

A Theoretical Study of the Favorskii Rearrangement. Calculation of Gas-Phase Reaction Paths and Solvation Effects on the Molecular Mechanism for the Transposition of the α -Chlorocyclobutanone

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Received July 25, 1996. Revised Manuscript Received November 1, 1996[⊗]

Abstract: The molecular mechanism of the α -chlorocyclobutanone transposition to yield cyclopropanecarboxylic acid, as a model of the Favorskii rearrangement, has been theoretically characterized *in vacuo* by means of *ab initio* molecular orbital procedures at the Hartree–Fock (HF) level of theory with the 6-31G* and 6-31+G* basis sets. The electron correlation has been estimated at the MP2/6-31G* level and calculations based on density functional theory, BLYP/6-31G*. The solvent effects are included at HF/6-31G* level by means of a polarizable continuum model. The questions related to the two accepted molecular mechanisms, the semibenzilic acid and the cyclopropanone transpositions, as well as the competition between both reaction pathways are addressed in this investigation. The dependence of the geometries of the stationary structures along the corresponding reaction pathways and the transition vectors associated with the transition structures upon theoretical methods is discussed. The analysis of the results shows that the electrostatic solute–solvent interactions modify appreciably the topology of the potential energy surface. The cyclopropanone mechanism is stabilized with respect to the semibenzilic acid mechanism, but this latter remains the energetically favorable reactive channel both *in vacuo* and in solution. The semibenzilic acid mechanism is a two-step process and the rate-limiting step corresponds to the nucleophilic attack of the hydroxyl ion on the carbon atom of the carbonyl group belonging to the α -chlorocyclobutanone ring. In the cyclopropanone mechanism three transition structures appear along the energy profile and the rate-limiting step is the dehydration process of the bicyclo[1.1.0]2-butanone intermediate with concomitant ring contraction and formation of the cyclopropanecarboxylic acid product.

1. Introduction

The Favorskii rearrangement, originally described in 1894,¹ corresponds to the nucleophilic attack of bases, e.g., hydroxide, alkoxide ions, or amines, on α -halo ketones to yield the salts, esters, or amides of the corresponding carboxylic acids, respectively, with a skeleton of the same number of carbon atoms.^{1–7} Due to its versatility, it has become an increasingly reliable and specialized instrument of organic synthesis and an appreciable number of experimental works on the Favorskii rearrangement can be found in recent literature.^{8–13} In particular, this reaction has found application for the preparation

of highly branched acyclic carboxylic acids and its derivatives, providing a direct method for ring contraction in simple alicyclic systems and steroids.^{14–17} However, some controversy over the nature of the molecular mechanism of this reaction persists, and at least five mechanisms have been proposed.

(i) The rearrangement was first considered by Favorskii¹⁸ and later by Aston¹⁹ to proceed by addition of alkoxide to the carbonyl carbon, with concomitant ejection of a halide ion, to produce an epoxyether, followed by the reaction to yield the corresponding product. Although the isolation of epoxyethers from the action of alkoxides on certain α -haloketones is well established, the postulated rearrangement of the epoxyether into the product is improbable.^{2–4,6} In particular, Stevens et al.²⁰ could obtain no evidence for rearrangement of epoxyether to an acid or ester and the epoxyether intermediate is clearly not

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[⊗] Abstract published in *Advance ACS Abstracts*, January 15, 1997.

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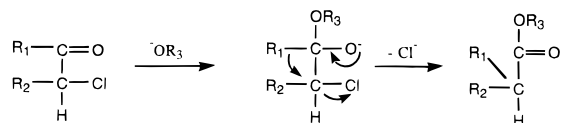
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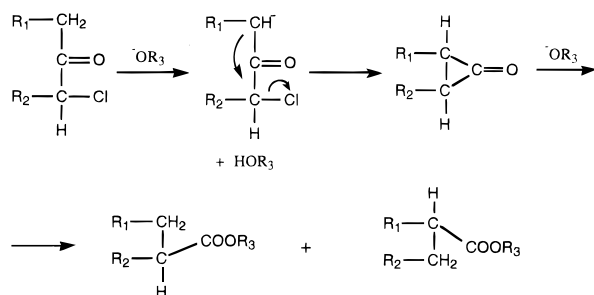
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Scheme 1



Scheme 2



involved in the main course of the Favorskii reaction, although it plays a central role in the formation of certain byproducts.

(ii) A second mechanism suggested by Richard²¹ proposes the action of a base on α -halo ketones to involve the abstraction of hydrogen halide and the intermediate formation of a ketene derivative, which would rapidly react with the nucleophile to give product. This mechanism fails to accommodate those numerous examples of the Favorskii rearrangement that produce esters of the trialkylacetic type, which cannot arise from a ketene precursor.²²

(iii) A third mechanism has seemed particularly attractive because of its analogy to the benzilic acid rearrangement. This features addition of alkoxide to the carbonyl carbon atom of the halo ketone, followed by a concerted displacement of the halide ion by the 1,2-migration of an alkyl group²³ (Scheme 1). This reaction has been called the semibenzilic acid mechanism, abnormal or quasi-Favorskii rearrangement.

