A Cyclic Transition State for the Darzen Reaction

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Introduction

The Darzen reaction, the base-induced addition of an α-halo ester to an aldehyde or ketone, provides a general route to glycidic acid derivatives. The development of enantioselective routes to the Darzen reaction[1] is of interest because both the intermediate α-halo-β-hydroxy esters and the Darzen α,β-epoxy esters are versatile precursors for many useful types of chiral compounds.

The reaction is a two-step reaction. The first step is an aldol-type reaction between the halo ester and the aldehyde, with the formation of two diastereomeric α-halo β-hydroxy esters, and the second step is the formation of the α,β-epoxy ester (Scheme 1). With most esters the second step favors the *trans* isomer. The stereochemistry of the Darzen reaction is probably determined by the steric requirements of the transition state of the aldol step. For the aldol reaction both cyclic and acyclic transition states have been proposed.[2−4] For a base-catalyzed reaction, the transition state involves the metal ion in a cyclic structure or it can combine the aldehyde with the ester enolate in an acyclic geometry.[5,6]

The question arose whether a cyclic transition state was possible for the Darzen reaction also in the absence of a metal catalyst. One possibility for such a reaction would be a reaction between the aldehyde and the enol form of the ester, where C−C bond formation would occur simultaneously with a proton transfer, in analogy with the ene reaction (Scheme 2). As a model for this reaction we have studied the gas phase mechanism for the reaction between benzaldehyde and methyl 1-chloroacetate, on the assumption that the amount of ester that exists in the enol form will react with the aldehyde via the cyclic pathway.

Methods

The aldol reaction between benzaldehyde and methyl 1-chloroacetate was studied using molecular orbital methods. The semiempirical AM1 optimization, as realized in the MOPAC6.0 program, was used for preliminary studies.[7] The Gaussian92 software was used for the *ab initio* calculations.[8] Geometries were optimized at the Hartree−Fock level (HF/3-21G*). Energies (including electron correlation effects) were obtained from single point calculations using the second-order perturbation theory according to Møller and Plesset (MP2/6-31G*//HF/3-21G*). The nature of each stationary point was verified by vibrational frequency analysis. The intrinsic reaction coordinate calculation was performed according to Gonzalez and Schlegel.[9]

Results and Discussion

Reactant geometries were optimized and their structural formulas and atom numbering are given in Scheme 3. Benzaldehyde has only one conformer. The keto form of the ester has six conformers but only four different energies due to mirror symmetry. The conformer with dihedrals angles C(5)−O(4)−C(2)−C(1) = 180° and Cl−C(1)−C(2)−O(4) = 180° had the lowest energy. There are two enol isomers of the ester, with the chlorine either *trans* (three conformers) or *cis* (five conformers, three different energies) with respect to the methoxy group. At the MP2 level, the energies of the three *trans*-enol conformers were within 1 kcal/mol. The same applies to the three energies of the *cis*-enol. Relative to the keto form, the *trans*-enol energy is 23.6 kcal/mol (HF/3-21G*; 33.0 kcal/mol at MP2/6-31G*//HF/3-21G*) higher, while the *cis*-enol energy is 26.8 kcal/mol (HF/3-21G*; 36.4 kcal/mol at MP2/6-31G*//HF/3-21G*) higher. As a consequence, the keto−enol tautomerism is shifted toward the keto form such that the enol forms will be only marginally populated. The energetics of the reaction was therefore calculated with respect to benzaldehyde + the keto isomer of the ester.

