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Enantiomerization Study of Some α-Nitroketones by Dynamic High-Resolution Gas Chromatography

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The kinetics of the reversible enantiomer interconversion of 3-nitrobutan-2-one (**1**), 3-nitropentan-2-one (**2**), and 2-nitropentan-3-one (**3**) have been studied by dynamic high-resolution gas chromatography (DHRGC) by using a β-cyclodextrin derivative chiral stationary phase; the process occurs via enolization of the keto forms. The DHRGC experiments involving the studied nitroketones and the chiral stationary phase show chromatographic profiles with a typical interconversion plateau in the temperature range between 130 and 160 °C. Computer simulation of the experimental chromatographic elution profiles was employed for the determination of rate constants and the corresponding enantiomerization barriers (k, $\Delta G^{\#}(T)$, $\Delta H^{\#}$, and $\Delta S^{\#}$). The highly negative entropy of activation ($\Delta S^{\#}$ values from −19 to −37 cal mol^{-1} K^{-1}) points to a transition state (TS) with large charge separation. The obtained results for **1**−**3** show the dramatic effect of an α-nitro-substituent on the rate of enolization of simple ketones, when compared with those for 3-chloro-2-butanone and 3-methyl-2-pentanone. To get some information on the separate contributions of the stationary liquid phase and the mobile gas phase on the studied process, some DFT ab initio calculations have been performed for the same compounds.

1. Introduction

α-Nitroketones containing an α-hydrogen atom are very acidic carbon acids[1,2] with pK_a values close to those of unsubstituted carboxylic acids. In aqueous solution they are also characterized by a relatively high enol content[1,2] and by the possible presence of the α-ketonitronic "aci" form at equilibrium.

The synthetic procedures and vast preparative potential of these compounds have been extensively reviewed.[3] However, kinetic and/or thermodynamic studies on the keto−enol interconversion in water are scarce and "the paucity of the data does not make it possible to examine structural effects on the enol content of α-nitroketones in detail".[1]

We have recently measured[2] the equilibrium constant for the keto−enol tautomerism of 3-nitrobutan-2-one (**1**) (pK_T = 2.34) in aqueous solution at 25 °C by combining the rate constants for ketonization of the enolate and the pK_a^{KH} (=5.15) of the keto form. Consequently the pK_a^{EH} of the enol form turned out to be 2.81. These values can be compared with the corresponding values[4] for acetone (pK_T = 8.33, pK_a^{KH} = 19.27, pK_a^{EH} = 10.94). This comparison highlights the strong influence of an α-nitro group on keto−enol tautomerism.

Ab initio calculations[5] suggest that the higher values of K_T = [enol]/[ketone] observed for nitroketones depend on the capability of the NO_2 group to destabilize the keto tautomer and to stabilize the enol tautomer through the π- and σ-electron-withdrawing effects of the substituent as well as the formation of an intramolecular H-bond in the enol form (see Scheme 1). However, experimental results[6] indicate that the latter effect is of minor importance in the case of acyclic α-nitroketones.

Even more scanty are the available data on the kinetics and the thermodynamics of the keto−enol interconversion in aprotic solvents and in the gas phase. The

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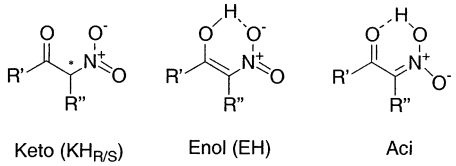
SCHEME 1. Tautomers of α-Nitroketones



SCHEME 2. Enantiomerization of α-Nitroketones via Enol and/or "Aci" Tautomers

$$KH_R \underset{k^t_{-1}}{\overset{k^t_1}{\rightleftharpoons}} EH / ACI \underset{k^t_1}{\overset{k^t_{-1}}{\rightleftharpoons}} KH_S$$

collected information is derive mostly from qualitative analysis of UV−vis, IR, and ^{1}H NMR spectra recorded in various organic solvents.[3b,7−10] In general, there is clear evidence of the presence of the enol form, while the corresponding "aci" form is hardly detectable. α-Nitroketones bearing on the α-carbon a R″ substituent (as in Scheme 1) are chiral species which can invert their configurations on passing from the keto tautomer, KH, to the achiral enol, EH, and/or "aci" tautomers (Scheme 2).

