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A Theoretical Study of Favorskii Reaction Stereochemistry. Lessons in Torquoselectivity

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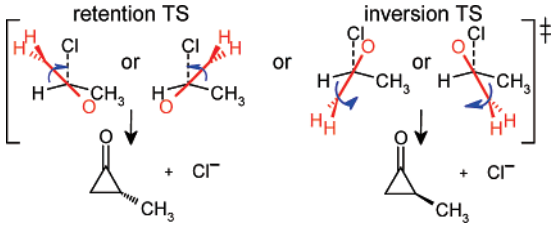

The mechanisms of the chloroenolate → cyclopropanone step of the "normal" Favorskii rearrangement have been investigated in detail using high-level ab initio calculations. A series of simple α-chloroenolates, based on chloroacetone (**6**), all monomethyl derivatives (**7**−**9**), a dimethyl analogue (**10**), and 1-acetyl-1-chlorocyclohexane (**11**) was first used to explore and define the basic features of the mechanism, which include the finding of both an "inversion" and a "retention" transition state and that in most cases these arise from separate ground-state conformations of the chloroenolate. These theoretical studies were then extended to an isomeric pair of chloroenolates **1** and **2**, the *cis*- and *trans*-2-methyl derivatives of **11**, which are the reactive intermediates involved in a well-known experimental study carried out by Stork and Borowitz (S−B). Finally, three α-chlorocyclohexanone enolate systems **12**−**14** were studied, since these intermediates have a more restricted enolate geometry. The "inversion" mechanism has been described as an S_N2 process but the present results, while supporting a concerted process, is better described as an oxyallyl structure undergoing concerted ring closure. The "retention" mechanism has been described as S_N1-like, but the calculations show that this process is also concerted, although much less so, and again involves oxyallyl-like transition-states. The model systems **6**−**8**, **10**, and **11** with a potential plane of symmetry have two enantiomeric transition states for inversion and another two for retention of configuration (at the C−Cl center). With **9** and the S−B models **1** and **2**, with no symmetry plane, there are a calculated total of four *diastereomeric* transition states for cyclopropanone ring closure in each case, two for inversion and two for retention. While the transition-state energies calculated for simple chloroenolates favor the inversion process, the S−B models **1** and **2** have almost equal inversion−retention transition-state energies. Solvation simulation calculations of ground states and transition states suggest that the retention mechanism becomes relatively more favored in polar solvents, in agreement with some experimental results. In the chloroenolates **12**−**14**, both inversion and retention mechanisms were also located, these arising from two different ground-state ring conformations of the enolate. In these models, one also finds similar inversion and retention transition-state energies, but again with a small preference for the inversion process.

Introduction

The well-known Favorskii rearrangement[1] is a reaction of a base, e.g., methoxide, with an α-halo ketone, to give a rearranged carboxylic acid ester. It has been the subject of numerous experimental mechanism studies, including some that are over 50 years old.[2] Two major mechanistic subtypes are known, the "quasi"[3] (or "semibenzilic"), and the "normal" Favorskii which involves both a chloroenolate and a cyclopropanone intermediate. The present study is concerned with the latter reaction (Figure 1).

(1) Reviews: (a) Kende, A. S. *Org. React.* **1960**, *11*, 261−316. (b) Chenier, P. *J. Chem. Educ.* **1978**, *55*, 286. (c) Hunter, D. H.; Stothers, J. B.; Warnhoff, E. W. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, p 391. (d) Baretto, A.; Waegill, B. *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1982; pp 527−585. (e) Mann, J. *Compr. Org. Synth.* **1991**, *3*, 839−859.

(2) (a) Aston, J. G.; Newkirk, J. D. *J. Am. Chem. Soc.* **1951**, *73*, 3900. (b) Sacks, A. A.; Aston, J. G. *J. Am. Chem. Soc.* **1951**, *73*, 3902.

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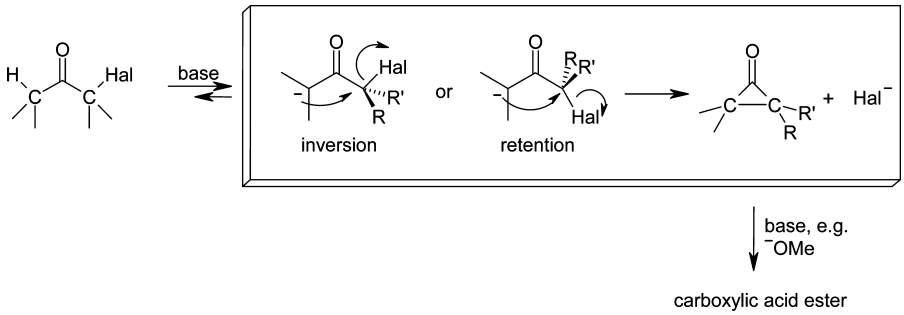
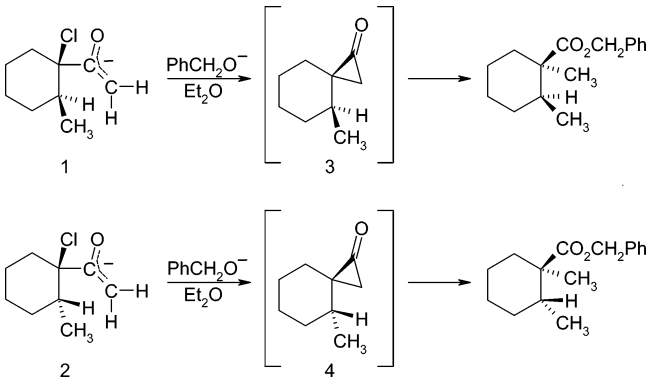


FIGURE 1. A rough schematic showing the possibility of inversion or retention in the chloroenolate → cyclopropanone-forming step. The arrows only imply that the C−C bond can eventually be formed on the backside of the C−halide bond (inversion) or same side (retention). We will be using this terminology even though identical products may be formed.

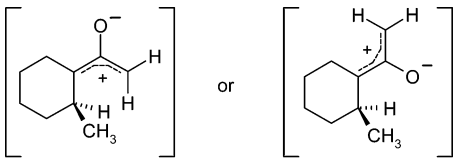
In both the cyclopropanone formation and the further rearrangement of this intermediate there are several possible stereochemical diversions. It is, however, the cyclopropanone-forming step (highlighted in Figure 1) which has been particularly controversial and which is the subject of this study. Three broadly defined mechanisms have been proposed for the cyclopropanone formation: (1) an S_N2-like displacement[5] of the halide by the enolate carbon, resulting in inversion of configuration at the carbon−halide carbon, (2) formation of an oxyallyl intermediate by an S_N1-like loss of halide ion,[6] the planar oxyallyl intermediate then undergoing disrotatory ring closure to potentially give inversion or retention (or a mixture of both) at the carbon−halide carbon, or (3) various hybrids of the above two mechanisms, with particular emphasis on explaining the role of solvent polarity on the reaction outcome. The classic stereochemical study of Stork and Borowitz (S−B)[7] is illustrative of the S_N2-like proposal (Scheme 1). Under their reaction conditions, the cyclopropanone intermediates **3** and **4** (which are non-epimerizable) must have been formed with inversion at the C−Cl center of the respective chloroenolates **1** and **2**, exactly what an S_N2 mechanism would accomplish.

The alternative formation of oxyallyl intermediates **5a** or **5b**, from **1** or **2**, was ruled out because these intermediates could in principle close to a cyclopropanone by either disrotatory mode, leading in both **1** and **2** to a stereoisomeric mixture of

SCHEME 1. Stork−Borowitz Reactions



cyclopropanones **3** and **4** and then to a resulting mixture of Favorskii esters.

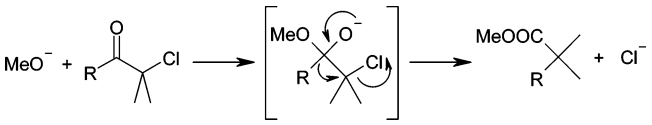


One should note, however, that there are also Favorskii rearrangement products where the stereochemical outcome is dependent on the solvent polarity. For example, House and Gilmore,[8] using one of the starting materials shown in Scheme 1, found that a selective inversion reaction only occurred in a nonpolar solvent.[9]

These retention−inversion issues are also relevant to an even older study, the classic α-halocyclohexanone → cyclopentanecarboxylic ester investigated by Loftfield using ^{14}C labeling, which established that a symmetrical intermediate (bicyclo[3.1.0]-hexan-6-one) must have been formed in the reaction.[10,11] The use of cyclohexanone itself does not allow for any reasonable possibility of an inversion−retention mechanistic determination, but a recent Favorskii reaction first reported by Lee et al.,[12] using a heavily substituted α-chlorocyclohexanone ultimately derived from *S*-carvone, gives a product which must be formed by a "normal" Favorskii mechanism and which would appear to proceed with inversion of configuration at the C−Cl bond center (Scheme 2).[13,14]

Our ultimate aim in the present investigation was to carry out a theoretical study of the S−B cyclopropanone-forming reactions (Scheme 1) and to also study the α-chlorocyclohex-

(3) The "quasi" Favorskii mechanism produces



rearranged carboxylic ester product, as does the "normal" mechanism, but they can be distinguished in several ways: (a) the opening of the cyclopropanone in the "normal" mechanism requires an external protonation, so that in an ROD/RO⁻ solvent system, a deuterium is incorporated into the product,[4] and (b) an unsymmetrical cyclopropanone intermediate can in principle open to give two different esters (see Scheme 2, intermediate **B**). In Scheme 2, the observed product could only have formed via the "normal" mechanism.