(iv) All these previous mechanisms predict different acids from the two isomeric mono-halo ketones in the course of the rearrangement. Since this is not the case, Richard²⁴ proposed a halide migration from the α - to the α' -carbon atom. McPhee and Klingsberg²⁵ repeated and extended Richard's work, postulating a carbonium ion mechanism in which a halo ketone undergoes unimolecular dissociation to a carbonium ion which can tautomerize through a common enol to the isomeric carbonium. The latter can then undergo rearrangement to the acid. This mechanism has the drawback that no key role is assigned to the base which is a normal requisite of the Favorskii rearrangement.

(v) The last type of mechanism, called the cyclopropanone or the Lofffield mechanism, involves initial removal of the α' -hydrogen followed by the intermediate formation of a cyclopropanone which is rapidly cleft by alkoxide to give the rearrangement product^{26,27} (Scheme 2). Lofffield's work²⁷ with ¹⁴C-labeled 2-chlorocyclohexanone established the need for a symmetrical intermediate (such as a cyclopropanone) to be formed in the reaction pathway at some point. Later, the work by Bordwell²⁸ and others^{29–31} has addressed on the exact way in which the symmetrical intermediate is reached and how the

experimental conditions and structural variations in the halo ketone affect its formation.

According to the current bibliography, only two of the above proposed mechanisms have been supported by most of the evidence and remain as the accepted mechanisms. In cases where α' -hydrogens are available, the Lofffield cyclopropanone mechanism is generally preferred,^{26,27} while the second accepted mechanism, the semibenzilic acid, is usually operative in cases where the Lofffield mechanism is prohibited either due to an absence of α' -hydrogens or structural features that prevent cyclopropanone formation.³² Nonetheless, there is a study where α -halo ketones with an α' -hydrogen atom can undergo rearrangement either by way of a symmetrical intermediate or by way of a semibenzilic intermediate depending on the experimental conditions,³³ and another study has been done on a halo ketone (2-bromocyclobutanone) that apparently reacts via the semibenzilic acid mechanism instead of the cyclopropanone pathway even though an α' -hydrogen is present.^{34–36}

In recent decades quantum mechanics calculations have been gradually recognized as a useful tool in research related to the elucidation of molecular reaction mechanisms.^{37,38} The understanding at molecular level of a reaction mechanism for a given chemical reaction requires a detailed knowledge of stationary points: reactants, transition structure (TS), products, and possible intermediates on the potential energy surface (PES). In particular, the theoretical characterization of TSs provides a source of information, independent from experimental studies, concerning the geometry, electronic structure, and stereochemistry along the reaction pathway.³⁹ On the other hand, much interest has been given recently to methods based on density functional theory (DFT)⁴⁰ as an alternative to conventional *ab initio* schemes.^{41,42} Although DFT took relatively long to find a wider acceptance among chemists, there is now rapidly increasing evidence that molecular density functional calculations give remarkably accurate results for molecular structures and electronic properties. Furthermore, since it takes into account most of the dynamic and nondynamic correlation effects, the DFT results are of a quality comparable to the conventional post-Hartree–Fock (HF) methods.^{43–49}

For chemical reactions where changes in polarity between the reactants and TS take place, solvent effects can vary the

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reaction rate and the mechanism.⁵⁰ Some efforts have been devoted in our laboratory to the theoretical treatment of solvent effects in chemical reactivity studies.^{51,52} We try to determine reaction mechanisms and how the solute–solvent interactions can affect the different barrier heights and the relative energies of reactants, possible intermediates, TSs, and products on PES. The computational approach for the theoretical treatment of solvent effects is based on continuum models,⁵³ the solute is embedded in a cavity while the solvent, treated as a continuous medium having the same dielectric constant as the bulk liquid, is incorporated in the solute Hamiltonian as a perturbation. In this reaction field approach, the bulk medium is polarized by the solute molecules. The electronic distribution of the solute polarizes the continuum which generates an electric field inside the cavity which in turn affects the solute's geometry and electronic structure. The implementation of this interaction scheme is achieved through the self-consistent reaction field method developed initially by Tapia.^{54,55}

As a part of a research program devoted to the study of solvent effects on the molecular mechanism of different chemical reactions,^{56,57} we describe herein a theoretical study of the two most accepted mechanisms for the Favorskii rearrangement of α -chlorocyclobutanone *in vacuo* and aqueous solution. Experimental data are available for this reaction; however, to our knowledge, this is the first theoretical study devoted to understanding the molecular mechanism for this type of transposition. It is of considerable interest to know the barriers and reaction energies of the corresponding reaction pathways, and in this work, we present accurate results which demonstrate the importance of the inclusion of the solvent effects in the characterization of the molecular mechanisms.

2. Computation Procedures

In vacuo calculations were carried out with the GAUSSIAN94 package of programs.⁵⁸ *Ab initio* calculations have been performed at HF/6-31G* and HF/6-31+G* levels, including electron correlation by using the second-order MP2 perturbation theory.⁵⁹ We have calculated the natural orbital population of the UHF wave functions. This test shows that no spin contamination of higher multiplicities is observed ($\langle s^2 \rangle = 0$), so the single determinant RHF wave function is good enough for the stationary structures.

