A Molecular Mechanics Approach to Determining the Diastereofacial Selectivity in the Reaction of Asymmetric Aldehydes with Achiral Enolates

Summary: A molecular mechanics calculation has been used to predict the diastereofacial selectivity in the reaction of asymmetric aldehydes with achiral lithium enolates.

Sir: The aldol condensation has been the focus of much research in the last few years. An extensive effort has been directed toward evaluation and prediction of the diastereofacial selectivity of the reaction (Figure 1).[1,2] In general, a combination of the Zimmerman six-centered transition state[3] and the useful models proposed by Cram,[4] Karabatsos,[5] and Felkin[6] have been used to explain the stereochemical course of the reaction but a general model which accurately predicts all cases as yet does not exist. As a result of the ambiguities between the three models we examined an alternative approach to predicting the diastereofacial selectivity in the aldol condensation.

We now report the rather *surprising* result that in the reaction of achiral lithium enolates with asymmetric aldehydes the diastereofacial preference and the degree of preference can be accurately predicted by a relatively simple molecular mechanics calculation.

Our approach assumes the controversial notion that the reaction is controlled primarily by the ground-state conformation of the aldehyde in question,[7] that is, the degree of bond formation and bond breaking is minimal at the transition state. In light of the rapidity, exothermicity, and stereoselectivity of the aldol condensation, this is not an unreasonable assumption. With this assumption in hand, we determined the conformational energy minima for a variety of asymmetric aldehydes which have been reacted with achiral lithium enolates. Conformational energy minima were calculated by using Allinger's MM2 program[8,9] by driving the dihedral angle θ (Figure 2) about the sp^3–sp^2 bond through 360° in 30° increments and minimizing the energy of each conformer. Each obvious potential well was then minimized from both sides to locate the minimum energy conformation represented by that well.[10] Finally, the preferred mode of enolate attack was determined by placing a dummy hydrogen atom on either face of these minimum energy conformers at a distance of 2.5 Å[11] from the carbonyl carbon at the Dunitz angle[12] (Figure 3). The use of hydrogen was for the sake of simplicity and was not meant to strictly model the enolate, but merely give the relative steric hindrance associated with each face of the carbonyl. The low-energy face of the carbonyl was expected to be the preferred site of attack for the enolate and define whether a threo or erythro product would result from that particular conformer.[13]

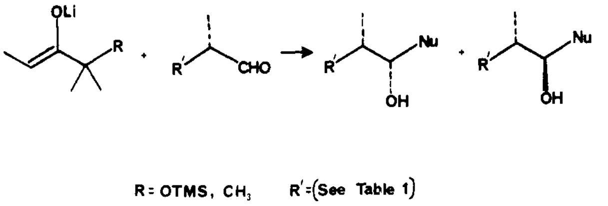

Figure 1.

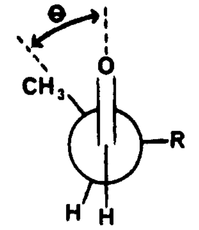

Figure 2.

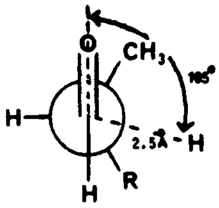

Figure 3.

The ratio of erythro to threo products was then calculated by assuming a Boltzmann's distribution among the stable conformers and summing over all conformers with the same facial preference for enolate attack.[14]

$$\text{ratio} = \frac{\sum e^{-E_E/RT}}{\sum e^{-E_T/RT}} \qquad (1)$$

Table I shows the aldehydes considered in our analysis, the energies of the various stable conformations along with the value of the dihedral angle for the conformer, and the experimental and calculated erythro/threo ratios.

The success of this simple model is evident given that it predicts the correct diastereomer in all cases and the unusual anti-Cram selectivity of 2-cyclohexylpropanal is reproduced (see entry 1 of Table I). Examination of the data in Table I reveals two generalities of considerable importance. First, all of the stable conformations determined by the calculation lie within a few degrees of having a group on the chiral center carbonyl-eclipsed.[15] Secondly,

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[1] Evans, D. A.; Nelson, J. O.; Taber, T. R. *Top. Stereochem.* **1983**, *13*, 1. Heathcock, C. H. "Comprehensive Carbanion Chemistry"; 1981; Vol. II, p 1.

[2] Dougherty, D. A. *Tetrahedron Lett.* **1982**, *23*, 4891. Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438. Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

[3] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

[4] Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

[5] Karabatsos, G. *J. Am. Chem. Soc.* **1967**, *89*, 1367.

[6] Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.

[7] A similar approach has been used by M. Hirota to predict the threo/erythro selectivity in the oxidation of alkyl 1-phenylethyl sulfides. Hirota, M.; Abe, K.; Tashiro, H.; Nishio, M. *Chem. Lett.* **1982**, 777.

[8] Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. The NMR program was obtained from Indiana University's Quantum Chemistry Program Exchange as program number 395. This utilizes Allinger's 1977 force field.

[9] For a discussion on the application of force field calculations to carbonyl compounds, see: Allinger, N. L.; Tribble, M. T.; Miller, M. A. *Tetrahedron* **1972**, *28*, 1173.

[10] For calculation of long chain aldehydes such as **5**, **6**, and **7** these were placed in their most extended form and were allowed free rotation during the minimization process.

[11] Initial calculations were done by varying this distance from 1.5 to 3.5 Å, but the distance did not affect the facial preference. Increasing the size of the dummy hydrogen also had no effect on the final outcome of the calculation.

[12] Burgi, H. D.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.

