

Stereocontrolled Synthesis of Cyclic Ethers by Intramolecular Hetero-Michael Addition. 6. A Computational Study of the Annelation to 2,3-Disubstituted Tetrahydropyrans

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A computational study at the ab initio level of the cyclization of (*E*)- and (*Z*)-7-hydroxy-4-substituted-2,3-unsaturated esters leading to 2,3-disubstituted tetrahydropyrans has been performed. The study showed the requirement of coordination between the pre-tetrahydropyranyl oxygen and that of the carbonyl of the α,β -unsaturated ester with the cation of the base used to obtain a suitable transition state model. The calculations using the 6-31G**/3-21G basis set show different relative stabilities for the final products and transition states leading to them. The 6-31+G* basis set was used as a calibration of the less energetic transition states. A model assuming a pre-chair conformation locating the chiral inductor equatorial and approaching the α,β -unsaturated ester in axial mode for the *E* isomer and equatorial for the *Z* geometry rationalizes the experimental results. The scope and limitations of the model applied to 2,3,5,6-functionalized cases are discussed.

Introduction and Experimental Results

The addition of nucleophiles to carbonyl groups has been extensively studied, providing different theoretical models such as the proposals made by Cram (Cornforth),¹ Karabatsos,² Felkin–Anh,³ or Cieplak,⁴ which attempt to account for the stereochemical preferences in such reactions. Less attention has been directed from the theoretical point of view to the addition of nucleophiles to α,β -unsaturated carbonyl compounds, attention focusing mainly on carbanionic Michael additions.⁵ In such systems the observed stereoselectivity is accounted by a Felkin–Anh^{5d} transition state or by studying the different geometries by semiempirical or ab initio^{5g,h} methods. The theoretical studies are even more limited when a hetero-Michael addition is considered, although this reaction is the key step in a series of synthetic processes in which the intramolecular version of such a reaction is used to build a tetrahydropyran unit.⁶ The intramolecu-

lar conjugate addition of an alkoxide to an α,β -unsaturated ester is also the basis of a new method developed in our group to gain access in a stereocontrolled manner to 2,3-disubstituted tetrahydropyrans.⁷ The stereoselective synthesis of the diastereoisomers in 2,6-dialkyl-3,5-dioxy-tetrahydropyrans has been performed using such a reaction as the key step.⁸

Our research is focused on the study of the influence of the stereochemistry of the chiral centers, the double-bond geometry, and the reaction conditions in the cyclization of substituted chiral hydroxy- α,β -unsaturated carbonyl compounds leading to tetrasubstituted oxanes. In Table 1⁸ we summarize some results obtained in the cyclization of simple γ -substituted systems.

As a rule of thumb in these studies we can conclude that the cyclization in aprotic basic conditions of a simple 7-hydroxy-4-substituted-(*E*)-2,3-unsaturated ester yields the *cis*-substituted tetrahydropyran while the use of the *Z* geometrical isomer affords the *trans* compound. Under our reaction conditions we have not observed any equilibrium between both 2,3-disubstituted stereoisomers even after maintaining them over periods of more than

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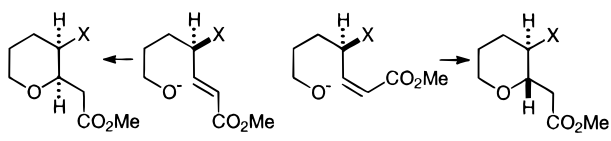
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Table 1. Influence of the Double-Bond Geometry and Reaction Conditions on the Stereochemistry in the Intramolecular Hetero-Michael Additions^a


