation under a dry argon atmosphere. After 4 h, the reaction mixture was quenched with aqueous NH_4Cl followed by extraction with diethyl ether. The solvent was removed at reduced pressure to yield the crude product, which was further purified using preparative TLC or flash chromatography with pentane/Et_2O (3:1 by volume) as eluent. It should be noted that the reaction mixture apparently *remained solid during the entire reaction period* prior to quenching. For the solution reactions, enolate **1** was prepared at -78 °C and reacted directly with the oxidant in THF. All the products were characterized by NMR spectroscopy. The enantiomeric excess (ee) and configuration were determined by comparison of optical rotations with literature values.[8] The results are summarized in Table I.

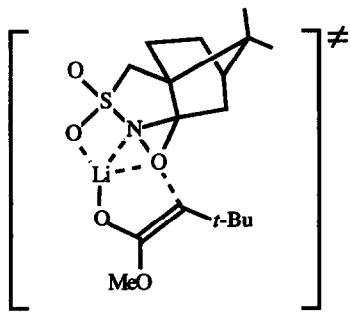
Table I. Oxidation of the Lithium Enolate of Methyl 3,3-Dimethylbutanoate (**1**) by Enantiopure (Camphorylsulfonyl)oxaziridines (**2**) in THF and in the Solid State for 4 h.

entry	condition	oxaziridine	T (°C)	% ee	yield (%)	Configuration
1	THF	(-)-**2a**	-78	58	29	*S*-(+)
2	Solid State	(-)-**2a**	-78	0	16	(±)
3	THF	(+)-**2a**	-78	68	35	*R*-(-)
4	Solid State	(+)-**2a**	-78	0	17	(±)
5	THF	(+)-**2a**	22	57	37	*R*-(-)
6	Solid State	(+)-**2a**	22	0	15	(±)
7	THF	(-)-**2b**	-78	73	48	*S*-(+)
8	Solid State	(-)-**2b**	-78	0	14	(±)
9	THF	(+)-**2b**	-78	75	66	*R*-(-)
10	Solid State	(+)-**2b**	-78	0	20	(±)

In general, the oxidation reactions in THF solution gave the α-hydroxyester **3** in 29-66% yield and 58-73% ee. In a striking contrast, all of the solid state oxidation reactions afforded *racemic* material with no measurable rotation in lower yields (≤ 20%). For example, treatment of the powdered lithium enolate **1** with powdered (-)-**2a** in the solid state at -78 °C for 4 h produced racemic methyl 2-hydroxy-3,3-dimethylbutanoate (**3**) in 16% yield after purification (Table I, entry 2). The same oxidation performed in THF produced *S*-(+)-**3** with 58% ee in 29% yield (Table I, entry 1). It is known that (+)- or (-)-(8,8-dichlorocamphorylsulfonyl)-oxaziridine (**2b**) often gives higher ee's than the corresponding **2a** in the asymmetric oxidation of metal enolates in solution.[7] Indeed, the oxidation of **1** by (-)-**2b** in THF at -78 °C afforded *S*-(+)-**3** in 73% ee. However, the product obtained in the solid state oxidation was, again, racemic. The reaction temperature appears to have little effect on both the yield and the stereochemical outcome of the solid state oxidation (compare entry 4 with 6). We have also found that increasing the amount of the enolate has no significant effect on the stereoselectivity or yield of the solid state reactions. For example, treatment of 2 equiv of **1** with 1 equiv of (+)-**2a** at -78 °C gave a racemic **3** in 14% yield. Furthermore, to rule out the possibility of racemization of **3** under the conditions in the

solid state reactions, the solid state reactions were performed in the presence of an enantioenriched **3** of a known ee (e.g. 58%) in the reaction mixture. The isolated α-hydroxyester after the reaction was found to be optically active. To check whether isolation of the enolate **1** would affect the reactions, the solid enolate **1** was prepared and kept at room temperature for 24 h in argon. It was then redissolved in THF followed by oxidation with (+)-**2a** at -78 °C. The product obtained (21% yield) had an ee of 48%, which is somewhat lower than, but still comparable with, the ee of the reaction employing freshly prepared **1** in THF (68%, Table I, entry 3).

All of the above observations suggest that the stereochemistry and reaction pathway in the solid state differ significantly from those in solution. In search for the reasons for the enantioselectivity in the solution oxidation of lithium enolates with chiral oxaziridines, Bach et al.[5] performed a series of molecular orbital calculations at the HF/6-31+G*//HF/4-31+G level. Their results suggest that oxygen atom transfer involves a "closed" transition state (e.g. **4**) with the lithium cation binding to the ring oxygen and nitrogen atoms, and possibly to the sulfonyl oxygen as well, in (camphorylsulfonyl)oxaziridines. Thus, as limited by the coordination number of lithium cation, the lithium enolate must react in a non-aggregated monomeric form.