We have also employed methods based on DFT,^{60,61} that have recently received increasing attention.⁶² We used Becke's exchange functional (B)^{63,64} which includes the Slater exchange along with corrections involving the gradient of the density, and the correlation functional of Lee, Yang, and Parr, which

includes both local and nonlocal terms (LYP).^{65,66} The selected procedure is BLYP/6-31G*.

The PESs have been calculated in detail to ensure that all relevant stationary points have been located and properly characterized. The exact location of the TS structures was achieved by using an algorithm,^{67–69} in which the coordinates describing the system are separated into two sets: the control space, which is responsible for the unique negative eigenvalue in the respective force constants matrix, and the remaining coordinates set that is called complementary space. The geometry optimizations are carried out alternatively on each subspace, one at a time, until a stationary structure is obtained. Finally, a complete analytical optimization of the TS structure was achieved with an "eigenvalue following" optimization method^{70,71} for all variables and by means of a normal mode analysis. The intrinsic reaction coordinate (IRC)⁷² pathways, from the TSs down to the two lower energy structures have been traced using the second-order González-Schlegel integration method^{73,74} in order to verify that each saddle point links the two putative minima.

The requested convergence on the density matrix was 10^{-9} atomic units, and the threshold value of maximum displacement was 0.0018 Å and that of maximum force was 0.000 45 hartree/bohr using the Berny analytical gradient optimization routine.^{75,76} The nature of each stationary point was checked by diagonalizing the Hessian matrix to determine the number of imaginary frequencies (zero for the local minima and one for the TSs). The unique imaginary frequency associated with the transition vector (TV)⁷⁷ of the different TSs has been analyzed.

Electrostatic interactions with the surrounding solvent can be expected to constitute a decisive factor when ionic and polar species are concerned in the reaction mechanism. The differential stabilization of one reaction path with respect to the other could indeed change the relative order obtained in the gas-phase calculation. Thus, we have included electrostatic solvent interactions in our study of the reaction mechanisms, thereby attempting to identify the influence of the solvent on the mechanics of the reaction. Bulk solvent effects have been taken into account by means of a cavity model. Recently, Tomasi and Persico have presented an overview of methods based on continuous distributions of the solvent.⁵³ In these procedures the solvent is assimilated to a continuous medium, characterized by the dielectric constant (ϵ), which surrounds a cavity in which the solute is placed. In this work we have employed the continuum model of Rivail et al.^{78–80} based on the use of cavities and a multipolar expansion of the solute

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electrostatic potential. Calculations were made using ellipsoidal cavities surrounded by a continuum of dielectric constant equal to 78.4 and multipolar expansion up to order 6. These calculations in solution were carried out using the SCRFPAC package⁸¹ added to the GAUSSIAN92 program⁸² at the HF/6-31G* level. We have reoptimized the stationary points on the PES at HF/6-31G* level of calculation using the continuum model described above. The first derivatives of the electrostatic term are obtained analytically,⁸⁰ while the second derivatives are computed numerically. The multipole expansion of the potential converges rapidly, but in some cases, namely when the molecular shape is quite irregular, a multicenter expansion⁸³ may be necessary to ensure convergence. After extensive preliminary tests, the inclusion of diffuse functions in the basis set produced SCF convergence problems in the cavity calculations, and thus they were not considered. It must be taken into account that the correct description of the solvation/desolvation processes of small ions such as the OH⁻ and Cl⁻ appearing in the course of the reaction would require the inclusion of not only a continuum medium but also of some discrete water molecules.⁸⁴ However, this limitation of the employed solvation model cannot be very relevant for the comparison of the two proposed reaction mechanisms of the Favorskii rearrangement.

3. Results and Discussion

In the study of a chemical reaction it is important to realize that the finding of one TS does not exclude the possibility of alternative reaction paths having other TSs. In order to discriminate between alternative molecular mechanisms for the Favorskii rearrangement of α -chlorocyclobutanone, an extensive exploration of the PES by means of *ab initio* and DFT methods has been carried out. The structures associated to the stationary points of both reaction pathways (semibenzilic acid and cyclopropanone mechanisms) are illustrated in Figures 1 and 2. The numbering of atoms is given in Figure 1. The calculated structures are named as follows: the reactants (α -chlorocyclobutanone + OH⁻) are designed by **R**, and the products (cyclopropanecarboxylic acid + Cl⁻) are named **P**. The label of the structures corresponding to transition structures and intermediates are designed by the letters **TS** and **I**, respectively. The stationary points are distinguished from each other by appending the numbers 1, 2, etc., as they are introduced. For the semibenzilic acid mechanism, label **A**, the localized stationary points are **R**, **RC**, **TS1A**, **I1A**, **TS2A**, and **P**, while for the cyclopropanone mechanism, label **B**, they are **R**, **RC**, **TS1B**, **I1B**, **TS2B**, **I2B**, **TS3B**, and **P**.