group X	double-bond geometry	reaction conditions	ratio (cis/trans)
OBz ⁸	<i>E</i>	THF (0 °C)	3:1
	<i>E</i>	benzene (0 °C)	2:1
	<i>E</i>	toluene (-78 °C)	8:1
	<i>E</i>	CH ₂ Cl ₂ (0 °C)	2.5:1
	<i>E</i>	CH ₃ CN (0 °C)	4:1
	<i>E</i>	THF (-78 °C)	8:1
	<i>Z</i>	THF (0 °C)	1:11
Br ^{7b}	<i>E</i>	THF (-78 °C)	only <i>cis</i>
	<i>Z</i>	THF (-78 °C)	only <i>trans</i>
Cl ^{7b}	<i>E</i>	THF (-78 °C)	15:1
	<i>Z</i>	THF (-78 °C)	only <i>trans</i>
OCH ₂ C≡CH ^{7c}	<i>E</i>	THF (-78 °C)	5:1
	<i>Z</i>	THF (-78 °C)	only <i>trans</i>
Me	<i>E</i>	THF (-30 °C)	2:1

^a The base used was NaH.⁸

24 h. We concluded that under such conditions a thermodynamically controlled process is highly improbable.

Recently, similar 1,4-conjugate cyclization studies of γ -oxygenated-(*E*)- α,β -unsaturated esters have been reported, the reaction also being found to be kinetically controlled and irreversible.^{9a} In order to rationalize the observed π -facial selectivity in the 1,4-conjugate nucleophilic additions for polar solvent/large cation conditions a transition state (TS) which resembles the ground state conformational distribution in the γ -oxygenated chiral alkenes is invoked, while in the presence of small cations/nonpolar solvent the Ahn–Eisenstein¹⁰ theory is preferred.^{9b–e}

In order to have the fewest possible restrictions in the obtained model we have only made a basic postulate: in the TS a prering will be partially formed, adopting a chair-like conformation. We have not considered any preferred orientation either in the chiral inductor or in the α,β -unsaturated system, since in preliminary studies using semiempirical calculations we have found that the axial orientation in the formed enolate may be quite stable and the resemblance of the TS with such products would depend on the position in the reaction coordinate.¹¹ Thus, considering the two possible diastereofaces of the unsaturated system and the conformational equilibrium between the two chairs, we have considered the four possible basic geometries of the TSs summarized in Figure 1.

The analysis of the four possible TSs considering the basic hypothesis was complemented with the study of the relative stabilities of the final products in order to

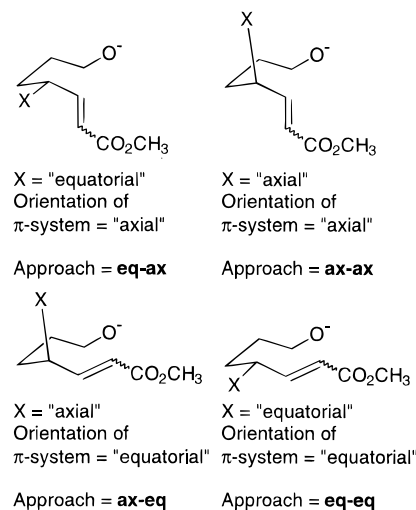


Figure 1. Basic geometries of possible transition states in the hetero-Michael addition.

consider the differences between kinetic and thermodynamic control and to provide us with the simplest system possible with which to evaluate possible solvent effects. Finally, the conformational analysis of the starting material was also evaluated in order to complete the whole reaction coordinate.

Computational Results and Discussion

(i) The Transition States. Preliminary analysis of the cyclization of 7-hydroxy-4-substituted-(*E*)-2,3-unsaturated systems was carried out using semiempirical calculations studying the reaction coordinate by the AM1¹² Hamiltonian as implemented in MOPAC 6.0.¹³ The reaction path for the intramolecular hetero Michael addition was calculated for "breaking" the $C\beta\cdots O$ bond, starting from all the free enolate esters, by systematically increasing the bond length value in successive increments and optimizing all the remaining geometrical parameters. However, net TSs were not detected when the free enolates were used (no counteraction).¹⁴ On the other hand, the gegenion structure is highly important in the geometry of the carbanionic moiety¹⁵ since it is well-known that alkali metal salts of carbanions exist predominantly as ion pairs in low-polarity solvents such as ethers¹⁶ and the associated cation may also play a crucial role in the stereoselectivity of further reactions of this carbanion.^{16a,17} The use of this approach led to the finding of reaction paths with maxima of energy. The obtained results are in agreement with the experimental observation that the intramolecular cyclization using γ -halo-(*Z*)- α,β -unsaturated esters led to *trans*-2,3-disubstituted tetrahydropyrans. The calculations, however,

