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CONCERNING THE RELEVANCE OF ETHANE CONFORMATIONAL ANALYSIS TO ACYCLIC ALDOL TRANSITION STATES

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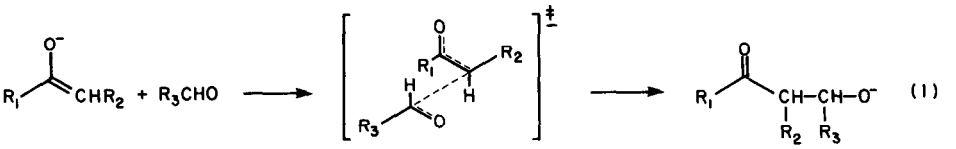
Abstract. Molecular mechanics calculations on model compounds are used to evaluate the steric interactions in acyclic aldol and related transition states.

The development of highly stereoselective aldol and related C-C bond-forming reactions continues to be a dominant theme of synthetic organic chemistry.[1a] In the presence of chelating counterions, a six-membered cyclic transition state has proven to be a very useful model.[1b] Relevant steric interactions and thus the more favorable transition states can be predicted by drawing an analogy to cyclohexane conformational analysis.

More recently, several erythro-selective reactions have been developed which, either because they represent substantial modifications of the basic aldol reaction or because they use non-chelating counterions, have been proposed to proceed through acyclic transition states.[2] Reasoning directly parallel to that applied to cyclic transition states, then, suggests that the basic tenets of ethane conformational analysis should be relevant to the acyclic transition states. The products of these reactions are tetrasubstituted ethanes (Eq. 1), and thus idealized anti (**1-A**) and gauche (**1-G**) conformations should be considered as transition state models. In general it is assumed that the oxygen-containing substituents (i.e., carbonyl and alkoxide in the product) are anti to one another.[2] Erythro stereoselectivity is then rationalized by assuming that a conformation with the hydrogens anti is preferred in such ethane-like transition states (Eq. 1). However, all tetraalkylethanes (**1**, R=alkyl) prefer the gauche conformation (**1-G**).[3,4] Thus, if the oxygen-containing substituents actually are anti, standard ethane conformational analysis would appear to predict threo selectivity.



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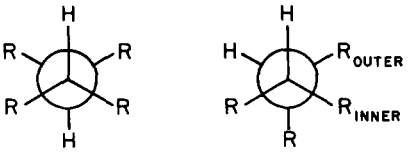

I-A I-G

In an effort to resolve this apparent conflict, we have applied the empirical force field (EFF, molecular mechanics) method[5] to several substituted ethanes, which are intended to serve as qualitative models for acyclic aldol transition states. Of course, this approach considers only steric interactions, and thus additional effects due to solvent, counterion, stereoelectronics, etc. must be superimposed upon the steric effects. Our model system is the product of equation 1 with C=O replaced by $C=CH_2$ and O^- replaced by OR_4 (Figure 1). This structure should provide a useful guide to the steric interactions in aldol condensations and the reactions of various allyl metal species with aldehydes, which also lead to erythro selectivity.[2] The possible conformations for such a structure are shown in Figure 1, where the first descriptor defines the relationship (anti or gauche) between the hydrogens, the second defines that between the "oxygen-containing" substituents, and the third whether the product is erythro or threo. "Enolate geometry" is determined by whether $C=CH_2$ is more nearly syn (Z) or anti (E) to the $C-R_2$ bond.

The results are summarized in Table I. Considering first the structures with the alkenyl and ether functions anti (_A_), AAE is preferred over GAT for all structures. The preference is quite substantial for E enolates, but for Z enolates with $R_1=R_2=CH_3$, the preference, while most likely real, is near the error limits of the EFF method. Nevertheless, the structure with the hydrogens anti is preferred, and erythro selection is generally expected. The reason that tetraalkylethanes are gauche is that the gauche conformer can better relieve adverse geminal repulsions.[3] Our results thus suggest that the alkenyl and/or the ether functions induce less severe geminal repulsions than alkyl groups. GAT is especially unfavorable because both R_2 and R_3 are in the more crowded, inner positions in the Newman projection.