3.1. Gas-Phase calculations. 3.1.1. Semibenzilic Acid Mechanism. The most relevant geometrical variables of the stationary points obtained with different methods for the semibenzilic acid mechanism are supplied as Supporting Information. Optimized geometries of all structures obtained

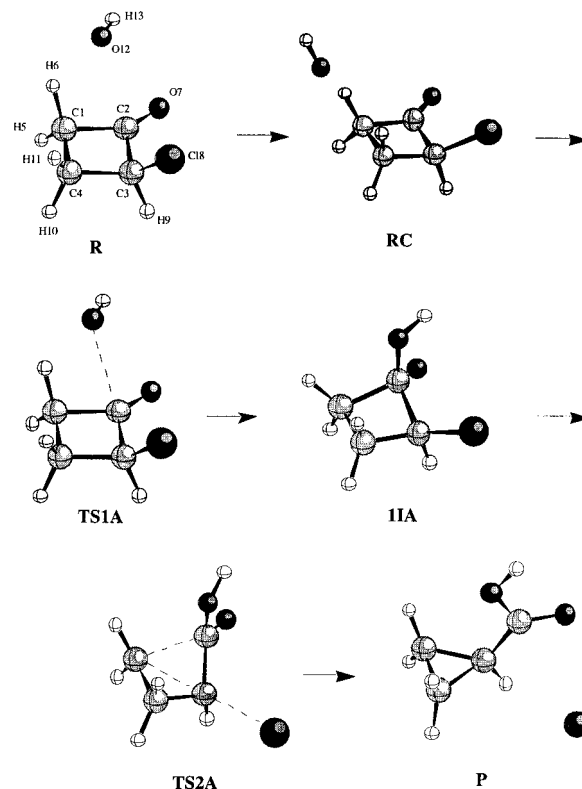


Figure 1. Representation of the stationary points for the semibenzilic acid mechanism.

by the different computing methods are available from the authors on request. The nucleophilic attack of the OH⁻ on the cyclopropanone ring takes place in a barrierless fashion, with formation of an interaction complex, **RC**, where a strong hydrogen bond between the hydroxyl anion and H6 atom of the α -carbon, C1, appears. The first chemical step of the semibenzilic mechanism, connecting the reactant complex **RC** with the product of the nucleophilic attack **IA**, occurs through **TS1A** with formation of the C2–O12 bond. This attack presents a pronounced inverted energy profile, and it is carried out on a very flat region of the PES, i.e., the lower positive vibrational frequencies are in the range of 50–200 cm⁻¹. This fact may explain why the HF/6-31G* method is not able to localize the **RC** and **TS1A** stationary points. The second step corresponds to a ring contraction from the four-membered ring, **IA**, to the reaction product **P**, via the **TS2A**.

The interatomic distances of the minima obtained at HF level, the MP2 method, and the results that were obtained based on the DFT are quite similar (except for the C2–O12 distance for **RC** where the HF/6-31+G* gives a large value of 3.883 Å) and present significant invariance compared with the semiempirical results. However, for the transition structure **TS1A**, the C2–O12 and C3–Cl8 distance values are in the range of 2.799–3.324 and 1.781–1.904 Å, respectively, while for the transition structure **TS2A**, the C2–O12 and C3–Cl8 distance values are in the range of 1.394–1.476 and 2.066–2.290 Å, respectively.

The imaginary frequency, the force constants for those selected geometric parameters with nonzero components in the TV, and the corresponding components of the control space for **TS1A** and **TS2A** are available from the authors on request. The values of the force constants associated to the components of TVs are qualitatively invariant within the *ab initio* levels. They are all positive, and the negative eigenvalue arises from the cross terms off diagonal in the force constants matrix. The normal mode analysis of these structures yields a relatively low

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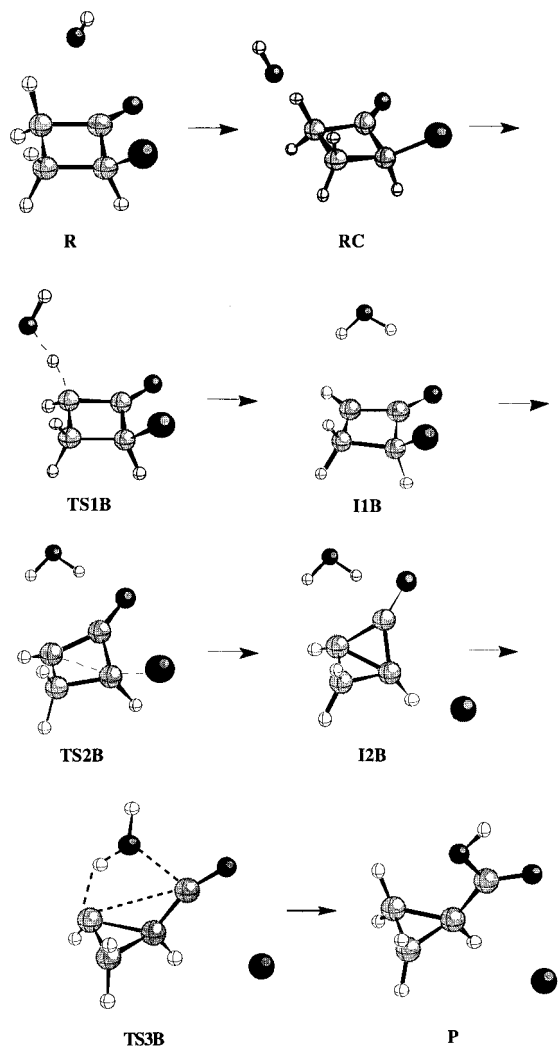