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(11) Semiempirical calculations using MOPAC/AM1 for the four possible enolates obtained in the cyclization, without counteraction, in accordance with the criterion outlined in Figure 1 showed the following heats of formation: ec-ax (-160.88 kcal/mol), ax-ec (-160.95 kcal/mol), ec-ec (-161.14 kcal/mol), and ax-ax (-164.47 kcal/mol).

Table 2. 3-21G//AM1 Energies of the Found Transition States

alkene geometry	X	config	approach	3-21G//AM1 ^a	6-31G*//AM1 ^a
<i>E</i>	Cl	<i>cis</i>	eq-ax	-1149.681 08	-1155.808 21
			ax-eq	-1149.665 63	-1155.797 15
		<i>trans</i>	ax-ax	-1149.676 67	-1155.797 27
			eq-eq	-1149.666 53	-1155.797 27
	Me	<i>cis</i>	eq-ax	-731.781 95	-735.939 49
			ax-eq	-731.764 87	-735.925 60
		<i>trans</i>	ax-ax	-731.779 99	-735.937 28
			eq-eq	-731.768 34	-735.929 30
	OAc	<i>cis</i>	eq-ax	-918.339 33	
			ax-eq	-918.327 19	
		<i>trans</i>	ax-ax	-918.335 86	
			eq-eq	-918.327 33	
	OBz	<i>cis</i>	eq-ax	-1107.794 05	
			ax-eq	-1107.774 55	
<i>trans</i>		ax-ax	-1107.790 51		
		eq-eq	-1107.781 81		
OCH ₂ C≡CH	<i>cis</i>	eq-ax	-881.457 10		
		ax-eq	-881.443 88		
	<i>trans</i>	ax-ax	-881.449 90		
		eq-eq	-881.442 51		
<i>Z</i>	Cl	<i>cis</i>	eq-ax	-1149.647 88	-1155.775 14
			ax-eq	-1149.656 76	-1155.784 10
		<i>trans</i>	ax-ax	<i>b</i>	<i>b</i>
			eq-eq	-1149.668 43	-1155.797 13

^a Total energy in hartree. ^b No net TS was found using AM1.

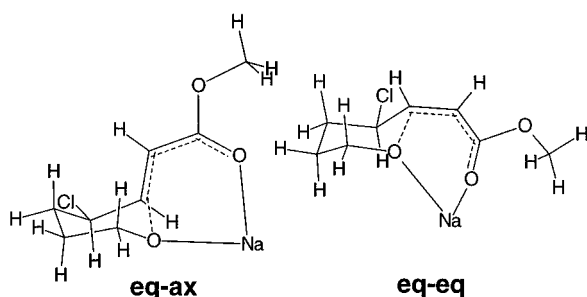


Figure 2. Geometries of found TSs for the intramolecular basic cyclization of (*E*)- and (*Z*)-7-hydroxy-4-chloro-2,3-unsaturated esters (AM1).

are not in concordance with the experimental results for the *E* esters. The analysis of the geometries for the obtained minor energy TSs, when the systems with chlorine are considered, shows the important role of the cation which coordinates with the nucleophilic oxygen of the alkoxide and the carbonyl group of the unsaturated ester, this group adopting the more stable conformation *s-cis* (C α -C)/*s-cis* (C-O)¹⁸ when the *E* ester locates axially (**eq-ax**) (Figure 2a) or the *Z* ester equatorially (**eq-eq**) (Figure 2b).^{19,20} The obtained geometries were similar when other chiral inductors (X) were used in the calculations.