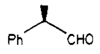
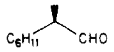
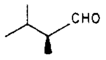
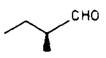
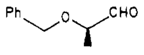
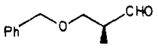
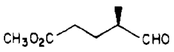
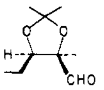
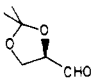
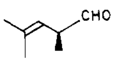
[13] Erythro and threo as defined by: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

[14] The value of −78 °C was used in the Boltzmann equation since the reaction is normally carried out at −78 °C.

[15] Studies have shown that the carbonyl eclipsed conformer is the most stable. See: Karabatsos, G.; Hsi, N. *J. Am. Chem. Soc.* **1965**, *87*, 2864. Abraham, R. J.; Pople, J. A. *Mol. Phys.* **1960**, *3*, 609. Butcher, S. S.; Wilson, E. B., Jr. *J. Chem. Phys.* **1964**, *40*, 1671. Abe, M.; Kuchitsu, K.; Shimanouchi, T. *J. Mol. Struct.* **1969**, *4*, 245. Shimanouchi, T.; Abe, Y.; Makami, M. *Spectrochim. Acta, Part A* **1968**, *24A*, 1037. Pierce, L.; Chang, C. K.; Hayashi, M.; Nelson, R. *J. Mol. Spectrosc.* **1969**, *5*, 449. Chapput, A.; Roussel, B.; Fleury, G. J. *J. Raman Spectr.* **1974**, *2*, 117.

0022-3263/84/1949-4573$01.50/0

Table I

no.	aldehyde	conformers (kcal/mol)			erythro/threo		ref
		−120 °C	0 °C	120 °C	calcd	exptl	
1		2.2693	1.1329	2.8325		3:1–4:1	*g*
		(−132°)[j]	(0°)	(143°)	94:6	81:19	*a*
2		10.9392	11.2228	11.1017		1.5:1	*g*
		(−116°)	(12°)	(118°)	27:73	23:77	*b*
3		6.1155	6.1482	6.0201			
		(−118.7°)	(−9.28°)	(114.2°)	29:71	*h*	*c*
4		4.7123	3.9780	3.9936			
		(−118.766°)	(−1.406°)	(127.50°)	45:55	*h*	*c*
5		5.3826	4.7119	6.4150			
		(−127.7°)	(−3.387°)	(142.19°)	1:99	34:66	*d*
6		4.1467	4.4833	5.3175			
		(−127°)	(2.5°)	(120°)	32:68	20:80	*e*
7		4.1977	3.7521	4.4663			
		(−128°)	(2.3°)	(117.3°)	68:32	74:26	*a*
8		15.3761	16.7057	18.2294			
		(−138°)	(−10°)	(122°)	99.9:0.1	75:25	*f*
9		12.0085	10.4027	11.2062			
		(−149°)	(1°)	(131°)	1:99	15:85	*d*
10		4.5646	2.711	3.5677		2:1	*g*
		(−141.697°)	(−0.209°)	(128.112°)	99:1	94:6	*i*

[a] Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 8109. [b] Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. [c] No reaction with simple lithium enolates for this compound could be found in the literature. It has been included as a comparison to entry **2**. [d] Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846. [f] Heathcock, C. H. et al. *J. Am. Chem. Soc.* **1979**, *101*, 7077. [g] Results of simple acetate enolate additions: Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667. The discrepancy in the facial preference for 2-cyclohexylpropanal in the results of Masamune and Heathcock is presently unexplained since neither author provides proof of stereochemistry. [h] No experimental data available. [i] Heathcock, C. H. "Comprehensive Carbanion Chemistry"; Elsevier Press: New York, 1981; Vol. II, p 1. [j] Energy minimized: torsional angle given is that for R–C–C–O (carbonyl) where R = $-CH_2-$ (no. 9) or R = CH_3 on the chiral center (all others).

correct diastereoselectivity is predicted in the case of both α- and β-oxy aldehydes (entries 5, 6, 8, and 9) without invoking metal ion complexation.

These calculations suggest that the direction of enolate addition is dictated pimarily by aldehyde structure and probably not by transition-state geometry, although the degree of selectivity is partially dependent upon the nature of the enolate (see entries 1 and 10), a well-known phenomenon which has been exploited in the process of double stereodifferentiation.[1] The poor ratios obtained in α-alkoxy aldehydes are probably due to dipolar effects between the carbonyl and the electronegative alkoxy group as indicated by Felkin in the development of his model.[6]

Although the approach we have taken in determining diastereofacial preferences in the aldol condensation may be subject to controversy, it nonetheless predicts the course of the reaction. The ultimate validity of this approach must await further experiment.[16]

Registry No. $CH_3CH(Ph)CHO$, 93-53-8; $CH_3CH(C_6H_{11})CHO$, 2109-22-0; $(CH_3)_2CHCH(CH_3)CHO$, 2109-98-0; $CH_3CH_2CH(CH_3)CHO$, 96-17-3; $PhCH_2OCH(CH_3)CHO$, 53346-05-7; $PhCH_2OCH_2CH(CH_3)CHO$, 73814-73-0; $MeOC(O)(CH_2)_2CH(CH_3)CHO$, 40630-06-6; $(CH_3)_2C{=}CHCH(CH_3)CHO$, 14690-10-9; $CH_3CH{=}C(OLi)C(CH_3)_2OSiMe_3$, 64869-22-3; $CH_3CH{=}C(OLi)C(CH_3)_3$, 64869-29-0; DL-*erythro*-5-ethyl-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde, 72523-81-0; (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde, 15186-48-8.

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[16] C. H. Heathcock is continuing his study of the asymmetric induction with asymmetric aldehydes and will compare his experimental results with our calculated results.

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