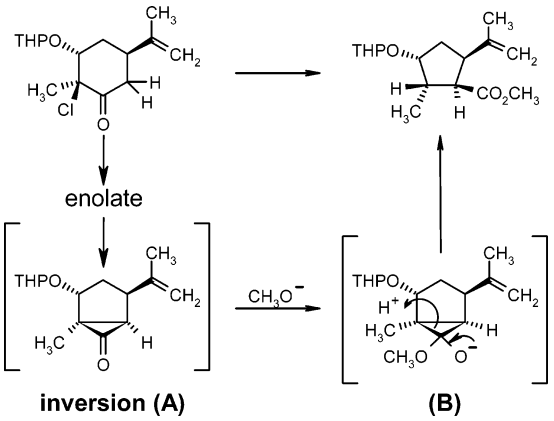
(4) Warnhoff, E. W.; Wong, C. M.; Tai, W. T. *J. Am. Chem. Soc.* **1968**, *90*, 514−515.

(5) The terms "concerted" and "S_N2" have been used to describe the inversion mechanism, and this step is often shown in textbooks and research papers using a displacement arrow formalism.

(6) Bordwell has described the proposal for an oxyallyl "intermediate" as the Aston−Dewar mechanism. (a) Bordwell, F. G.; Frame, R. R.; Scamehorn, R. G.; Strong, J. G.; Meyerson, S. *J. Am. Chem. Soc*. **1967**, *89*, 6704−6709. (b) Bordwell, F. G.; Scamehorn, R. G. *J. Am. Chem. Soc.* **1968**, *90*, 6751−6758.

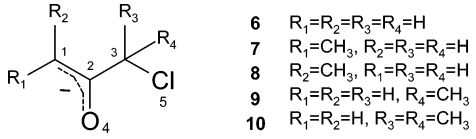
(7) Stork, G.; Borowitz, I. J. *J. Am. Chem. Soc.* **1960**, *82*, 4307.

SCHEME 2. Inversion α-Chlorocyclohexanone Favorskii Rearrangement

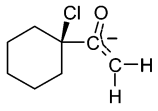


anone → bicyclo[3.1.0]hexan-6-one system for comparison to the results shown in Scheme 2, the latter case to also include some ring substituents on the α-chlorocyclohexanone in order to assess what additional effect these might have on the course of the reaction.

Locating unknown transition states in systems as complex as the S−B enolates can be challenging, and we chose to first investigate a series of much simpler chloroenolates. Although most of these reactions are of no practical interest as Favorskii reactions they did provide us with a basic understanding of how cyclopropanones could be formed via transition states involving both inversion and retention of configuration at the C−Cl center. The chloroenolate model systems **6**−**11** will be described first, with each of these providing important mechanistic insights and in many ways completely unexpected computational outcomes.



6 $R_1=R_2=R_3=R_4=H$
7 $R_1=CH_3$, $R_2=R_3=R_4=H$
8 $R_2=CH_3$, $R_1=R_3=R_4=H$
9 $R_1=R_2=R_3=H$, $R_4=CH_3$
10 $R_1=R_2=H$, $R_3=R_4=CH_3$



11

There have been several previous theoretical studies of the Favorskii rearrangement,[16,17] but the most recent of these has concentrated on comparisons of the "normal" vs "semibenzilic" (or "quasi") mechanisms and has involved calculations of all of the steps in each of these mechanisms, with the aim of predicting which mechanism is favored. These calculations have not involved a detailed consideration of the stereochemical details of the crucial cyclopropanone-forming step.

Initial studies focused first on the simplest chloroenolate **6**, a C_3 system, and **6** was also used for some diagnostic checks regarding the validity of the TS calculations.

Computational Methods

All calculations employed the Gaussian 03 suite of programs.[18] The first computations were done with the hybrid DFT B3LYP method, a method which would be ideally suited for some of the anticipated calculation needs, e.g., solvation studies using the SCI-PCM method (optimizations of the substrate geometry in the presence of an electrostatic field) and the rapidity of the calculations even for relatively large systems. However the B3LYP procedure consistently gave longer C−Cl bonds than for MP2- or MP4-based calculations. Since α-chloroenolates are reactive intermediates there is no experimental X-ray data available for the carbon−chlorine bond length in these salts, but comparisons of calculated C−Cl bond lengths in neutral compounds show the same trend, with MP2 and MP4(sdq) methods producing bond lengths closer to experimental values compared to B3LYP calculations, as shown in Tables S1−S4 in the Supporting Information. A couple-cluster (CCSD(T)) single-point energy evaluation of B3LYP, MP2, and MP4(sdq)/6-311+G* enolate geometries, Table S5 (Supporting Information), provides further support for the superiority of the Møller−Plesset methods. Calculated transition-state energies (ΔTS = transition state minus ground state) also show considerable variation, involving both the method and the basis set used. As shown in Table S1 (Supporting Information), the B3LYP transition-state energies are markedly smaller than the MP2 and MP4(sdq) values using the same basis set. There is also a basis set variation within a given method, with a minimal 6-31G* set giving significantly smaller TS energies compared to larger basis sets. This trend is not surprising since enolates are electron rich, and calculations of these should benefit from added basis set flexibility. As shown in Table S1 comparisons, an MP2/6-311+G* procedure appears to give energies similar to those obtained with a full basis set or by using MP4(sdq) methods,

(8) House, H. O.; Gilmore, W. F. *J. Am. Chem. Soc.* **1961**, *83*, 3980. See also: Skrobek, A.; Tchoubar, B. *C. R. Acad. Sci. (Paris)* **1966**, *263*, 80−83.

(9) Miller describes the S−B[7] and the House−Gilmore[8] results in terms of S_N2 (inversion) and S_N1 (retention) terminology. Miller, B. *Advanced Organic Chemistry. Reactions and Mechanisms*; Prentice Hall, Inc.: Upper Saddle River, NJ, 1998; Chapter 8.1, p 221.

(10) (a) Loftfield, R. B. *J. Am. Chem. Soc.* **1950**, *72*, 632. (b) Loftfield, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 4707.

(11) Substituted bicyclo[3.1.0]hexan-6-ones have been prepared and characterized in situ using Favorskii-like experimental conditions: Sorensen, T. S.; Sun, F., *Can. J. Chem.* **1996**, *74*, 79−87.

(12) (a) Lee, E.; Yoon, C. C. *J. Chem. Soc., Chem. Commun.* **1994**, 479−481. (b) Lee, E.; Yoon, C. H.; Lee, Y. J.; Kim, H. J. *Bull. Korean Chem. Soc.* **1997**, *18*, 1247−1248. (c) Lee, E.; Lim, J. W.; Yoon, C. H.; Sung, Y.; Kim, Y. K. *J. Am. Chem. Soc.* **1997**, *119*, 8391−92. See also: Oliver, S. F.; Högenauer, K.; Simic, O.; Antonello, A.; Smith, M. S.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5996−6000.

(13) The cyclopropanone ring opening as in (**B**) has been shown to occur with retention of configuration: Wharton, P. S.; Fritzberg, A. R. *J. Org. Chem.* **1972**, *37*, 1899−1902.

(14) Unlike the S−B ester products, the ester shown in Scheme 2 is potentially epimerizable. However, it is formed in high yield, and it seems unlikely that it is the product of a retention−epimerization process.[15]

(15) However for an example of this, see the preparation of *trans*-2,3-di-*tert*-butylcyclopropanone under Favorskii-like conditions: Pazos, J. F.; Pacifici, J. G.; Pierson, G. G.; Sclove, D. B.; Greene, F. D. *J. Org. Chem.* **1974**, *39*, 1990−95. This product is almost certainly produced by the base-catalyzed isomerization of the first formed *cis*-2,3-di-*tert*-butylcyclopropanone, see: Sorensen, T. S.; Sun, F. *Can. J. Chem.* **1997**, *75*, 1030−1040.

(16) (a) Castillo, R.; Andrés, J.; Moliner, V. *J. Phys. Chem. B* **2001**, *105*, 2453−2460. (b) Moliner, V.; Castillo, R.; Safont, V. S.; Oliva, M.; Bohn, S.; Tuñón, I.; Andrés, J. *J. Am. Chem. Soc.* **1997**, *119*, 1941−1947.

(17) Schaad, L. J.; Andes Hess, B., Jr.; Zahradník, R. *J. Org. Chem.* **1981**, *46*, 1909−1911.

(18) Gaussian 03, Revision A.1, Frisch, M. J. et al. Guassian, Inc, Pittsburgh PA, 2003. A full list of authors is given in the Supporting Information.

(19) (a) Grimme, S. *J. Chem. Phys.* **2003**, *118*, 9095−9102. (b) Goumans, T. P.; Ehlers, A. W.; Lammertsma, K.; Wurthwein, E. U.; Grimme, S. *Eur. J. Chem.* **2004**, *10*, 6468−6475.