Figure 2. Representation of the stationary points for the cyclopropanone mechanism.

imaginary frequency, and the weight of the components of the TV is independent of computing method. The C2–O12 distance is the main component of the TV for **TS1A**, while the C1–C2 and the C3–Cl8 bond distances present the large contribution to the corresponding TV for **TS2A**.

3.1.2. Cyclopropanone Mechanism. The selected geometrical variables of the stationary points obtained with the different methods for the cyclopropanone mechanism are supplied as Supporting Information. The results obtained also depend on the computational level. When the OH⁻ ion is approached to the α -chlorocyclobutanone, the same reactant complex, **RC**, located in the semibenzilic acid mechanism, is obtained. From this minima, the transition structure, **TS1B**, corresponding to H6 hydrogen transfer from C1 of the ring to O12 with formation of a water molecule, can be reached, connecting the **RC** with **I1B**, **RC** \rightarrow **TS1B** \rightarrow **I1B** step. As occurs for the semibenzilic acid mechanism, the corresponding region on the PES where this dehydration takes place is very flat, and the corresponding curvature is in the range 50–200 cm⁻¹. Therefore, the HF/6-31G* method is not capable of localizing the transition structure **TS1B**.

The geometry and transition vector components of the **TS2B**, controlling the second step, **I1B** \rightarrow **TS2B** \rightarrow **I2B**, at HF, MP2, and DFT methods are similar. The HF, MP2, and DFT calculations describe the formation of the product **P** from **I2B** along one step in which the C1–C2 breaking bond and the H6–

Table 1. Relative Energy in kcal/mol of the Stationary Points Obtained *in vacuo*^a

	HF/6-31G*	HF/6-31+G*	MP2/6-31G*	BLYP/6-31G*
R	0.0	0.0	0.0	0.0
RC		-19.07	-36.57	-54.21
TS1A		-17.58	-33.90	-45.56
I1A	-63.97	-44.86	-73.70	-75.22
TS2A	-48.55	-27.21	-62.56	-73.21
P	-115.16	-94.03	-107.07	-109.58

	HF/6-31G*	HF/6-31+G*	MP2/6-31G*	BLYP/6-31G*
R	0.0	0.0	0.0	0.0
RC		-19.07	-36.57	-54.21
TS1B		-15.46	-32.83	-48.36
I1B	-49.50	-31.28	-56.14	-64.35
TS2B	-42.17	-22.83	-50.05	-60.79
I2B	-47.68	-29.79	-45.49	-49.89
TS3B	-6.91	12.80	-9.18	-24.14
P	-115.16	-94.03	-107.07	-109.58

^a Total energy of **R** = -764.023 665 au (HF/6-31G*), -764.078 906 au (HF/6-31+G*), -765.026 772 au (MP2/6-31G*), and -766.413 061 au (BLYP/6-31G*).

C1 and O12–C2 forming bonds processes take place simultaneously through a single transition structure, **TS3B**.

The total and relative energies for both reaction mechanisms are collected in Table 1. All computational methods describe the transposition of chlorocyclobutanone as an exothermic reaction (in the range from -94 kcal/mol, HF/6-31+G* level, to -115 kcal/mol, HF/6-31G* level). The reaction pathway presents an inverted energy profile at HF/6-31G*, MP2/6-31G*, and BLYP/6-31G* levels. However, the HF/6-31+G* level presents a positive relative energy value for **TS3B**.

The barrier height for the first chemical step of the semibenzilic acid mechanism, **RC** \rightarrow **TS1A** \rightarrow **I1A**, presents small values of 1.5, 2.7, and 8.6 kcal/mol for HF/6-31G*, MP2/6-31G*, and BLYP/6-31G* levels, respectively, showing that this region on PES is very flat as the low imaginary frequency values of **TS1A** (in the range 64–382 cm⁻¹) points out. The value for the barrier height corresponding to the step, **I1A** \rightarrow **TS2A** \rightarrow **P**, is very dependent on the computing method, yielding a wide range of values, from 17.6 kcal/mol (HF/6-31+G* result) to 2.0 kcal/mol (BLYP/6-31G* result). This **TS2A** characterizes the rate-limiting step by all methods but the BLYP/6-31G*. For the cyclopropanone mechanism, all methods reveal that the last step, via **TS3B**, is the rate-determining step. A comparison of the energetic values for both reaction mechanisms shows that the semibenzilic acid mechanism is favorable with respect to the cyclopropanone pathway in the gas phase.