The implicit oversimplification of the AM1 calculations can be overcome by a Hartree-Fock (HF) ab initio single-point calculation employing the geometry obtained by AM1 with the 3-21G²¹ basis set using HONDO.²² Grati-

fyingly, the results shown in Table 2 are now in complete agreement with those obtained experimentally. For the most simple cases (X = Cl, Me) the relative order of the energies was similar when the 6-31G* basis set was used,²³ which is known to be superior for the description of anions.²⁴

Finally, we have performed the finding of the TSs using exclusively ab initio methods for the simplest system (X = Cl) for both geometries *E* and *Z* in the α,β -unsaturated esters, using the 3-21G basis set. The starting geometries used were those obtained for the TSs available using AM1. In these the positions of the metal and the ester chain were initially optimized, using such a basis, in order to obtain the best possible Hessian to initiate the finding of the TSs. These were performed using the algorithm originally described by Cerjean and Miller²⁵ implemented in HONDO, working with internal coordinates and without any restriction in the optimization of the obtained geometries. Single-point calculations employing the geometry obtained by 3-21G using the 6-31G* and 6-31+G*²⁶ basis sets led to the same less energetic TSs. The main results are shown in Table 3 and Figures 3 and 4.

It is clear that the less energetic TSs obtained from the analysis of the *E* geometry are those in which the unsaturated ester is located in an axial mode in the alkoxide approach, with a minimum of energy corresponding to the location of the chiral inductor in equatorial mode (**eq-ax**). This TS is reached very early in the reaction coordinate (2.502 Å), a very important role being played by the coordination of the metal with the oxygen of the nucleophile and that of the carbonyl ester (Figure 3a).

Although only three of the four hypothetical TSs were determined for the (*Z*)-unsaturated ester using AM1, net

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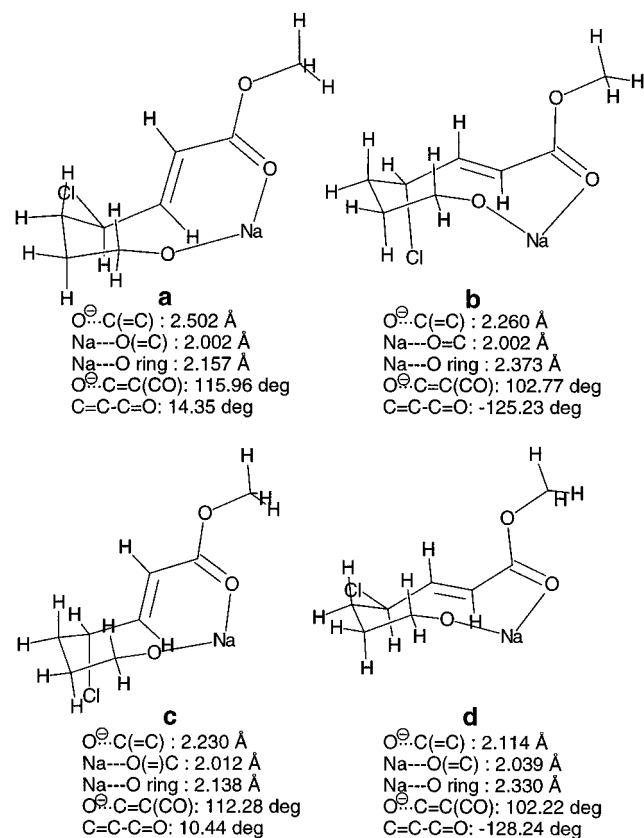
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Table 3. Main Features of the Found Transition States Using *ab Initio* Calculations in the Intramolecular Hetero-Michael Addition of the Anion of Methyl 4-Chloro-7-hydroxyhept-2-enoate