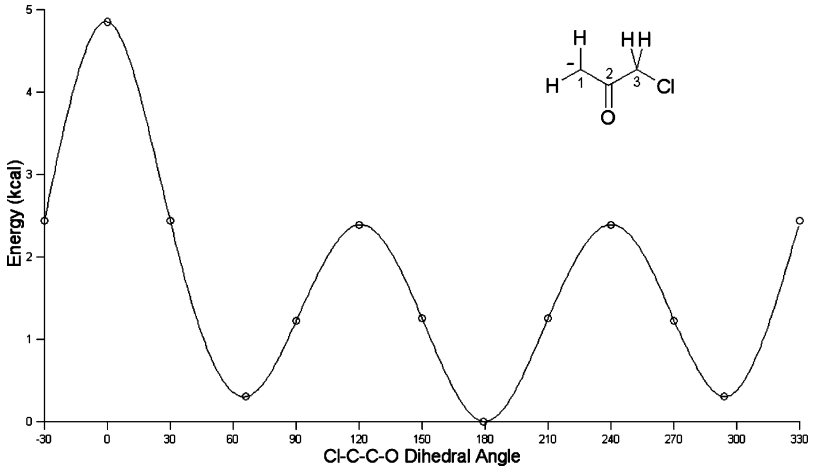


FIGURE 2. Rotation profile for enolate **6** (MP2/6-311+G**).

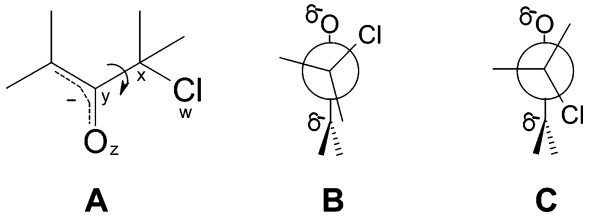
and this MP2/6-311+G* calculation was adopted as our standard procedure. The MP2 energies were "corrected" using recently proposed scaling parameters.[19] In spite of the above discussion, B3LYP methods were used for some solvation simulations since the SCI-PCM procedure of Tomasi[20] (optimization under the influence of an electrostatic potential) is not readily available for Møller−Plesset methods. Several preliminary structure optimizations were also first carried out at the B3LYP level to obtain reasonable inputs for more time-consuming MP methods.

We will revisit these computational procedures later in this paper because one set of the B3LYP-based transition states have an RB3LYP-UB3LYP instability, thus requiring a further look at TSs calculated with these restricted wave functions.

Results

α-Halo ketones are of course the starting materials for Favorskii reactions, but the "normal" Favorskii process first involves the formation of an enolate.[21] The ketone−enolate equilibrium will be dependent on a number of variables, and we make no attempt in this work to relate our calculated transition-state energies to experimental data which start from an α-halo ketone. As stated earlier, the aim of this study is to explore the TS structure(s) and energies involved in the key cyclopropanone-forming step.

Enolate ground-state (GS) and transition-state (TS) structures were eventually obtained for systems **6**−**11**, but only after encountering some initially perplexing problems. As is usual, these GS and TS structures were independently arrived at, but one can then hope to correlate these by carrying out a coordinate following IRC (intrinsic reaction coordinate) procedure starting at the TS and ending with either reactant or product GS. However, in some of our cases, this IRC correlation did not lead to the same chloroenolate GS structure that we had independently calculated. Eventually, it was realized that five of the six chloroenolate systems, **6**−**7** and **9**−**11**, had two geometrically different GS rotamers as minima, these rotamers arbitrarily defined by the dihedral angle *w*−*x*−*y*−*z* in **A** (one GS having a dihedral angle less than 90° (**B**) and the other one close to or equal to 180° (**C**)). Furthermore, each of these rotamers was connected by a *different* TS to the cyclopropanone product.



Because of the stereochemical importance of the enolate rotamers, rotation energy profiles were calculated for each of **6**−**11** by freezing the dihedral angle in units of 30° and optimizing all other parameters. The rotation profile for enolate **6** is shown in Figure 2; that for **9** is shown in Figure 3, where the presence of a stereogenic center at C3 in **9** leads to a full 360° profile. This latter Figure also shows that the calculated profile itself is not very method sensitive and that solvation simulation in the calculations (see later) still produces the same two major minima.

Rotation profiles for **7**−**8** and **10**−**11** are provided as Supporting Information (Figures S3−S7), with all of the projected minima structures separately optimized, and these values are listed for **6**−**11** in Table 1.

Chloroenolates **6**−**7** and **9** are most stable as the 60−80° dihedral rotamer, and with **10**−**11** as the 180° counterpart (Table 1). Chloroenolate **8** is unique in having a single 88° dihedral. In all cases, there is minimal distortion of the enolate planarity in the rotamer structures.

Transition States for Chloride Loss−Cyclopropanone Formation. As already mentioned, for chloroenolates **6**−**7** and **9**−**11** one can locate two different TSs for the title reaction, each connected to its own GS chloroenolate rotamer (IRC). In both TSs, for the individual systems there is a reduction in the GS Cl−C−C−O dihedral angle in going to the TSs (these angles are defined in the same way as GSs), as listed in Table

(20) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.

(21) Although our calculations start with chloroenolates, real Favorskii reactions involve α-halo ketones and a base (normally an alkoxide). The present study is concerned with comparisons of inversion and retention TSs for a given system and not with attempts to calculate actual rates of reaction starting with the ketone and alkoxide. Bordwell and co-workers[6] have carried out extensive Favorskii rearrangement studies using deuterated (−OD) solvents. The extent of H−D exchange at the enolate position (the α'-position in their nomenclature) is usually not complete and is quite variable in different systems. These authors have also used Hammett $\sigma-\rho$ studies to show that there is extensive C-Cl bond weakening in the transition state for the cyclopropanone-forming step.

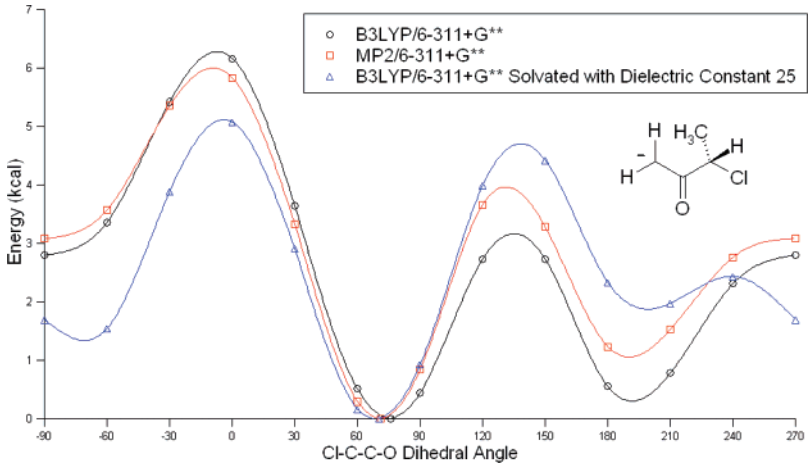


FIGURE 3. Rotation profile for *S* enolate **9**.

TABLE 1. Optimized Dihedral Angles for Enolates 6−11

structure	Cl−C−C−O dihedral angle of optimized minima (deg)	energy difference[a] (kcal/mol)
6	**66.2**, 180.0	0.41
7	**67.8**, 179.1	0.17
8	88.4	
9	**70.9**, 192.1	0.68
10	66.6, **180.0**	1.72
11	68.1, **180.0**	1.87

[a] The most stable rotamer is shown in bold.

TABLE 2. Changes in Dihedral Angle from GS to TS for Enolates 6−11

	Cl−C−C−O dihedral angle (deg)	
structure	ground state	transition state
6	66.2	53.8
	180.0	110.0
7	67.8	59.1
	179.1	106.2
8	88.4	60.0
		116.3
9 (*S*)	70.9	68.3
		−44.5
	192.1	118.1
		−110.5
10	66.6	57.0
	180.0	116.9
11	68.1	63.1
	180.0	118.6

2. For example, the connected chloroenolate GSs-TSs for **6** have dihedral angles of 66.2° → 53.8° and 180.0° → 110.0°, with similar patterns seen for **7**, **9**, **10**, and **11**. Chloroenolate **8**, with a single 88.4° GS dihedral, is connected to two transition states with 60.0° and 116.3° dihedrals, the latter providing an exception to the retention TS dihedral motion changes for **6**−**7** and **9**−**11** shown in Table 2.

In each of these chloroenolate systems, the reactant GS having the ca. 60−80° dihedral angle leads to a TS where the cyclopropanone is being formed with *inversion of configuration* at the C−Cl center (see Figure 4), and in contrast, the reactant GSs having a ca. 180° dihedral angle lead to the cyclopropanone by a process involving *retention of configuration.* Projections of each of these calculated TS structures for enolate **6** are shown in Figure 4, illustrating the opposite rotation directions of the enolate carbon in each case.

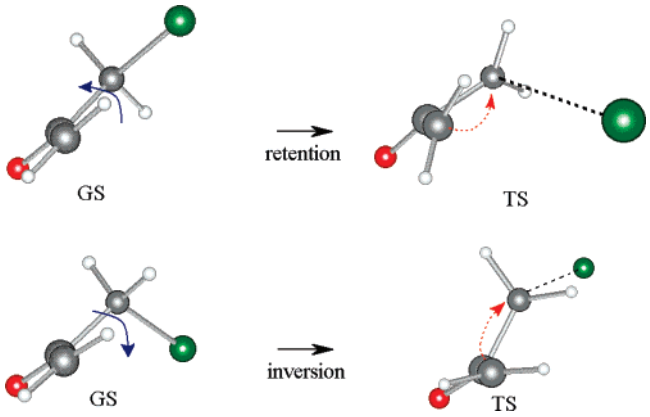
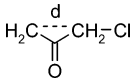


FIGURE 4. Inversion and retention TS structures for enolate **6**: carbons = gray, oxygen = red, chlorine = green. In each case, the enolate carbon is in front, sighting along the enolate carbon−CO carbon bond (i.e., the latter is partly hidden). The navy arrows indicate the enolate rotation direction. The orange arrows show the direction of the forming C−C bond of cyclopropanone.