Our calculations have emphasized that the structure of the stationary points and energies are sensitive to the computing method used. The qualitative features of the reaction profile can be characterized in terms of two regions on the PES. There is a wide region corresponding to the initial steps of both mechanisms where the coulombic interaction between the reactants **R**, α -chlorocyclobutanone + OH⁻ dominates. The resulting surface is rather flat in this region, and the details of the reaction path are very sensitive to the choice of the basis set and the inclusion of electron correlation. At HF/6-31+G*, MP2/6-31G*, and BLYP/6-31G* levels, we identified one intermediate, **RC**, and two transition structures, **TS1A** and **TS1B**, on the reaction surface. Except for the BLYP results, this shallow intermediate was only marginally stable, and the presence of these stationary points are likely to be kinetically insignificant, i.e., the barriers for the conversion of **RC** to **I1A**, via **TS1A**, of the semibenzilic acid mechanism or **RC** to **I1B**, via **TS1B**, of the cyclopropanone mechanism, are low.

Table 2. Relative Energy in kcal/mol of the Stationary Points Obtained in Aqueous Solvent^a

semibenilic acid mechanism		cyclopropanone mechanism	
R	0.0	R	0.0
RC	-20.74	RC	-20.74
TS1A	-15.59	TS1B	-19.36
I1A	-29.60	I1B	-23.14
TS2A	-26.56	TS2B	-20.04
P	-100.55	I2B	-41.79
		TS3B	-11.63
		P	-100.55

^a Total energy of *R* = -764.178 751 au.

3.2. Solvent Effects Calculations. The next step in our investigation is the study of the solvent effects on the basic features of the chemical reaction. The differential stabilization of one reaction path with respect to the other could change the relative order obtained in gas-phase calculation,^{51,57} and the inclusion of the solvent effects appears to be both qualitatively and quantitatively significant.

The relevant geometrical data of reactants, transition structures, intermediates, and products obtained for both mechanisms in solution are supplied as Supporting Information. The relative energies of the stationary points for both mechanisms in solution are given in Table 2, while the shapes of the corresponding reaction profiles *in vacuo* and in solution obtained at the HF/6-31G* level are depicted in Figure 3.

An analysis of the results shows that solute-solvent interactions leads a noticeable change on the topology of the PES. In particular, the initial steps of the semibenilic acid and cyclopropanone mechanisms. The curvature of the regions around **RC** and **TS1A** and **TS1B** stationary points increase. In solution, these stationary points are enhanced due to the stabilization of the hydroxide anion by electrostatic solute-solvent interactions. Slight geometrical changes on the rest of stationary structures in solution with respect to the gas phase values are detected, except those for the **TS2A** and **TS2B**. In the former, the C1-C2 bond-breaking process is less advanced in solution (1.620 Å) than in the gas phase (1.878 Å) and in the latter both the C1-C3 bond-forming and the C3-C18 bond-breaking processes are also less advanced in solution (1.948 and 2.148 Å, respectively) than in the gas phase (1.883 and 2.298 Å).

As could be expected from electrostatics arguments, the molecules with ionic character are stabilized when solvent effects are included. Consequently, the exothermic character of the reaction is reduced by more than 15 kcal/mol. In the semibenilic acid mechanism, the reaction pathway, as in the gas phase, presents an inverted energy profile. The rate-limiting step for this mechanism in solution is the nucleophilic attack of the hydroxyl anion to the α -chlorocyclobutanone ring, **RC** \rightarrow **TS1A** \rightarrow **I1A** step, with an energy barrier of 5.1 kcal/mol. The solvent effects increase the relative energy of **I1A** and **TS2A**, this increment being 34.4 and 22.0 kcal/mol, respectively. Therefore, the energy barrier for the **I1A** \rightarrow **TS2A** \rightarrow **P** step is reduced from the value of 15.4 kcal/mol obtained *in vacuo* to 3.0 kcal/mol in solution. Similar trends are obtained in the study of the cyclopropanone mechanism. The reaction pathway corresponding to a dehydration process, **RC** \rightarrow **TS1B** \rightarrow **I1B** step, takes place by surmounting a very low barrier height of 1.4 kcal/mol. The energy barrier for the second process **I1B** \rightarrow **TS2B** \rightarrow **I2B** is also reduced from 7.2 to 3.1 kcal/mol. The energy barrier for the third and rate-limiting step **I2B** \rightarrow **TS3B** \rightarrow **P** is 40.8 kcal/mol *in vacuo* and 30.2 kcal/mol in aqueous solvent. In the cyclopropanone mechanism, the relative energy of all stationary points is destabilized, except for the **TS3B** which is stabilized at about 4.7 kcal/mol. The result is a

smoothing of the shape of the reaction profile when solvent effects are included (see Figure 3). Thus, the solvent has the general effect of reducing the energy barriers of the cyclopropanone mechanism. As in the gas phase, the semibenilic acid mechanism has an energy barrier for the rate-limiting step lower than that corresponding to the cyclopropanone mechanism (5.15 kcal/mol versus 30.16 kcal/mol) and thus it should be the preferred reaction mechanism.