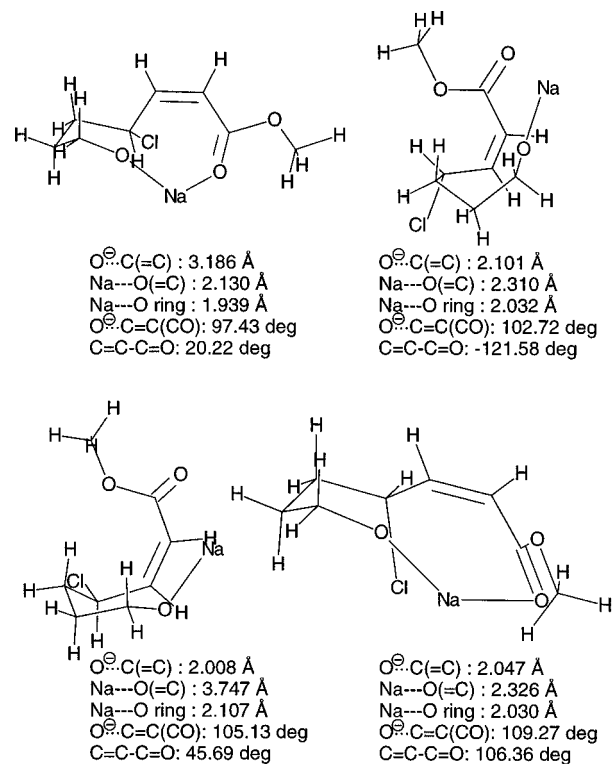
alkene geometry	config	approach	3-21G//3-21G ^a	$\Delta\Delta H^c$	ν^b (cm ⁻¹)	6-31G*//3-21G ^a	$\Delta\Delta H^c$	6-31+G*//3-21G ^a	$\Delta\Delta H^c$
<i>E</i>	<i>cis</i>	eq-ax	-1149.740 06		70.37	-1155.855 02		-1155.869 21	
		ax-eq	-1149.726 34		102.68	-1155.840 79		-1155.854 19	
	<i>trans</i>	ax-ax	-1149.737 96		189.87	-1155.848 95		-1155.862 95	
		eq-eq	-1149.729 03	-1.32	149.66	-1155.839 49	-3.80	-1155.852 32	-3.93
<i>Z</i>	<i>cis</i>	eq-ax	-1149.707 16		239.30	-1155.814 13		-1155.820 59	
		ax-eq	-1149.722 40		211.36	-1155.827 59		-1155.840 14	
	<i>trans</i>	ax-ax	-1149.719 61		214.90	-1155.827 28		-1155.840 78	
		eq-eq	-1149.734 66	7.63	58.04	-1155.847 78	12.67	-1155.861 97	13.70

^a In hartree. ^b Imaginary frequency obtained in vibrational analysis. ^c Energy difference between the TSs of less energy leading to the *cis* and *trans* products, in kcal/mol.

**Figure 3.** Geometries of representative TSs obtained using 3-21G for the *E* ester.

minima were obtained for the four approaches working with HONDO/3-21G basis set, using as starting geometry for the **ax-ax** approach the one outlined in Figure 3a (**eq-ax**), performing the exchange between the substituents in C-4 between the chlorine and hydrogen. It should be mentioned that the hypothetical **eq-ax** TS available through the 3-21G//3-21G basis set with the non-carbonyl oxygen of the ester chelated to the metal is 1.34 kcal/mol more stable than when the oxygen of the carbonyl ester is bonded (Figure 4). However, when the single-point calculation with the 6-31G* basis set is performed, inversion of the levels of energy was produced. In any case, the TS with the minimum level of energy is the one in which the α,β -unsaturated ester is located equatorially during the alkoxide attack and the chiral inductor is also equatorial in the chair-like TS (**eq-eq**) with the metal chelated to the oxygen of both carbonyl and nucleophile.

(ii) The Cyclization Products. Although the former discussion is in agreement with a kinetically controlled process in concordance with the experimental results, we wondered if the use of a naked cation would provide a model sufficiently reliable to be considered from a

**Figure 4.** 3-21G-Optimized geometries of representative TSs obtained for the cyclization of the *Z* ester.

theoretical point of view. Because the utilization of discrete solvent molecules coordinated to the cation makes the calculation of geometries and energies in the TS studies very difficult, we analyzed such possible modifications in the final enolates, which are actually the final products in the intramolecular Michael addition, in order to see if our model is oversimplified or needs further solvent considerations. This is certainly a risky assumption that forces us to consider the obtained result with due precaution.