The carbon framework in both TSs can be described as a partially cyclized oxyallyl structure and a key TS parameter in this description is the distance of the



"bond." In the inversion TS, this distance is 2.05 Å, about halfway (50% formed) between that in the enolate GS and the cyclopropanone GS, while in the retention TS, this distance is 2.22 Å, about 30% formed. The corresponding C−Cl bond lengths are also quite different, 2.49 Å in the inversion TS vs 2.68 Å for retention. In the case of chloroenolate **6**, the inversion process is calculated to be considerably lower in energy than the corresponding retention one, as detailed in the top entry in Table 3.

The planar oxyallyl molecule

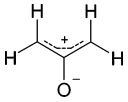


TABLE 3. Transition States for Enolates 6−11

structure	configuration		C1−C3[a] (Å)	C−Cl (Å)	Cl−C−C−O dihedral angle (deg)	transition-state energies (kcal/mol) (ΔTS) own ground state	transition-state energies (kcal/mol) (ΔTS) most stable[b] ground state
6	retention		2.22	2.68	110.0	31.6	31.6
	inversion		2.05	2.49	53.8	22.0	22.4
7	retention		2.24	2.69	106.2	25.8	26.0
	inversion		2.07	2.52	59.1	20.3	20.3
8	retention		2.30	2.68	116.3	25.2	25.2
	inversion		2.10	2.47	60.0	19.8	19.8
9	retention	C	2.29	2.81	118.1	27.8	28.5
		D	2.27	2.71	−110.5	32.3	32.9
	inversion	A	2.09	2.57	68.3	22.7	22.7
		B	2.10	2.53	−44.5	28.7	28.7
10	retention		2.32	2.83	116.9	29.3	29.3
	inversion		2.13	2.62	57.0	25.9	27.6
11 (axial)	retention		2.33	2.92	118.6	29.0	29.0
	inversion		2.13	2.71	63.1	28.2	30.1

[a] C−C of the forming cyclopropanone bond. [b] Since the individual GS enolates have much lower TS interconversion barriers than the overall ΔTSs for cyclopropanone formation, comparisons between inversion and retention processes should be based on the lowest energy GS.

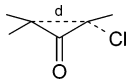
TABLE 4. Structure 6 TS Data (6-311+G*)

	inversion			retention		
	C−Cl (Å)	C1−C3[a] (Å)	ΔTS (kcal/mol)	C−Cl (Å)	C1−C3[a] (Å)	ΔTS[b] (kcal/mol)
B3LYP	2.67	2.04	14.4 (stable)	2.91	2.22	21.9 (unstable, 21.8[c])
BLYP	2.82	2.04	14.3	3.10	2.23	17.6
MP2	2.49	2.05	22.0	2.68	2.22	31.6
MP4(sdq)	2.51	2.07	22.8	2.75	2.25	27.6
CCSD(T)est	2.52	2.08	20.8	2.78	2.27	27.5

[a] C−C of the forming cyclopropanone bond. [b] ΔTS = calcd TS energy − calcd GS energy. [c] Unrestricted B3LYP calculation.

has been the subject of a number of calculations,[23] with singlet and triplet electronic states determined to be about equal in energy. The singlet state is spin contaminated, and both multiconfigurational and correlated single configurational approaches have been used to obtain energies. Our TS structures differ from planar oxyallyl in having a partial C−Cl bond present and also in having the beginning formation of a C−C cyclopropanone bond.[24]

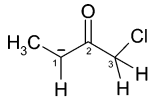
In order to test the RHF stability of our TS structures for **6** (Table 3 and Figure 4), it was convenient to use B3LYP/6-311+G* calculations (the STABLE test in Gaussian). The organic part of these TSs, when optimized at this level, have a very similar



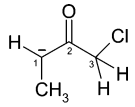
structure to those obtained at MP2, $d = 2.04$ Å vs 2.05 (MP2) for inversion, and 2.22 Å (both) for retention (Table 4). It is the C−Cl TS bond which is quite different, 2.67 Å vs 2.49 Å (MP2 inversion) and 2.91 Å vs 2.68 Å (MP2 retention), illustrating again our concern with the B3LYP C−Cl bond lengths, as described in a previous section for GS structures. For enolate **6**, the RB3LYP wavefunction is stable for the inversion TS, but RHF → UHF unstable for the retention TS. The new UB3LYP energy (spin annihilation) is 0.1 kcal/mol lower than for the RB3LYP value (summarized in Table 4).

As shown in Table 4, the inversion and retention TSs for **6** were also obtained at the MP4(s,d,q) and CCSD(T) (estimated) levels.[25] For the inversion TS, the geometries are very similar, while for the retention TS both the C−Cl and C−C distances are modestly larger, probably a result of the additional correlation. The CCSD(T) and MP4 ΔTS energies are also somewhat reduced compared to the MP2 values. The CCSD(T) minima were estimates based on a probe of the energy surface of the lowest real MP4 numerical frequency, by systematically varying the frequency displacement coordinates until a CCSD(T) energy minimum profile was located (this assumes that the same frequency mode was present). The actual curves produced by the above procedure are shown in Figures S8 and S9 (Supporting Information).

Chloroenolates **7** and **8** were studied for two reasons:



7



8

(22) We have not attempted a full statistical treatment in those cases where the two GSs are close in energy. This would involve including the calculated entropies and thermal parameters in the ΔG calculations.

(23) (a) Coolidge, M.; Yamashita, K.; Morokuma, K.; Borden, W. T. *J. Am. Chem. Soc.* **1990**, *112*, 1751−54. (b) Ichimura, A. S.; Lahti, P. M.; Matlin, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 2868−75. (c) Lim, D.; Hrovat, D. A.; Borden, W. T.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1994**, *116*, 3494. (d) Hess, Jr., B. A.; Eckhart, U.; Fabian, J. *J. Am. Chem. Soc.* **1998**, *120*, 12310−12315.

(24) The TS for the disrotatory closure of oxyallyl itself to cyclopropanone has also been studied computationally; in the first report,[23c] the TS was located close in energy and structure to oxyallyl, C−C−C angle = 110.2° vs 114.2° in the oxyallyl GS. A later study by Hess et al.[23d] (UB3LYP) found a somewhat further advanced TS, C−C−C angle = 104.8°. For our inversion TS, this angle is 90.6°, and 102° for retention (B3LYP and MP2).

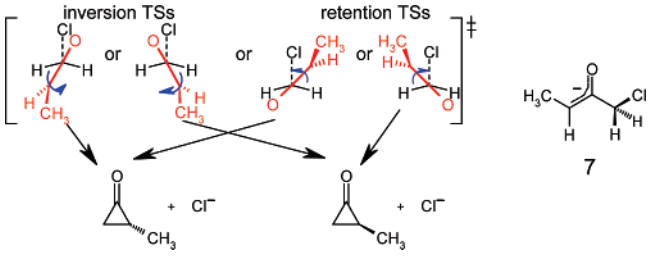


FIGURE 5. Sketches of the expected TSs for cyclopropanone formation in enolate **7**, sighting along the C−C bond (O−C−C−Cl). These simple drawings illustrate the small angle (±60°) for inversion TSs and the larger ±116° angle for retention TSs.

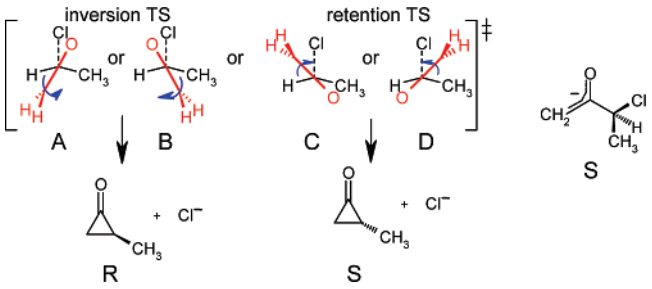


FIGURE 6. Sketches of the expected TSs for cyclopropanone formation in enolate **9**, sighting along the C−C bond (O−C−C−Cl).

(1) As shown in the *flat* projections above, one would expect **7** to be more stable than **8** on steric grounds, i.e., a less favorable interaction of the *anti*-CH_3 in **8** with the substituents on C3, and this is indeed the case. Only one GS rotamer was found for **8** (dihedral Cl−C−C−O = 88°), but two for **7** (Table 2), the latter both more stable than the enolate **8** GS, by 4.7 kcal/mol for the inversion GS, and 4.3 kcal/mol for the retention one. In our calculations, chloroenolates **7** and **8** have similar sized inversion and retention TSs measured from their own GSs (see Table 3), but under experimental conditions **7** and **8** are expected to be in rapid equilibrium, thus favoring **7** as the only important chloroenolate structure.

(2) 2-Methylcyclopropanone would be the product produced from enolate **7** (or **8**), and since this has a chiral center, one can now show two TSs for inversion and two for the retention mechanism, in order to complete the stereochemical picture (a racemic mixture). Figure 5 shows the opposing rotations leading to either *R* or *S* product, i.e., within an inversion or retention TS process, an opposite face of the enolate is being used for each. As shown in Table 3, the inversion TS is calculated to be more favorable than the retention process.