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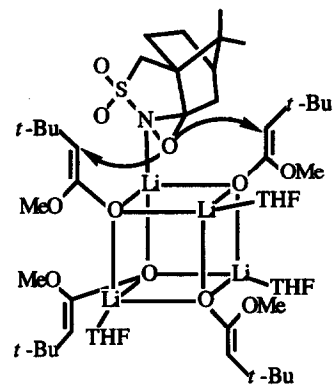

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Seebach et al.[6] have demonstrated by X-ray crystallographic studies that the solid enolate **1** exists as a tetrameric aggregate, which has a Li_4O_4 cubic structure with each lithium atom being surrounded by three enolate oxygens and one THF oxygen. In the solution reactions, the tetrameric enolate **1** could dissociate into, and equilibrate with, other aggregates (e.g. dimer) and non-aggregated monomer. The monomeric enolate **1** could react with the oxaziridine, leading to the observed high ee's. In the solid state reactions, the aggregated **1** is unlikely to undergo the dissociation to a monomer that is necessary to form the highly coordinated transition state **4**. Therefore, enolate **1** may react directly in aggregated form in the solid state as illustrated in structure **5**, leading to racemic α-hydroxyester **3**. At the present time, we *cannot* establish the exact identity of the reacting enolate species and the transition state involved in the solid state oxidation for lack of detailed knowledge about the nature of interface between the solid reactants. The lattice structure of **1** could also be modified during the reactions and become different from the X-ray picture.[6] Moreover, there are other possible interpretations of the enantioselectivity observed in the solution reactions,[9] though our results are apparently in consistence with the model proposed by Bach et al. Further investigation along this line is in progress.

In summary, we have presented the first solid state oxidation of the lithium enolate of methyl 3,3-dimethylbutanoate with enantiopure (camphorylsulfonyl)oxaziridines. The stereochemical outcome of the solid state reactions was found to be strikingly different from those performed in solution. The reactions in THF afforded the enantiomerically enriched α-hydroxyester in 53-73% ee, but the product obtained from the solid

state reactions was racemic. The most likely reason for the lack of stereoselectivity in the solid state is that the enolate exists and *reacts as an aggregate* in the solid state, while in solution the enolate may react as a monomer.

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References and Notes

(1) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624 and references cited therein.

(2) (a) McGarrity, J.F.; Ogle, C.A. *J. Am. Chem. Soc.* **1985**, *107*, 1805. (b) McGarrity, J.F.; Ogle, C.A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810. (c) Jackmann, L.M.; Dunne, T.S. *J. Am. Chem. Soc.* **1985**, *107*, 2805. (d) Seebach, D. Proceedings of The Robert A. Welch Fouundation Conferences on Chemical Research, XXVII, Houston, TX, 1984, pp. 93-145; (e) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1992**, *57*, 613.

(3) (a) Wei, Y.; Bakthavatchalam, R. *Tetrahedron Lett.* **1991**, *32*, 1535. (b) Wei, Y.; Bakthavatchalam, R. *Tetrahedron* **1993**, in press.

(4) For a most recent review, see: Davis, F.A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919.

(5) Bach, R. D.; Andres, J.L.; Davis, F.A. *J. Org. Chem.* **1992**, *57*, 613.

(6) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W.B.; Dunitz, J.D. *J. Am. Chem. Soc.*, **1985**, *107*, 5403.

(7) (a) Davis, F. A.; Weismiller, M.C.; Murphy, C. K.; Reddy, R. T.; Chen, B.C. *J. Org. Chem.* **1992**, *57*, 7274. (b) Davis, F.A.; Sheppard, A.C. *Tetrahedron* **1989**, *45*, 5703. (c) Davis, F.A.; Sheppard, A.C.; Chen, B. C.; Haque, M.S. *J. Am. Chem. Soc.* **1990**, *112*, 1990.

(8) (a) Brown, H. C.; Cho, B. T.; Park, W. S. *J. Org. Chem.* **1986**, *51*, 3398. (b) Frazee, W. J.; Eliel, E. L. *Tetrahedron* **1974**, *40*, 1333.

(9) For example, the observed ee in the solution reactions could be due to reaction of complex consisting of some of the chiral products of the oxaziridine after initial oxidation, similar to the model proposed by Alberts, A.H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265.

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