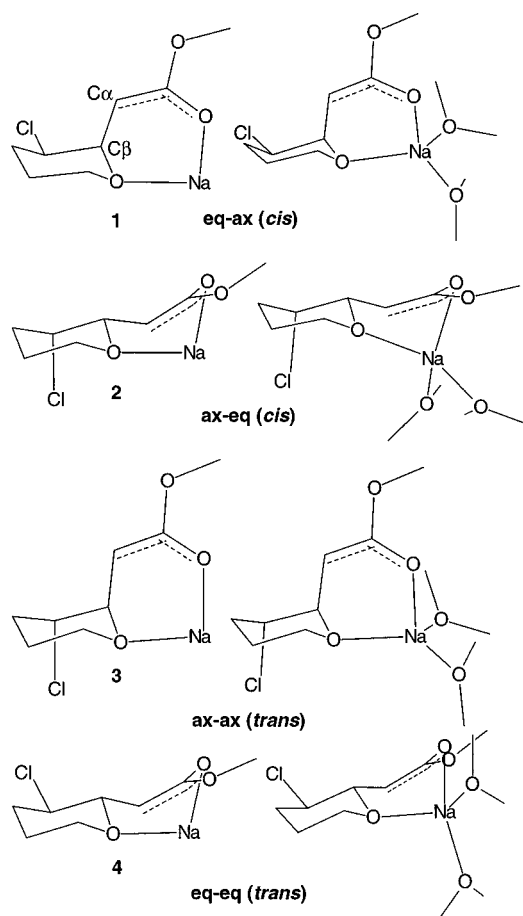
As before, the calculations were initiated with MOPAC/AM1 and the obtained geometries used as the starting point in *ab initio* studies. The results obtained using 3-21G//3-21G as well as those by the single-point calculation using the 6-31G* basis set showed that while the thermodynamically more stable compound is this one in which both the chiral inductor (Cl) and ester enolate are located *trans* (**ax-ax**), the relative energies of the most energetic species are interchanged (Table 4).

In order to fulfill the usual coordination in alkaline metals²⁷ and using as starting point the former geom-

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Table 4. Energies Found (in hartree) in the Anion of Methyl (3-Chlorotetrahydropyran-2-yl)acetate

config	approach	3-21G//3-21G	6-31G*//3-21G
<i>cis</i>	ax-eq	-1149.765 59	-1155.865 82
	eq-ax	-1149.768 22	-1155.864 23
<i>trans</i>	eq-eq	-1149.764 41	-1155.866 31
	ax-ax	-1149.774 28	-1155.867 70

**Figure 5.** 3-21G//3-21G geometries of calculated structures of the anion of methyl (3-chlorotetrahydropyran-2-yl)acetate.

etries, two molecules of methyl ether were added and the recalculation performed. Although it is usual to use water instead of ethers to facilitate the calculations, we have considered as a more realistic situation the inclusion of two molecules of dimethyl ether as model ligands for THF.²⁸ In Figure 5 we compare the obtained geometries with and without solvents.

The comparative analysis of the obtained geometries (Figure 5 and Table 5) shows altogether small changes in the structures considering solvent effects relative to those obtained with the naked cations. The tetrahydropyran ring is practically unaffected, and the ester enolate is planar in all the analyzed cases. Small modifications of the torsional angles in the linear chain are produced probably as the result of bond length enlargement between the metal and the coordination centers. When the energies are evaluated the relative ordering is maintained when the two more stable structures are considered (**ax-ax** followed by **eq-ex**). However, an inversion of the order is manifested when the two more energetic structures are contemplated. Thus, if we

extend these considerations to the finding of the transition states it appears that the use of solvents in such evaluation is not critical.