Although chloroenolate systems **7** and **8** (and **6**[24]) involve enantiomeric TSs, the situation with chloroenolate **9** is potentially more interesting since the presence of a chiral center at C3, together with the usual chiral nature of these TSs, leads to *diastereomeric* TSs, two for inversion and two for retention. These four TSs are sketched in Figure 6 for the *S* enantiomer of **9**, and the TS energies are given in Table 3. One can now also use these diagrams to predict the relative sizes of the various TS energies within a given inversion or retention regime without relying on calculations. For example, in the inversion series TS**B** looks less stable than TS**A** because a hydrogen on the enolate interacts with the CH_3 group, while TS**C** looks less stable than TS**D** because of interaction between the oxygen and the methyl group. As shown in Table 3, TS**B** is 6.0 kcal/mol larger than TS**A**, while TS**C** is 4.4 kcal/mol larger than for TS**D**.

The 3-methylbut-2-enolate structure **10** is of interest because the chlorine atom is in a tertiary position, as it also is in the S−B enolates. As one moves from a primary chlorine, to secondary, and finally a tertiary position, there is a gradual change in calculated TS geometry parameters. For the inversion process (Table 3), the C−C distance increases from 2.05 Å in **6**, to 2.07−2.10 Å in **7**−**9**, and to 2.13 Å in **10**, while the C−Cl distances show less change. For the retention TS, the C−C distance increases from 2.22 Å in **6**, to 2.24−2.30 Å in **7**−**9**, and to 2.32 Å in **10**. From a structural viewpoint, the symmetry considerations in enolate **10** are similar to those of enolate **6**, i.e. single energy dual (enantiomeric) inversion and single energy dual (enantiomeric) retention TSs, so **10** was chosen as another candidate for a more detailed evaluation of the validity of the restricted wave function TS geometries employed in this work, using higher correlated levels (MP4 and CCSD(T)). This evaluation follows that already described for enolate **6**, and the data are included in Table 5 and Figures S10 and S11 (Supporting Information). As for chloroenolate **6**, the retention TS for **10** at RB3LYP/6-311+G* was RHF → UHF unstable, with the UHF energy lowered by 0.6 kcal/mol (Table 5). On evaluation of the single-point CCSD(T) surface, starting from the MP4(sdq)-optimized structures of the inversion and retention TSs using the lowest real frequency coordinate displacements for the inversion TS, and the second lowest for retention, one finds changes somewhat similar to those found for **6**. Both the CCSD(T) inversion and retention TSs are little changed in geometry from the MP4 minima (see Figures S10 and S11, Supporting Information). However, as shown in Table 5, there is a significant geometry change from the MP2 parameters compared to MP4 or CCSD(T) results, and there is some noticeable spread in the calculated ΔTS energies. The increased energy difference between UB3LYP and RB3LYP results for **10** (0.6 kcal/mol) compared to **6** (0.1 kcal/mol) is very likely a result of the increased C1−C3 distance in the former, i.e., a more oxyallyl-like structure.

The last chloroenolate that was studied in this preliminary series was the cyclohexyl-based system **11**. This system was included because it is a simpler version of the two S−B chloroenolates, and we also wanted to use **11** to probe the added conformational complication of having possible axial and equatorial C−Cl conformations. The ground-state enolate rotation profile for the axial chlorine conformer (Figure S6, Supporting Information) closely resembles that for chloroenolate **10**, and as in **10** one can locate both retention and inversion TSs for cyclopropanone ring closure (Table 3). In contrast, the equatorial chlorine conformer has a very different rotamer profile (Figure S7, Supporting Information), with only one distinct GS conformation (dihedral ± 85°), and we were able to locate only the retention TS. The rotamer profile in Figure S7 shows a large energy maximum at a 0° dihedral, and this clearly results from both an unfavorable $^{\delta+}C{=}O^{\delta-}$ vs $^{\delta+}C{-}Cl^{\delta-}$ dipole interaction and steric strain caused by the enolate hydrogens being close to the axial ring hydrogens, as shown in red in **11A**. Any motion toward an inversion TS (i.e., toward a small angle Cl−C−C−O dihedral) would appear to accentuate these steric interactions and likely accounts for us not locating an inversion TS, the only case where this has happened. The retention TS for this

(25) Multireference CASSCF calculations are often carried out on systems with triplet instabilities, but these calculations (with added dynamic correlation methods) require large computer resources and there is some arbitrariness regarding the size of the active space to be used.

TABLE 5. Structure 10 TS Data (6-311+G*)

	inversion			retention		
	C−Cl (Å)	C1−C3[a] (Å)	ΔTS (kcal/mol)	C−Cl (Å)	C1−C3[a] (Å)	ΔTS[b] (kcal/mol)
B3LYP	unable to locate the TS			2.39	3.22	16.1 (unstable, 5.5[c])
MP2	2.62	2.13	25.9	2.32	2.83	29.3
MP4(sdq)	2.73	2.15	25.6	2.34	2.97	27.8
CCSD(T)est	2.74	2.15	23.6	2.34	2.96	24.8

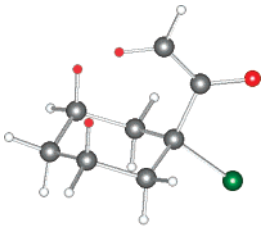
[a] C−C of the forming cyclopropanone bond. [b] ΔTS = calcd TS energy − calcd GS energy. [c] Unrestricted B3LYP calculation.

TABLE 6. Calculated MP2/6-311+G* TS Geometry Parameters and ΔTS Values for All Transition States of Enolates 1 and 2

						transition-state energies (kcal/mol)	
structure	configuration		C1−C3[a] (Å)	C−Cl (Å)	Cl−C−C−O dihedral angle (deg)	relative to own ground state	relative to most stable ground state
1	inversion	**A**	2.13	2.62	−51.4	26.7	31.8
		B	2.14	2.65	53.1	26.6	31.5
	retention	**C**	2.33	2.87	129.3	30.0	30.0
		D	2.35	2.85	−126.2	33.7	33.7
2	inversion	**E**	2.23	2.86	−76.2	31.2	31.2
		F	2.13	2.74	64.5	27.5	27.5
	retention	**G**	2.33	2.93	119.1	27.1	27.4
		H	2.35	2.93	−113.1	27.9	28.2

[a] C−C of the forming cyclopropanone bond.

equatorial chlorine conformer could be obtained, but was calculated to be slightly higher in energy than either of the axial chlorine conformer TSs (see Table 3), and we have considered only the axial chlorine conformers in our following discussion of the S−B enolates.

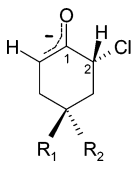


11A

Stork−Borowitz (S−B) Enolates. The *cis*- and *trans*-chloroenolates **1** and **2** were modeled in our work in a similar manner to the previously discussed **6**−**11** enolates. Both **1** and **2** have two possible chair conformations, but we have restricted our calculations, for reasons mentioned above in connection with the chloroenolate **11** discussion, to the axial chlorine conformers in each case. Unlike in the simple cyclohexyl system **11**, the presence of a symmetry-reducing 2-methyl substituent creates the possibility of two diastereomeric inversion and two diastereomeric retention TSs for a given enantiomer, each of **1** and **2**. The TS energies for all eight of these are listed in Table 6, along with selected geometric parameters.

One can now use the general principles developed for enolates **6**−**11**, particularly enolate system **9**, to draw a priori predictions regarding the steric factors which are likely to be present in the two possible inversion and two possible retention TSs for each of the S−B enolates **1** and **2**, without the absolute need for calculations. The partial TS diagrams in Figure 7 are illustrative. In the *cis* isomer **1**, only TS(**D**) is predicted to have a small adverse steric interaction between an enolate C−H bond and the equatorial methyl group of the ring. Structure **E** in Figure 7 is shown because it is the only member of the *trans* **2** series where one would also predict an adverse steric interaction. As shown in Table 6, the relative size of the calculated TSs is in agreement with the Figure 7 predictions. Overall, considering the various multiple TSs, the actual TS values for the lowest energy inversion and retention TSs are remarkably similar, a point to be discussed later.

2-Chlorocyclohexanone Enolates. Three 2-chlorocyclohexanone enolate systems were studied, the parent system **12**, and the corresponding *cis*- and *trans*-4-methyl derivatives **13** and **14**. The latter were used to probe any changes which might occur with substituted cyclohexanones. No rotamers are possible in these enolate structures, and the calculated ring conformation has a half chair structure similar to that of cyclohexene (two sp^2 centers).[27] In this half-chair structure it appeared that two different C−Cl orientations would be possible and optimized GS structures for these were indeed found. The resulting dihedral angles are listed in Table 7, and these fall into two groups, ca. −48° and ca. 64−72° for the 2*R* enantiomers of **12**−**14** respectively. Both inversion and retention TSs were located for each of **12**−**14**, and the important data for these are given in Table 8. In agreement with the previously discussed chloroenolates, the small dihedral angle GS was connected to the inversion TS, and vice versa for the larger angle GSs (IRC). In the data reported in Table 8, the inversion TS was favored in each case, by ca. 2 kcal/mol for **12** and **14**, and by 5.5 kcal/mol for **13**.



12 $R_1 = R_2 = H$
13 $R_1 = H$ $R_2 = CH_3$
14 $R_1 = CH_3$ $R_2 = H$

The geometric parameters associated with the inversion and retention TSs for **12**−**14** are given in Table 8. For the inversion

(26) Chloroenolate **6** also has enantiomeric TSs for both inversion and retention reactions, but these are trivial since an identical "product" results.