The reaction can occur via four routes depending on whether the phenyl ring is axial or equatorial with respect to the transition state (TS) pericyclic ring and on the *cis−trans* isomerism at the C1−C2 bond of the enol. The chlorine is equatorial in the transition state for the *cis*-enol but axial for the *trans*-enol. In addition, the routes involving the *trans*-enol possess two transition states, each with a different orientation of the methoxy group. All six transition states were optimized at the HF/3-21G* level, and the one with both the phenyl ring and the chlorine atom in equatorial positions (Figure 1b) was found to have the lowest activation energy. The difference in energy to the TS with the phenyl group in the axial position was small, about 1 kcal/mol. The six-membered ring is a halfboat, with the five atoms C−O···H···O−C almost in a plane. In the TS the C−C distance in the forming bond is 2.191 Å, while the migrating proton is somewhat closer to the enol oxygen (1.142 Å) than to the aldehyde oxygen (1.274 Å). The two involved oxygens are considerably closer to each other (2.236 Å) than their van der Waals radii would normally allow (>3 Å). This conformation is, not surpris-

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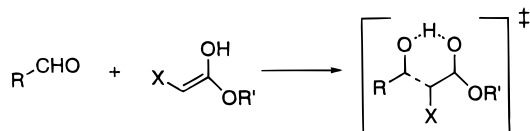
Scheme 1

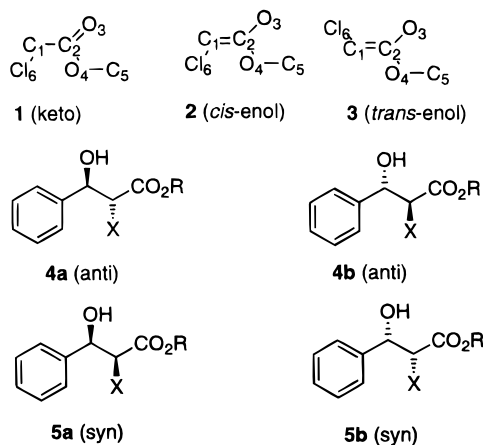**Table 1.   Reaction Energies (kcal/mol)[a]**

state		HF/3-21G*	MP2/6-31G* //HF/3-21G*
benzaldehyde + keto ester		0	0
cis-enol path:			
benzaldehyde + *cis*-enol ester		26.8	36.4
hydrogen-bonded complex		12.5	26.2
transition state (Figure 1)	a	33.9	34.9
(two possibilities)	b	34.4	32.9
product		−11.6	−11.1
trans-enol path:			
benzaldehyde + *trans*-enol ester		23.6	33.0
transition state (Figure 1)	c	37.6	36.3
(four possibilities)	d	38.7	37.6
	e	42.3	39.0
	f	45.0	41.9

[a] The bold letters indicate the corresponding conformation as given in Scheme 4.

Scheme 2

Scheme 3

Scheme 4

Table 2.   Reaction Energies (kcal/mol) for Some Aldol Reactions

reaction	ΔH (kcal/mol)	comment
benzaldehyde + methyl-1-chloroacetate	−38.3	this work, HF/3-21G*
benzaldehyde + methyl-1-chloroacetate	−47.4	this work, MP2/6-31G*// HF/3-21G*
acetaldehyde enolate + formaldehyde	−11	estimate of exptl ΔH, ref 5
acetaldehyde enolate + formaldehyde	−9.7	RHF/3-21G, ref 5
lithium acetaldehyde enolate + formaldehyde	−40.2	RHF/3-21G, ref 5
boron acetaldehyde enolate + formaldehyde	−32.0	RHF/3-21G, ref 5
silyl acetaldehyde enolate + formaldehyde	−33.2	MP2/6-31G*, ref 2

ingly, similar to that obtained for the reaction between lithium acetaldehyde enolate and formaldehyde.[5] Atomic coordinates and energies are given for all compounds as supporting information.