In accordance with this study the cyclization of both (*E*)- and (*Z*)-unsaturated esters should lead to the same *trans* compound (**ax-ax**) if the reaction were thermodynamically controlled. The assumption that the intramolecular Michael addition is a kinetically controlled process, using our reaction conditions for the cases discussed in the present paper, is strongly reinforced by the former study and is in agreement with the experimental results.

(iii) The Reactants. The evaluation of the reactant in the cyclization of (*E*)-methyl 4-chloro-7-hydroxyhept-2-enoate is of great interest in order to confirm that the preferred TS is essentially reactant-like. However, considering this starting point in the reaction coordinate, two possible alternatives were taken into account: one in which the origin is the sodium alkoxide in the linear chain adopting the more stable conformation or, contrarily, a species doubly chelated to the two oxygens present in the precursor, more similar to the found TSs.

In order to investigate approximately the energies of the two possibilities, molecular mechanical calculations were performed over the two overall species, considering in the monochelated alkoxy case the rotation around the C(Cl)-C(=C) bond with an alternate conformation of the chain. The most representative structures were used as input in 3-21G//3-21G calculations showing that the double bond between the metal and both oxygens (alkoxide and carbonyl oxygen) (Figures 6b and 6c) is a strong stabilizing factor relative to the linear mono-chelated species (Figure 6a).²⁹ Thus, we can conclude that the starting point in the reaction coordinate needs to take into consideration a metal double-bonded to both the oxygen of the alkoxide and the oxygen of the carbonyl group. On the other hand, a simple comparison among Figures 3, 4, and 6 shows the high structural resemblance within the reactants and TSs.

Scope and Limitations of the Model

The experimentally obtained stereoselectivities for the cyclization of chiral (*E*)- and (*Z*)-7-hydroxy-4-substituted-2,3-unsaturated esters leading to 2,3-disubstituted tetrahydropyrans (entries 1 and 2 in Table 6, $R^i = H$) are in agreement with a kinetically controlled process: a model in which both the pre-tetrahydropyranyl oxygen and that of the carbonyl of the α,β -unsaturated ester are coordinated with the cation of the base used during all the reaction coordinate. The calculations using the 6-31G*//3-21G basis set show different relative stabilities for the final products and TSs leading to them. The geometries of those with minor energies are consonant with the fact that the basic cyclization of 7-hydroxy-4-substituted-(*E*)-2,3-unsaturated esters leads to *cis*-2,3-disubstituted tetrahydropyrans, while the use of the *Z* geometry leads to the *trans* isomer. The transition states in these reactions are, in all cases, essentially "reactant-like", rather than "product-like", adopting a pre-chair conformation locating the chiral inductor equatorially and approaching the α,β -unsaturated ester in axial mode for the *E* isomer and equatorial for the *Z* geometry. The major stability of the *s-cis* conformation over the *s-trans* in conjugated di-unsaturated systems^{18,19} can be invoked

(28) Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 11016.

(29) 3-21G//3-21G total energy of structures of Figure 6 in hartree: (a) -1149.707 41. (b) -1149.755 68. (c) -1149.737 05.

Table 5. Solvent Influences of the Calculated Structures on the Final Enolate (3-21G)

	ax-eq (<i>cis</i>)		eq-ax (<i>cis</i>)	
	+2 CH ₃ OCH ₃		+2 CH ₃ OCH ₃	
total energy (au)	-1149.765 59	-1456.264 29	-1149.768 22	-1456.272 85
Na...O ring (Å)	2.112	2.171	2.153	2.192
Na...O=C (Å)	2.144	2.223	2.048	2.144
Na...O ether (Å)		2.213, 2.227		2.178, 2.198
C β -C α -C=O (deg) ^a	-4.39	-5.08	-8.23	-8.49
O _{ring} -C β -C α -C(O) (deg) ^a	-76.54	-62.81	69.94	73.95
	eq-eq (<i>trans</i>)		ax-ax (<i>trans</i>)	
	+2 CH ₃ OCH ₃		+2 CH ₃ OCH ₃	
total energy (au)	-1149.764 41	-1456.266 51	-1149.774 28	-1456.278 87
Na...O ring (Å)	2.116	2.162	2.144	2.186
Na...O=C (Å)	2.128	2.195	2.056	2.154
Na...O ether (Å)		2.198, 2.200		2.190, 2.194
C β -C α -C=O (deg) ^a	24.88	15.42	-4.39	-5.08
O _{ring} -C β -C α -C(O) (deg) ^a	-82.01	-73.36	67.96	71.15

^a See Figure 5 for definitions.