(27) *Stereochemistry of Organic Compounds*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley and Sons, Inc.: New York, 1994; pp 726−730,

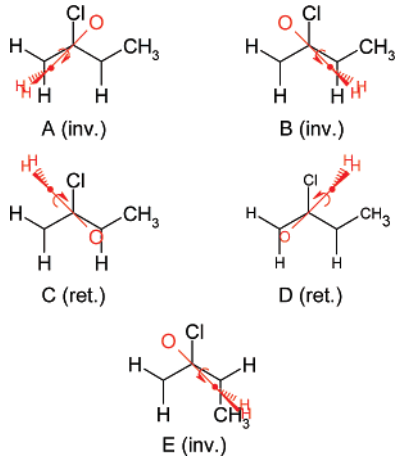


FIGURE 7. Sketches of the expected TSs for cyclopropanone formation in chloroenolates **1** and **2**, sighting along the C−C bond of O−C⁻−C−Cl, and where we have removed the rear $-CH_2-CH_2-CH_2-$ portion of the cyclohexane ring for clarity. Structures **A**, **B**, **C**, and **D** illustrate the four possible TSs for the cis isomer **1** (both **1** and **2** are shown in the **S** configuration at C1 of the ring). Dihedral angles O−C⁻−C−Cl of ca. ±40−60° correspond to inversion TSs and ca. ±120−140° for retention TSs. Structure **E** is one of a similar four TSs for isomer **2**. The rotation direction of the enolate carbon in the ring closure is also shown for each structure. Note also that we have left out the overall negative charge on each of these structures, and that the enolate carbon is shown as a dot.

TABLE 7. Ground-State Dihedral Angles for Enolates 12−14

ground-state structure	configuration	Cl−C−C−O dihedral angle (deg)
12	inversion	−48.1
	retention	71.9
13	inversion	−47.8
	retention	63.8
14	inversion	−48.9
	retention	72.0

TS, the cyclopropanone closing C−C bond distances of 2.12 Å in each case are very similar to those for chloroenolates **1**−**11** where the enolate is "free" to rotate, and the inversion C−Cl bond distances for the **12**−**14** TSs are also similar to those for **1**−**11**. This is partly true for the retention mechanism as well, with C−C distances of 2.31−2.33 Å, but with slightly longer C−Cl values, 2.81−2.88 Å. As was done for chloroenolate systems **6** and **10**, we have carried out extra calculations regarding the stability of the RHF-derived wave function in **12** for both the inversion and retention TSs and these data are shown in Table 9. At the B3LYP/6-311+G* level the inversion TS is stable, the retention analogue, unstable, with the UB3LYP energy ca. 1.0 kcal/mol lower than the RHF value. The single-point CCSD(T) minimum starting with an MP4(sdq)-optimized geometry and frequency, and modifying the lowest real frequency coordinate displacements, gave a reasonably similar geometry for the inversion TS, but the largest geometry change seen using this procedure for the retention TS, with a C−C increase from 2.32 Å to 2.34 Å, and a C−Cl increase from 2.93 Å to 2.97 Å (MP4 comparison, see Table 9). These long C−Cl bonds represent a virtual "breakage" of the C−Cl bond, but, as discussed later, the retention geometry cyclopropanone formation (2.34 Å) is also clearly underway. There is also a significant decrease in the value for the CCSD(T) retention ΔTS value, ca. 3.5−4 kcal/mol compared to MP2 and MP4 values, again a possible result of a better correlation treatment.

Solvation Simulation Calculations. Favorskii rearrangements are of course conducted in solution, so we have applied the PCM (polarizable continuum model)[28] solvation simulation procedure to all of the GSs and TSs obtained in this work (the solvent dielectric constant of methanol, 32.6, being used in most cases, along with the MP2/6-311+G* basis set). These data are summarized in Supporting Information Table S5, but overall the results show only modest changes to the relative inversion-retention energies, although the absolute values are of course quite different (calculated solvation energies range from 55 to 60 kcal/mol for the various GSs and from 60 to 68 kcal/mol for the more ionic-like TSs). Analyzing the data in Table S5 in more detail, there is a slight preference favoring the retention TS energy under solvation modeling conditions. In the case of chloroenolate **6**, the retention GS is less stabilized by solvation, whereas the inversion and retention TSs have nearly equal calculated solvation values, resulting in a ca. 1.5 kcal/mol net decrease in retention ΔTS energy compared to the inversion analog. For the S−B enolate systems **1** and **2**, solvation simulation favors both the inversion GS and TS, but somewhat less for the TS comparison, resulting again in a net stability gain for the retention process. For the cyclohexanone enolates **12**−**14**, solvation selectively stabilizes the retention GSs to a small extent, but the retention TSs are even more stabilized, again resulting in solvation slightly favoring a retention mechanism.

The PCM method produces a solvation energy estimate using the fixed gas-phase geometry and a potentially more useful solvation simulation model is the SCI-PCM procedure (self-consistent isodensity polarized continuum model) of Tomasi,[18] in which solute structures can be optimized in the presence of the simulated solvent field. However this method is only readily available for HF and B3LYP calculations,[29] and the latter, as already discussed, appears to give somewhat unrealistic C−Cl bond lengths. Nevertheless, we have carried out SCI-PCM calculations using chloroenolate **6** as our model, at the B3LYP/6-311+G* level. These calculations involved using the SCI-PCM procedure on the *fixed* gas-phase geometries of the inversion and retention GSs and TSs and comparing these energies to identical calculations where the geometries were allowed to optimize, and the results are listed in Supporting Information Table S6. The GS structures as one might expect are little changed in geometry but there are marked changes in the inversion and retention TS structures; for inversion, curiously, the C−Cl bond becomes shorter (from 2.67 to 2.61 Å) and the C1−C3 "bond" becomes longer (2.04 to 2.17 Å). For retention, the C−Cl bond becomes longer (2.91 to 3.01 Å), as does the C1−C3 "bond" (2.22 to 2.28 Å). However, the most significant result is that structure optimization under the influence of the solvent field vs solvation of the fixed geometry favors the retention process by an additional 0.9 kcal/mol. This additional amount due to solute geometry change added to the ca. 1.5 kcal/mol from our previously derived GS-TS solvation changes gives a ca. 2.4 kcal/mol total favoring the retention mechanism.

(28) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669−681.

(29) For a discussion of solvation modeling, see Cramer, C. J.; Truhlar, D. G. *Science* **1992**, *256*, 213.

TABLE 8. Transition States for Enolates 12−14

structure	configuration	C1−C3[a] (Å)	C−Cl (Å)	Cl−C−C−O dihedral angle (deg)	transition-state energies (kcal/mol) relative to own ground state	transition-state energies (kcal/mol) relative to most stable ground state
12	inversion	2.12	2.53	−48.2	22.2	23.6
	retention	2.31	2.81	−97.1	26.4	26.4
13	inversion	2.12	2.53	−48.4	22.2	22.2
	retention	2.33	2.88	−84.8	26.4	27.7
14	inversion	2.12	2.51	−47.8	21.8	24.2
	retention	2.32	2.81	−97.2	26.0	26.0

[a] C−C of the forming cyclopropanone bond.

TABLE 9. Structure 12 TS Data (6-311+G*)

	inversion			retention		
	C−Cl (Å)	C1−C3[a] (Å)	ΔTS (kcal/mol)	C−Cl (Å)	C1−C3[a] (Å)	ΔTS[b] (kcal/mol)
B3LYP	2.86	2.13	15.2 (stable)	3.21	2.30	16.2 (unstable, 15.2[c])
MP2	2.53	2.12	22.2	2.81	2.31	26.4
MP4(sdq)	2.581	2.132	23.8	2.934	2.321	26.9
CCSD(T)est	2.596	2.137	21.3	2.97	2.34	22.7

[a] C−C of the forming cyclopropanone bond. [b] ΔTS = calcd TS energy − calcd GS energy. [c] Unrestricted B3LYP calculation.

These PCM and SCI-PCM results suggest that in cases where the gas-phase energies for the inversion and retention cyclopropanone transition-states are of similar magnitude, but perhaps slightly favor inversion, that retention reactions could become increasingly competitive in higher dielectric constant solvents.

Calculations Involving the Overall Thermochemistry for Formation of Some Cyclopropanone Products. Our primary concern in this study has been to calculate the geometries and energies of reactants (chloroenolates), particularly their transition states for cyclopropanone formation. However, it is of interest to examine the overall thermochemistry for a few representative cases. Moliner[16] et al. have previously studied the overall thermodynamics for both the "normal" and "quasi" mechanisms, so we have restricted our efforts to examining only the chloroenolate → cyclopropanone + Cl^- step, using three representative systems, the parent chloroenolate **6**, 1-chloro-1-acetylcyclohexane enolate **11**, and the 2-chlorocyclohexanone enolate **12**. The corresponding organic products are cyclopropanone, spiro[2,5]octan-1-one, and bicyclo[3.1.0]hexan-6-one. In each case, the gas-phase reaction is calculated to be endothermic, as expected, but with PCM solvation modeling each one becomes exothermic.[30,31] These data are shown in Table S7 (Supporting Information), with the smallest exothermicity found for enolate **12**, an indication, not unexpected, that this bicyclic ketone is relatively more strained than in the other two examples.