Considering the other conformers for $R_2=R_3=CH_3$, the GGT form is generally quite competitive with AAE. Thus, a clearcut erythro preference is predicted only if some

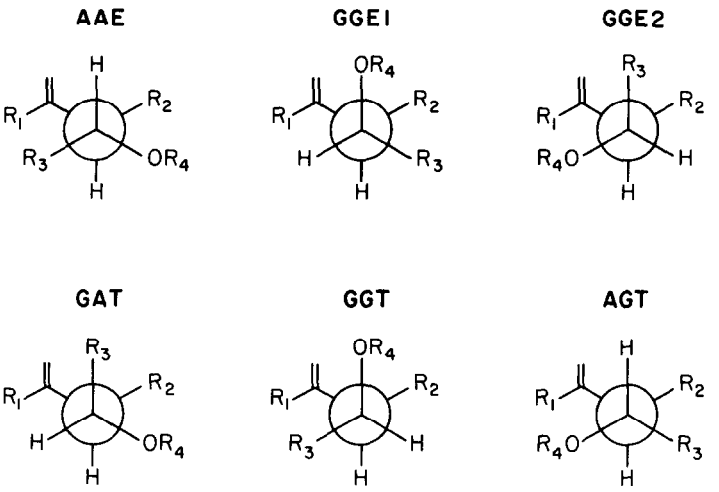

Figure 1. Structures considered in the present work. Only Z enolates are shown.

non-steric factor (eg., dipole, stereoelectronic, or counterion effects) requires the oxygen-containing substituents to be anti to one another. For _G_ conformers, GGT is preferred for all E enolates and for Z enolates if R_1=t-Bu. The GGE2 conformer is essentially equienergetic with GGT for Z enolates with R_1=CH_3. The E enolate form of GGE2 is apparently destabilized by R_1 ··· R_3 repulsions.

The severe steric repulsions present in the structure with R_2=R_3=t-Bu alter the overall picture slightly. The GGT form is now clearly the global minimum, consistent with the gauche tetraalkylethane effect. AGT input structures rotated into a second GGT minimum, and GGE1 input structures produced final structures with non-alternating, F_2BFB_2 Newman projections.[6]

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Table I. Relative Conformer Energies (kcal/mol).[a]

R_1	R_2	R_3	R_4	Enolate	GGT	GGE1	GAT	AAE	AGT	GGE2
CH_3	CH_3	CH_3	CH_3	E	0.01	0.78	2.28	0	1.18	2.01
				Z	0.39	1.19	0.81	0	1.11	0.34
t-Bu	CH_3	CH_3	CH_3	E	0.75	1.56	5.09	0	1.57	5.03
				Z	0.43	1.24	2.58	0	1.22	2.11
CH_3	CH_3	CH_3	t-Bu	E	0	1.15	2.93	0.34	0.97	2.35
				Z	0.16	0.73	0.92	0	0.81	0.29
CH_3	t-Bu	t-Bu	CH_3	E	0[b]/1.01[c]	2.37[d]	8.28	1.29	b	6.26
				Z	0[b]/0.51[c]	0.61[d]	5.13	1.07	b	1.52

[a]Comparisons between different enolates or different diastereomers are not meaningful. See Figure 1 for structures. [b]AGT input structure gave the GGT global minimum. [c]From GGT input [d]F_2BFB_2.

References and Notes

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2. See, for example, S. Murata, M. Suzuki, and R. Noyori, J. Am. Chem. Soc., **102**, 3248 (1980); R. Noyori, I. Nishida, and J. Sakata, ibid., **103**, 2106 (1981). For related reactions of allyl metal species see: H. Yatagai, Y. Yamamoto and K. Maruyama, ibid., **102**, 4548 (1980); Y. Yamamoto, H. Yatagai, Y. Naruta and K. Maruyama, ibid., **102**, 7108 (1980).
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