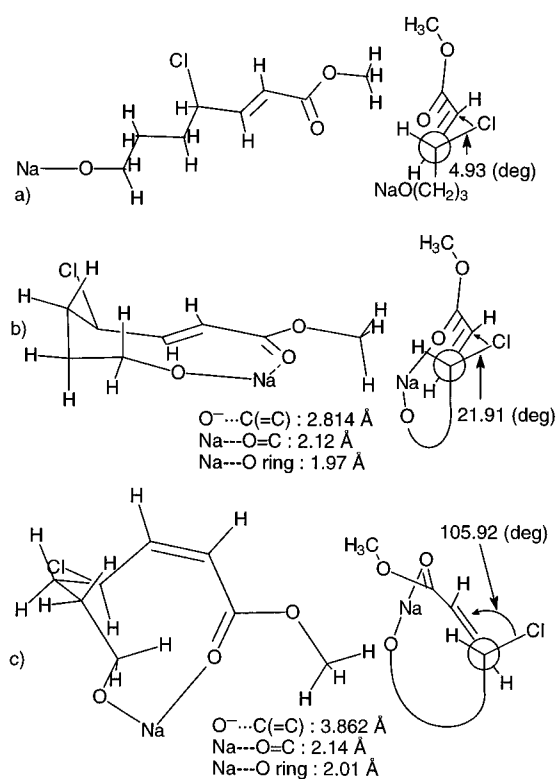


Figure 6. 3-21G salient geometrical features of reactants. (a) Representative rotamer for the linear alkoxide (*E* ester). Double-bonded less energetic structures: (b) *E* ester; (c) *Z* ester.

as the principal reason to explain the relative order of the found TSs. Furthermore, a minor distortion from the planar geometry of the unsaturated π -system is observed for the found TSs with minimal energy.

When the full 2,3,5,6-substituted tetrahydropyrans are considered, two major observations should be made: (a) those systems in which a hydrogen is located axially in the carbon where the nucleophilic oxygen is situated (entries 1, 2, 3, and 4 in Table 6) and (b) those having an alkyl group in that position (entry 5 in Table 6). In the former, 1,3-diaxial interactions³⁰ between such an alkyl group and the α,β -unsaturated ester directs its approach in the equatorial mode regardless of the stereochemistry

Table 6. Summary of Observed Stereochemistries in O-Hetero-Michael Additions Leading to 2,3,5,6-Substituted Tetrahydropyrans

Entry	7-Hydroxy 2,3-unsaturated ester ^a	Main observed stereochemistry ^a	Ref.
1.			7 8
2.			7 8
3.			8
4.			8
5.			6h 6k

^a Rⁱ = H or ring

of the C3 carbon.^{6h} In contrast, if a hydrogen is the group located in the axial mode, the C2 stereochemistry in the ring formation can be predicted in accordance with two possibilities depending on whether the chiral inductor can adopt an equatorial conformation, following the "empirical rule" outlined above (entries 1 and 2 in Table 6, Rⁱ \neq H), or those systems having geometrical restrictions that exclude this group from locating in such a conformation, in which case the *trans*-2,3-difunctionalized tetrahydropyran is always obtained. In this case,

(30) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124.

the well-known 1,3-allylic interactions³⁰ may be the cause of the preferred approach although a different mechanistic pathway is also possible in such cases.

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Supporting Information Available: 3-21G//3-21G full geometries of calculated structures for transition states and cyclization products and a table of the energy data of the found TSs using MOPAC/AM1 (7 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 ordering information.

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