Discussion

In the comprehensive text *Organic Chemistry* by Clayden et al.,[32] the postulated S_N2 cyclopropanone-forming step of the Favorskii rearrangement is described as "a reaction that looks bizarre but that many chemists think is not unreasonable." To be fair, the textbook authors also add that "many others favor a pericyclic (oxyallyl) description." The experimental fact that there needs to be inversion of configuration at the C−Cl center in the reaction of the S−B enolates (at least in nonpolar solvents), and in other systems, is at the heart of this problem. As would be true of an S_N2 mechanism, our calculations show that for *inversion* the cyclopropanone formation is taking place in a concerted manner, and this can be clearly seen in an intrinsic reaction coordinate (IRC) plot of the C1−C3 "cyclopropanone" ring distance (closure) in enolate **7** vs the C−Cl bond length increase (Figure 8, red curve), a profile in itself not unlike what one might envisage for an S_N2 process. However the results provide much more detail than this simplistic interpretation, and show that, for example, in achiral chloroenolates like **7**, the inversion ring-closure process takes place via a pair of enantiomeric transition-states in which opposite faces of the enolate carbon are eventually bonded to the backside of the C−Cl carbon.[33]

Oddly enough, the calculated retention TSs have some similarities to the inversion counterparts, once again involving dual TSs and bonding to opposite faces of the enolate carbon, but obviously differing in bonding to the front face of the C−Cl bond (retention of configuration). The Cl−C−C−O dihedral angle for all of the retention TSs for the chloroenolates in which "free" rotation is possible fall in the range of ±106−129°. Since most of the connected GS dihedral angles are much larger, there is considerable early rotation of this bond before there is much change in C−Cl bond distance or of closure of the C−C cyclopropanone "bond". As shown in the IRC profile for the retention TS for chloroenolate **7**, the cyclopropanone formation is initially much more asynchronous (Figure 8, blue line) compared to the inversion case. At the TS the C−C bond (2.24 Å) is only about 30% formed, and the C−Cl bond (2.69 Å) is considerably longer than in the inversion mechanism (2.52 Å).[34]

If one accepts the validity of these calculations, one has to conclude that the inversion mechanism for chloroenolate **7** is unlikely to ever involve a "free oxyallyl", even accounting for

(30) The chloride anion "solvation" energy provides the largest driving force.

(31) On a free energy basis, the positive entropy change in going to the products will further contribute to the exergonicity of the reaction.

(32) *Organic Chemistry*; Clayden, J., Greeves, N., Warren, S., Wothers, P., Eds.; Oxford University Press: New York, 2001; pp 990−991.

(33) On examination of the structure of the inversion GS for **6**, one already finds a slight nonplanarity in the enolate (±1.277°) in the selective rotation direction eventually leading to the TS.

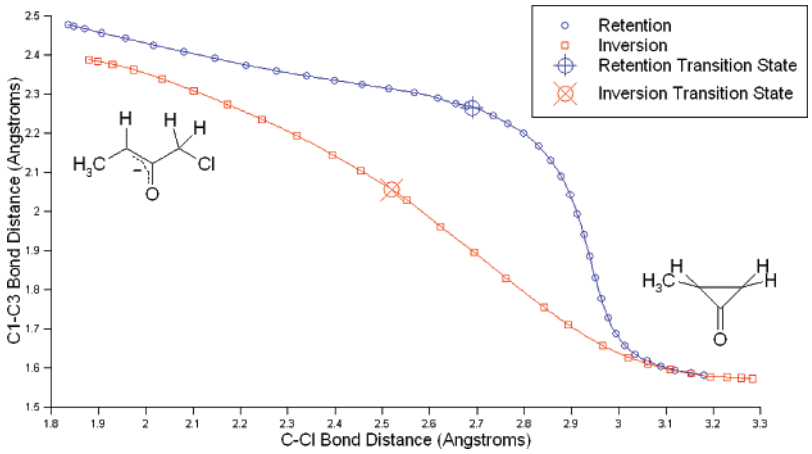


FIGURE 8. "Cyclopropanone" ring closure as a function of C−Cl bond distance in enolate **7** (MP2/6-31G*).

the fact that our solvent simulations, as discussed previously, are imperfect. For the retention mechanism, the profile as noted above is considerably more asynchronous. However, if one examines the structures from the Figure 8 IRC profile, where the C−Cl distance is, for example, 2.3 Å (some C−C bond "strength" certainly remaining), the retention enolate rotation has already been established.[35]

As noted in the Introduction, the S−B study of chloroenolates **1** and **2**, carried out in diethyl ether solvent ($\epsilon = 4.3$), gave inversion product esters in both cases. In a subsequent investigation by House and Gilmore,[8] where the rearrangement of **2** was carried out separately in two different solvents, 1,2-dimethoxyethane (DME, $\epsilon = 5.5$) and methanol ($\epsilon = 32.6$), it was shown that the inversion product was almost exclusively produced in the former solvent, but that in methanol, a mixture of inversion and retention products were obtained. The solvation energy calculations that we report compare solute gas-phase energy values with those in a simulated solvent of $\epsilon = 32.6$, and one might suppose that there could be a significant calculated solvation energy difference between $\epsilon = 32.6$ and $\epsilon = 5.5$ dielectric constant "solvents". However, this calculated difference is actually quite small,[36] and it seems more likely that hydrogen-bonding effects (CH_3OH vs DME) in real experimental situations is a more important solvation factor. Neither the PCM nor SCI-PCM models specifically account for hydrogen bonding.

Overall, our calculated energies with solvation simulation taken into account provide numbers which accord very well with experimental results, and ultimately these comparisons do provide some assurance that the structures and energies obtained in this work have validity. The detailed inversion and retention TS structures obtained, and the illustration of simple models that can be used to evaluate steric effects and probe the question of inversion vs retention TS preferences should also have practical applications.

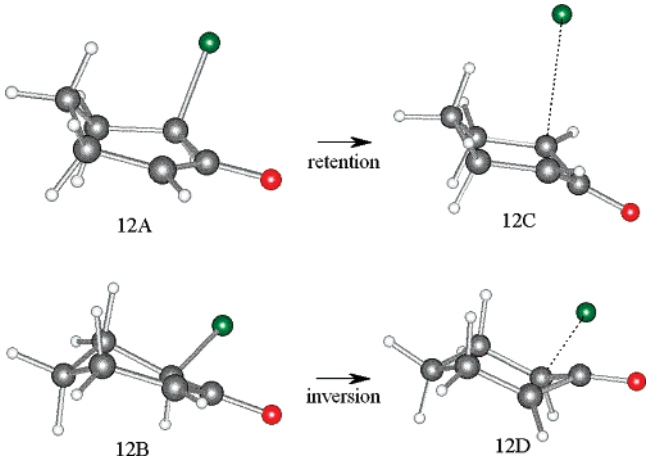
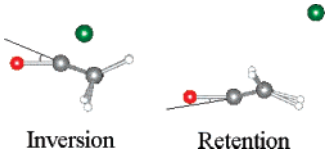
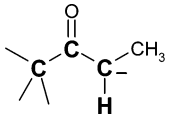


FIGURE 9. Retention and inversion geometries for the respective GSs and TSs of chloroenolate **12**.

(34) In both the inversion and retention TS structures for **6**, as shown below, the carbonyl oxygen is markedly nonplanar. Similar results have been seen in the TS for the oxyallyl → cyclopropanone reaction[23d] and in the GS structure of bicyclo[1.1.0]butan-2-ones: Barghava, S.; Hou, J.; Parvez, M.; Sorensen, T. S. *J. Am. Chem. Soc.* **2005**, *127*, 3704−3705. All of the other TSs obtained in our study showed the same distortion.



(35) At a C-Cl distance of 2.1 Å, the enolate dihedral angle



is 3.6°, 9.7° at C−Cl = 2.3 Å, and 17.8° at 2.5 Å. For the parent system **6**, the corresponding values are 5.5°, 7°, and 12°. The use of IRC energy profiles in cases where one is attempting to distinguish between a bond dissociation mechanism involving a flat profile concerted reaction vs a short-lived intermediate (shallow PE minimum) has been questioned: Ussing, B. R.; Singleton, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 2888−2899. A related paper (Bekele, T.; Christian, C. F.; Lipton, M. A.; Singleton, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 9216−9223, see Figure 5) contrasts an IRC profile with molecular dynamics (MD) results, showing in this case the ambiguity of the terms "concerted" and "asynchronous" as applied to the ene reaction. In our present "retention" mechanism, entropic factors inherent in a free energy surface, such as those involved in MD simulations, should favor a dissociative reaction process to a larger extent than indicated by an IRC profile. On the other hand, CASPT2N calculations[23c] of the oxyallyl system indicate an extremely low barrier for cyclization (0.33 kcal/mol); i.e., oxyallyl is almost a transition state in itself.

(36) Solvation simulations use the Born equation, where solvation energies vary as $1 - 1/\epsilon$ = dielectric constant). The relative solvation energies for gas phase, DME, and methanol become 0:0.8:0.97. For a solvation energy of 60 kcal/mol in methanol, one has a value of about 50 kcal/mol in DME. For a calculated difference of 2 kcal/mol solvation energy between two solutes in methanol, one has a difference in DME of 1.7 kcal/mol, i.e., a 0.3 kcal/mol difference.