Table 1 gives the energies obtained from single point calculations at the MP2/6-31G*//HF/3-21G* level. At this level, the axial phenyl position is favored over the equatorial by about 2 kcal/mol in the TS. All transition states have a low activation energy with respect to the reactant enol so that the fraction of reactant existing in the enol form will react easily. The total reaction is exothermic, cf. Figure 2. At both levels of calculation, both *cis*-enol involving transition states are 3−10 kcal/mol lower in energy than any transition state involving the *trans*-enol. The calculated transition states would yield both the *anti* product **4a** and the *syn* product **5b**, since the axial and equatorial phenyl position have similar energy but only small amounts of the *anti* product
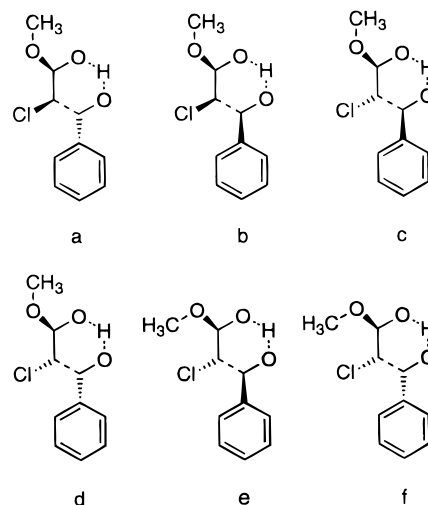
4b and the *syn* product **5a**, as an axial chlorine position raises the energy by several kcal/mol. In practice, both mirror images of the TS are present and thus both *anti* and *syn* products are expected.

The reaction energy can be compared to those for other aldol reactions, but the comparison has to be made relative to the enol form (Table 2). The reaction energy is comparable to those for the aldol reactions involving lithium,[5] boron,[5] and silyl[2] acetaldehyde enolates, but far more exothermic than the reaction between acetaldehyde enolate and formaldehyde. For reasons both of energy and geometry it thus seems clear that the hydroxyl hydrogen is capable of fulfilling the role normally played by the metal ion in aldol reactions.