The values of imaginary frequencies and the force constants of the components of TV *in vacuo* and in solvent are similar for **TS2B** and **TS3B**. However, an appreciable decrease is found for the unique imaginary frequency of **TS2A**: the solvent smooths the quadratic region associated to this point from 634i to 358i cm⁻¹. The force constant corresponding to the C1-C3 bond distance decreases from 0.3 to near zero, the component of C1-C2 bond distance in the TV goes from 0.54 to 0.19, and the C3-C18 bond distance increases its contribution to TV from 0.58 to 0.84. All force constants associated to the components of TV are positive, so the negative eigenvalue arises from the cross terms off diagonal in the force constants matrix.

A more balanced measure of the extent of bond formation or bond breaking is provided by the Pauling bond orders.⁸⁵ They are defined as

$$\text{BO} = \exp\{[R(\text{SP}_0) - R(\text{SP}_1)]/0.3\} \quad (1)$$

where $R(\text{SP}_1)$ represents the bond length in the stationary point considered and $R(\text{SP}_0)$ represents the reference bond length. The reference value considered for the bonds that are being broken were the equilibrium distances at the beginning of the step. This is the case of C3-C18, C1-C2 and O12-H6. For the bonds that are being formed, the reference values were the equilibrium distances at the end of the step. This is the case of C1-C3, C2-O12, and C1-H6.

The progress of the chemical process at transition structure was then evaluated through the following expression:

$$\% \text{ evolution} = \frac{\text{BO}(\text{TS}) - \text{BO}(\text{X})}{\text{BO}(\text{Y}) - \text{BO}(\text{X})} \times 100 \quad (2)$$

where X and Y represent possible reactants/intermediates and intermediates/products, respectively, linked along a particular reaction pathway: X \rightarrow TS \rightarrow Y. Calculated percentages of evolution at TSs are reported in Table 3 *in vacuo* and in solvent.

An analysis of these data shows that the solvent effects have a great influence on the percentage of C1-C2 bond breaking process at **TS2A**, from 64.7% (*in vacuo*) to 17.0% (in solvent). The percentage of C3-C18 bond breaking process and C1-C3 bond forming at **TS2A** increase from 74.1 to 79.4% and from 12.0 to 13.0%, respectively while an opposite trend is found at **TS2B**, from 77.8 to 61.5% and 21.2 to 11.2%, respectively. At **TS3B**, the percentage of C1-C2/O12-H6 bond breaking and C2-O12/C1-H6 bond formation are weakly dependent on the inclusion of solvent effects.

One step further in this analysis implies understanding the electronic distribution change along the reaction pathways for the semibenilic acid and cyclopropanone mechanisms. The behavior of the reactive channels would be significantly affected in the presence of the solvent as a result of the charge transfer along the corresponding reaction pathways. For this purpose, a Mulliken atomic population analysis is carried out. Mulliken charges calculated at the HF/6-31G* level generally show a good correlation with charges determined using more sophisticated methods; they have been used successfully in interpreting solvent effects on a reaction profile in Monte Carlo calculations.⁸⁶ At the **TS2A**, the negative electronic charge transfer

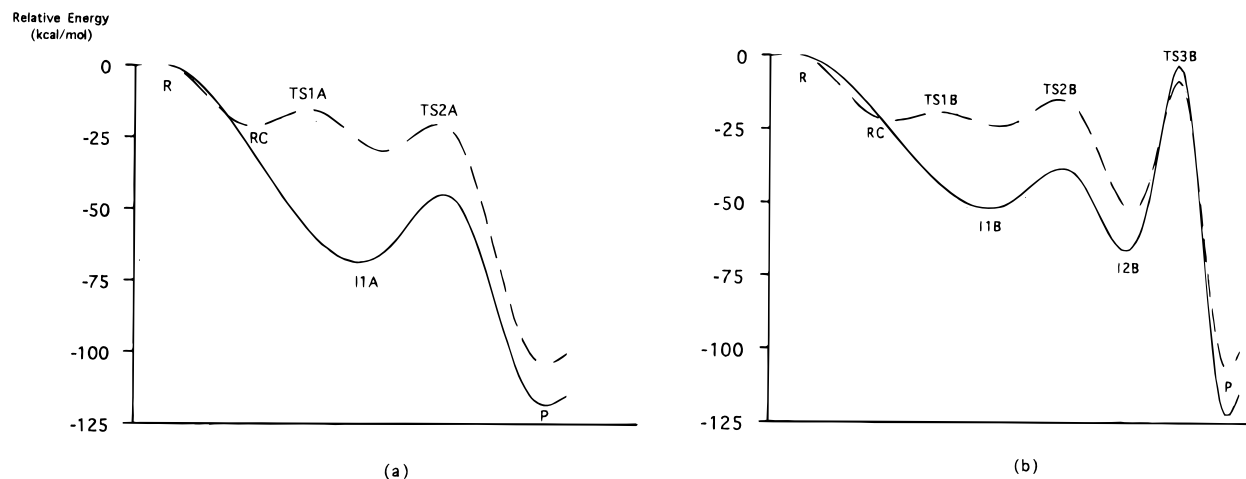


Figure 3. Schematic potential energy diagram showing the relative energies (kcal/mol) of the stationary points located on the reactive potential energy surface at the HF/6-31G* level. (a) Semibenzilic acid mechanism (b) Cyclopropanone mechanism. Continuous line *in vacuo* and broken line in aqueous media.