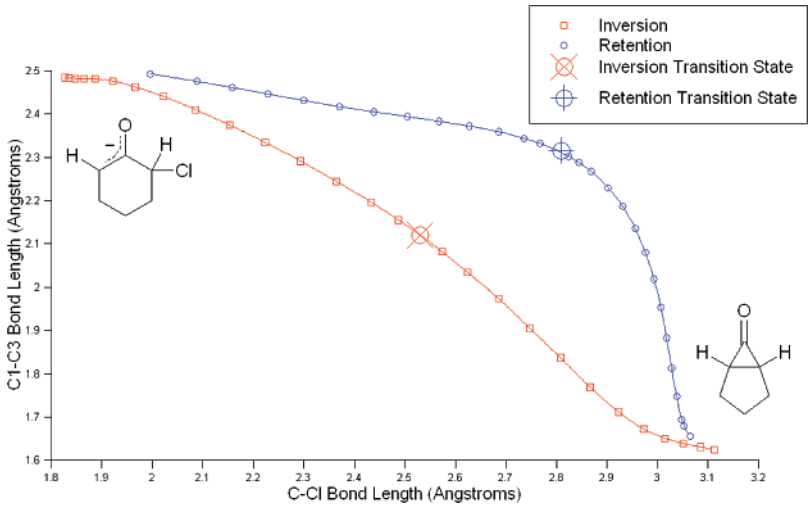


FIGURE 10. "Cyclopropanone" (bicyclo[3.1.0]hexan-6-one, chair conformation) ring closure as a function of C−Cl bond distance in enolate **12**, obtained from IRC calculations, plotting the data from every fifth step (stepsize = 10, MP2/6-31G*).

We have also shown in this work that the S−B chloroenolates **1** and **2** have two TS structures for both inversion and retention mechanisms. In each of **1** and **2**, each dual TS leads to the same product because the enolate carbon is not a prochiral face. However, if the enolate were monosubstituted (prochiral), each of these TSs would be capable of producing their own diastereomer, perhaps selectively if one TS was more favorable than the other (already shown to be the case for **1** and **2**).

The cyclohexanone chloroenolate systems **12**−**14** were chosen in this study as examples of Favorskii rearrangement substrates where there was no possibility of "free" rotation about an O−C−C−Cl dihedral angle. As mentioned in the Introduction, α-chlorocyclohexanone itself was used by Loftfield[10] in an early example of a ^{14}C-labeling experiment to show that a symmetrical intermediate, bicyclo[3.1.0]hexan-6-one, was involved in the reaction (the "normal" Favorskii rearrangement).[10] In an unsubstituted cyclohexanone, as in our test systems **6**−**11**, inversion and retention mechanisms lead to the same Favorskii product, but Loftfield's use of an arrow formalism in his papers implied an S_N2-like inversion mechanism for formation of this intermediate. Four years later (1954), Dewar published[37] what may be regarded as the first theoretical study in this area, pointing out that in a planar α-chloroenolate system, the enolate carbon is poorly aligned for an S_N2 reaction. Although not discussed by Dewar, one might suppose that a cyclic α-chloroenolate would be even more constrained for a possible S_N2 process.

In fact, the inversion and retention TSs obtained in this study for **12** appear surprisingly free of steric problems in the cyclic ring, since a chairlike conformation (structures **12**C and **12**D) is seen in both cases. These contrast with the half-chair structures calculated for the two GSs (**12**A and **12**B).

As mentioned earlier in the Results section, the inversion ΔTS is smaller than for retention, even though the inversion GS is the less stable of the two ring conformers. The IRC profile for **12** is shown in Figure 10, with the inversion mechanism showing a highly concerted profile for C−C bond formation vs C−Cl bond length increase. The retention mechanism IRC profile resembles those for the other enolates **6**−**11** and **1**-**2**, but appears to be somewhat more asynchronous than these.[38]

(37) Burr, Jr., J. G.; Dewar, M. J. S. *J. Chem. Soc.* **1954**, 1201−1203.

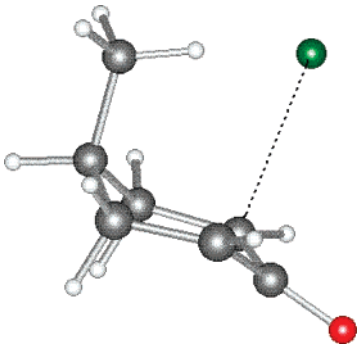


FIGURE 11. Chloroenolate **13** retention transition state.

There is also some indication in our calculations that extra substituents on the chlorocyclohexanone skeleton can have a sizable influence on the relative inversion-retention ΔTS energies, since the *cis*-4-methyl isomer **13** has a considerably larger inversion-retention energy difference compared to the *trans* isomer **14**, 5.5 vs 2 kcal/mol (both favoring inversion). This difference arises almost entirely from a larger retention TS energy value in **13** vs **14** because the 4-methyl substituent in **13** (Figure 11) occupies an axial position, placing the departing "chloride" within the van der Waals radius of the methyl group.

The Favorksii rearrangement product recently obtained by Lee et al.[12] (see Scheme 2, Introduction) has clearly been produced by an "inversion" mechanism. The TS structures shown in Figure 9 for **12** can in principle offer some insights into how the steric effects of added ring substituents could influence the inversion-retention balance, and such an analysis could in principle be applied to the modified **S**-carvone starting material used by these authors. Such modeling should include solvation simulation calculations and in this regard the **12**−**14** systems show similar trends to those already discussed for **1**−**2** and **6**−**11**, i.e., a slight relative stability gain for the retention ΔTSs.

(38) The α-chlorocyclohexanone retention mechanism leading to bicyclo-[3.1.0]hexan-6-one appears to be the least concerted of the retention mechanisms studied in this work, cf. a comparison of the IRC profile in Figure 8 for chloroenolate **7**, vs that in Figure 10 for the α-chlorocyclohexanone enolate **12**. This difference is probably a result of the ring restricted O−C−C−Cl dihedral angle in the retention GS of **12** (72°), compared to the >90° in most of the enolates where "free" rotation is possible.

Although the present results give new insights into the cyclopropanone-forming step of the Favorskii reaction, e.g., detailed pictures of the TS structures and the presence of multiple TSs are two examples, some of our conclusions regarding "concertedness" and other features of this reaction have already appeared in the literature based on experimental work.

In a series of publications, Bordwell[6,39] and co-workers have reported extensive mechanism studies of the Favorskii rearrangement, and in one report (1969) suggest[6] "a dipolar-ion-like *transition-state* in which the stereochemistry for ionization and participation are defined." This description could roughly apply to either the inversion or retention TS calculated in our work, particularly the retention TS (in Bordwell's studies this inversion-retention stereochemistry issue was not explored). In a 1980 review article on the Favorskii rearrangement,[1c] Hunter et al. discuss the stereochemical problems with a converted S_N2 cyclopropanone cyclization in aprotic and nonpolar media, wherein the S−B study is discussed, and these authors suggest that "disrotatory closure of the developing oxyallyl (dipolar intermediate) commences before the bond to the leaving (halogen) group is completely broken." Following up on this in 1982, Engel et al.,[40] using α-bromoketones with a steroid skeleton where inversion and retention Favorskii products could be distinguished, state "the stereochemical spectrum of Favorsky rearrangements of α-halogenated 20-keto steroids could thus be explained by the assumption of a competition between such a reaction, *stereochemically* equivalent to an S_N2 displacement, and a reaction involving the intervention of a true dipolar *intermediate*. One could possibly also consider, alternatively, gradients of mechanisms corresponding to the degree to which the departure of the halogen substituents is effectively completed at the onset of the disrotatory ring closure."[41] This description comes close to the picture that our calculations would support, with the exception that there could be *two* inversion and *two* retention TSs using their starting α-bromoketones.

Side reactions are a common feature of the Favorskii reaction, and in this regard we should mention that in several of our attempts to locate a retention TS we obtained instead a TS for alleneoxide formation, which can be seen to be a true S_N2 reaction. Although these were competitive in ΔTS energy with the cyclopropanone-forming ΔTSs, the alleneoxide TSs were less stabilized by solvent simulation. In all cases we were subsequently able to locate the correct retention TSs.

Finally, like the Favorskii rearrangement, some 2,3-disubstituted cyclopropanones have been prepared via a mechanism which is proposed to involve a bromoenolate intermediate. The stereochemistry of these cyclopropanones is invariably *cis*, and calculations involving the same mechanisms as reported in this paper are in complete accord with this finding.[42,43]

Acknowledgment. We thank NSERC (Canada) for generous financial support (T.S.S.) and for summer undergraduate research awards (G.D.H.). We are also grateful to Arvi Rauk for helpful discussions.

Supporting Information Available: Evaluation of computational methods; plots of enolate Cl−C−C−O dihedral angles vs energy; solvation energies for computed ground-states and transition-states; comparison of SCI-PCM and PCM solvation methods; thermochemistry energy calculations; probe of CCSD(T) TS energy profiles; coordinates and ZPVE values for all of the MO calculations reported in this work. This material is available free of charge via the Internet at http://pubs.acs.org. Animations of intrinsic reaction coordinate (IRC) calculations are available at http://www.ucalgary.ca/∼sorensen.

JO701351P

(39) (a) Bordwell, F. G.; Scamehorn, R. G.; Springer, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 2087−2093. (b) Bordwell, F. G.; Carlson, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3370−3377. (c) Bordwell, F. G.; Almy, J. *J. Org. Chem.* **1973**, *38*, 575−578.

(40) Engel, Ch. R.; Mérand, Y.; Côté, J. *J. Org. Chem.* **1982**, *47*, 4485−4491.

(41) See footnotes 31 and 33 of ref 40.

(42) Sorensen, T. S.; Sun, F. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1053−1061.

(43) Föhlisch, B.; Gerlach, E.; Stezowski, J. J.; Kollat, P.; Martin, E.; Gottstein, W. *Chem. Ber.* **1986**, *119*, 1661.