Starting from the transition state with the lowest HF/3-21G* energy (Figure 1b) the reaction path was followed to the nearest minima by means of an intrinsic reaction coordinate (IRC) calculation. In reverse, the IRC calculation produced an intermediate noncovalent complex stabilized by a hydrogen bond (Figure 1a). In the forward direction the *anti* product **4a** was obtained in a conformation with an internal hydrogen bond (Figure 1c). Contrary to what is the case for the silicon-directed aldol reaction,[2] the C−C bond formation precedes the proton migration only slightly (data not shown). No intermediate could be found, and the reaction is thus concerted.
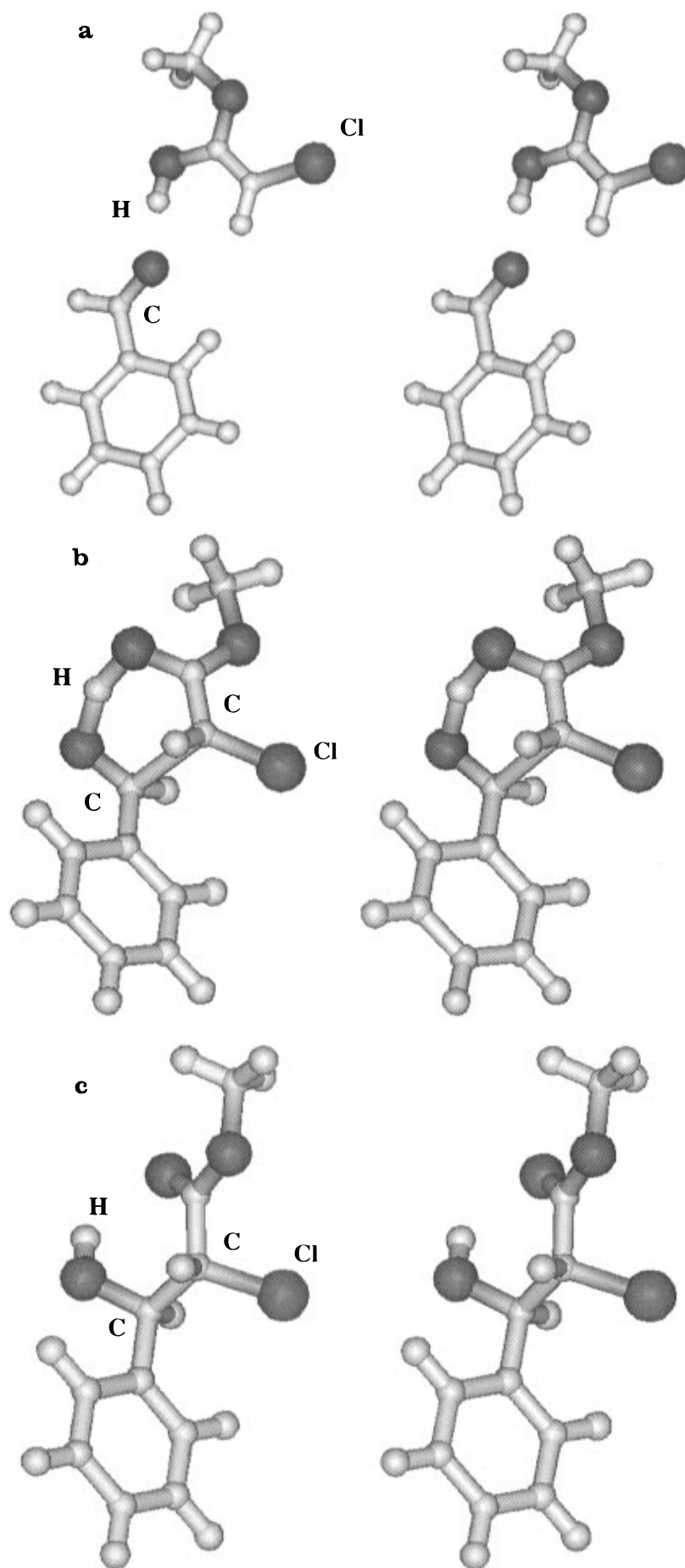
Figure 1. Stereo view of (a) the hydrogen-bonded complex preceding (b) the transition state with the lowest HF/3-21G* energy and (c) the ensuing product. Carbon and hydrogen atoms have been drawn as small light gray spheres. Oxygen atoms and the chlorines have been drawn at 1/3 of their van der Waals radii. The two carbon atoms that form the new C−C bond have been indicated, as has the migrating proton.
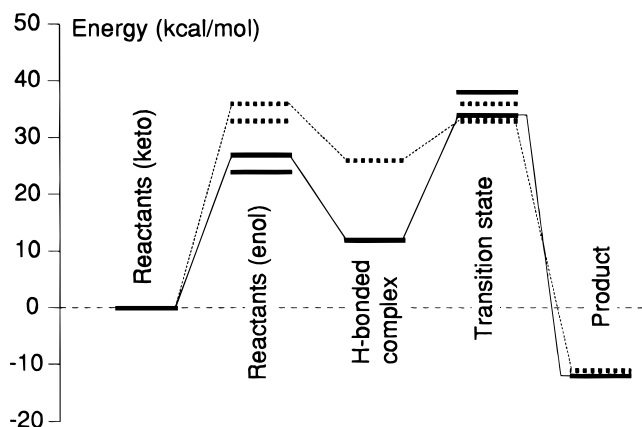
Figure 2. Reaction energetics. The energy levels have been connected by thin lines for the reaction path involving the *cis*-enol, for which the IRC calculation was performed. Unconnected levels concern the *trans*-enol reaction path. Both HF/3-21G* (full lines) and MP2/6-31G*//HF/3-21G* levels (dashed lines) are given.

The conclusion is that the ester fraction existing in the enol form easily reacts with benzaldehyde. A hydrogen-bonded complex is succeeded by a cyclic transition state in analogy to the metal ion-directed aldol reactions. The rate-limiting step is the transition from the keto to the enol form. Our results will aid the search for a stereo-selective catalyst, possibly in the form of a catalytic antibody. The catalyst would have to (a) lower the energy considerably of both the ester enol form and the TS as compared to the keto form of the ester (cf. Figure 2), (b) accommodate the equatorial chlorine position, and (c) accommodate the phenyl group in the specific position that produces the desired diastereomer.

Supporting Information Available: Energies and Cartesian coordinates of all optimized species reported in this paper (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for odering information.

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