Table 3. Percentages of Evolution of the Reaction at **TS2A**, **TS2B**, and **TS3B** Transition Structures Calculated through eq 2, for the C3–C18, C1–C2 and O12–H6 Breaking Bond Processes and the C1–C3, C2–O12, and C1–H6 Forming Bond Process *in vacuo*^a

TS2A	C3–C18	74.1	(79.4)
	C1–C3	12.0	(13.0)
	C1–C2	64.7	(17.0)
TS2B	C3–C18	77.8	(61.5)
	C1–C3	21.2	(11.2)
TS3B	C1–C2	99.8	(99.2)
	C2–O12	10.2	(9.7)
	O12–H6	26.5	(28.2)
	C1–H6	14.9	(16.4)

^a Values in solution in parentheses.

from the ring to the incipient chlorine anion is 0.63 a.u. and 0.72 a.u. for *in vacuo* and in solvent calculations, respectively. The solvent effects yield an advance of the C3–C18 bond-breaking process, in agreement with the results obtained for the evolution of the bond order indices. However, the **TS2B** presents an opposite behavior, the inclusion of solvent effects retards the C3–C18 bond-breaking process and the charge transfer from the ring to Cl8 decreases from 0.68 a.u. to 0.59 a.u. At **TS3B**, there is no charge separation, and this fact yields that the evolution of making/breaking bond processes and the charge transfer are not dependent on the inclusion of solvent effects.

4. Conclusions

In this work, we have carried out a theoretical study of the solvent effects along the reaction profiles on the corresponding PES for the semibenzilic acid and cyclopropanone mechanisms of the Favorskii rearrangement. The selected model is the reaction of the OH⁻ with the α -chlorocyclobutanone to yield the cyclopropanecarboxylic acid. The reaction pathways were calculated using the HF/6-31G*, HF/6-31+G*, MP2/6-31G*, and BLYP/6-31G* methods in gas phase. The polarizable continuum model is used to introduce solvent effects at HF/6-31G* level. The following conclusions can be drawn from the results reported in this study.

(i) The results obtained *in vacuo* show that the transposition of chlorocyclobutanone seems to take place by the semibenzilic acid mechanism better than through the cyclopropanone mechanism. Gas-phase calculations show that, although the general shape of the reaction profiles is almost invariant, some details of the surface are sensitive to the choice of the basis set and to

the inclusion of electron correlation. In particular, the existence of a shallow minima associated to the interaction of OH⁻ and the α -chlorocyclobutanone ring on a rather flat region alters the shape of the reaction pathways. However, the presence of this intermediate is kinetically insignificant due to the barrierless fashion of the initial steps for the semibenzilic acid and cyclopropanone mechanisms.

(ii) As could be expected from electrostatic arguments, when solvent effects are considered, ionic molecules are stabilized, and the electrostatic effect of the solvent is critical in the prediction of the nature of the Favorskii rearrangement of the α -chlorocyclobutanone. The solvent reaction field was found to have a noticeable effect on the reaction pathways, suggesting that the solvent is capable of modulating the molecular mechanism for the Favorskii rearrangement.

(iii) Solvent effects reduce the energy barriers for both mechanisms, but the semibenzilic acid mechanism remains the preferred path, being the rate-limiting step (intrinsic barrier 5.15 kcal/mol) the nucleophilic attack of the hydroxyl ion on the α -chlorocyclobutanone ring, while for the cyclopropanone mechanism, the rate-limiting step (intrinsic barrier 30.16 kcal/mol) corresponds to the hydration process of the bicyclo[1.1.0]butanone intermediate with concomitant ring contraction and formation of the cyclopropanecarboxylic acid product.

(iv) Our results show for the first time the nature of the molecular mechanism for the α -chlorocyclobutanone transposition to yield cyclopropanecarboxylic acid from theoretical calculations. Although the present results are very encouraging, more studies should be carried out with inclusion of electron correlation energy or by the use of multiconfigurational methods in the presence of solvent.

Acknowledgment. This work was supported by research funds of the Ministerio de Educación, DGICYT (Project PB93-0661). We are most indebted to the Servei d'Informàtica de la Universitat Jaume I for providing us with multiple computing facilities. I.T. acknowledges M.E.C. for a postdoctoral contract and DGICYT Project PB93-0699. S.B. acknowledges Universitat Jaume I for travel facilities. M.O. thanks the Ministerio de Educación y Ciencia for a FPI fellowship. R.C. thanks IBM for a fellowship.

Supporting Information Available: Tables of geometrical parameters (3 pages). See any current masthead page for ordering and Internet access instructions.

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