In this paper we have studied the enantiomerization (i.e. the reversible enantiomer interconversion which occurs via enolization of the keto form) of the following α−nitroketones **1**−**3** at different temperatures by dynamic high-resolution gas chromatography (DHRGC) using a chiral stationary phase (CSP) made of 6-*O*-[(*tert*-butyldimethyl)silyl-2,3-di-*O*-acetyl-*β*-cyclodextrin].

In the investigated temperature range the obtained chromatograms showed typical[3b,11−13] plateaus between the peaks of the separated enantiomers. Comparison of the experimental chromatographic elution profiles with the corresponding computer-simulated profiles has allowed the determination of the apparent rate constants, k_{app}, of enantiomerization. These rate constants are averaged values that bring contributions from the process occurring in the mobile gas phase (k_m) and in the stationary liquid phase (k_1^s and k_{-1}^s) according to Scheme 3.

The detailed kinetic analysis which underlies this model has been previously reported.[12]

The enthalpy, $\Delta H^{\#}$, and entropy, $\Delta S^{\#}$, components of the standard free energy of activation, $\Delta G^{\#}$, have been separated by plotting $\Delta G^{\#}/T$ against $1/T$.

Finally some DFT ab initio calculations have been performed to test if enantiomerization in the mobile gas phase can possibly occur by an intramolecular mechanism with a four-membered transition state. This mechanism of enolization is generally considered as very unlikely for simple ketones either in the gas phase, as suggest by ab initio calculations,[11] or in protic solvents.[1,4]

2. Results and Discussion

Enantioselective chromatographic methods based on CSPs represent the most commonly used technique for the determination of enantiomeric excess in scalemic mixtures. Moreover the same technique has been used in recent years to obtain kinetic data [k, $\Delta G^{\#}(T)$, $\Delta H^{\#}$, and $\Delta S^{\#}$] for suitable enantiomerization processes monitored at different temperatures.[12−26] The latter procedure, generally referred to as dynamic chromatography (DC), to be applicable requires that the studied reversible $R \rightleftharpoons S$ interconversion occurs during the time scale of the enantiomeric separation. If this is the case, characteristic peak profiles are obtained.

Peak-form analysis through the iterative comparison of simulated and experimental chromatograms[12−26] allows the determination of the desired kinetic parameters of enantiomerization. So far the most widely investigated enantiomerizations by DC are conformational enantiomerizations. In fact configurational enantiomerizations are usually characterized by $\Delta G^{\#}$ values which are too high for the equilibration times to be compatible with the times of the chromatographic separation. Noticeable exceptions are some enantiomerizations of chiral species which rapidly interconvert their configurations by passing through achiral tautomeric forms[17,18,27] as, for example, those of Scheme 2.

In these cases as, at a statistical level, only one-half of the achiral tautomer originated from a given enantiomer is transformed into the other enantiomer, the rate constants of tautomerization, k^t, and enantiomerization, k, are related by the equation $k^t = 2k$ and the $\Delta G^{\#}$ values for the reversible enantiomerization can be calculated from k values according to the Eyring eq 1 with a transmission factor γ of 0.5.[17]

$$\Delta G^{\#}(T) = RT \ln \frac{\gamma k_B T}{hk} \qquad (1)$$

In eq 1 k_B is the Boltzmann constant, T is temperature, h is the Planck constant and R is the gas constant. In the present DHRGC experiments the enantiomerization of nitroketones **1**−**3** has been investigated in the temperature range 130−160 °C by using 30% 6-*O*-[(*tert*-butyldimethyl)silyl]-2,3-di-*O*-acetyl-*β*-cyclodextrine in OV-1701 w/w as the CSP. Under the adopted experimental conditions the enantiomers of nitroketones **1**−**3** are effectively discriminated by the column, with enantioselectivity values (α) in the range 1.10−1.93. The obtained chromatograms also showed typical interconversion be-

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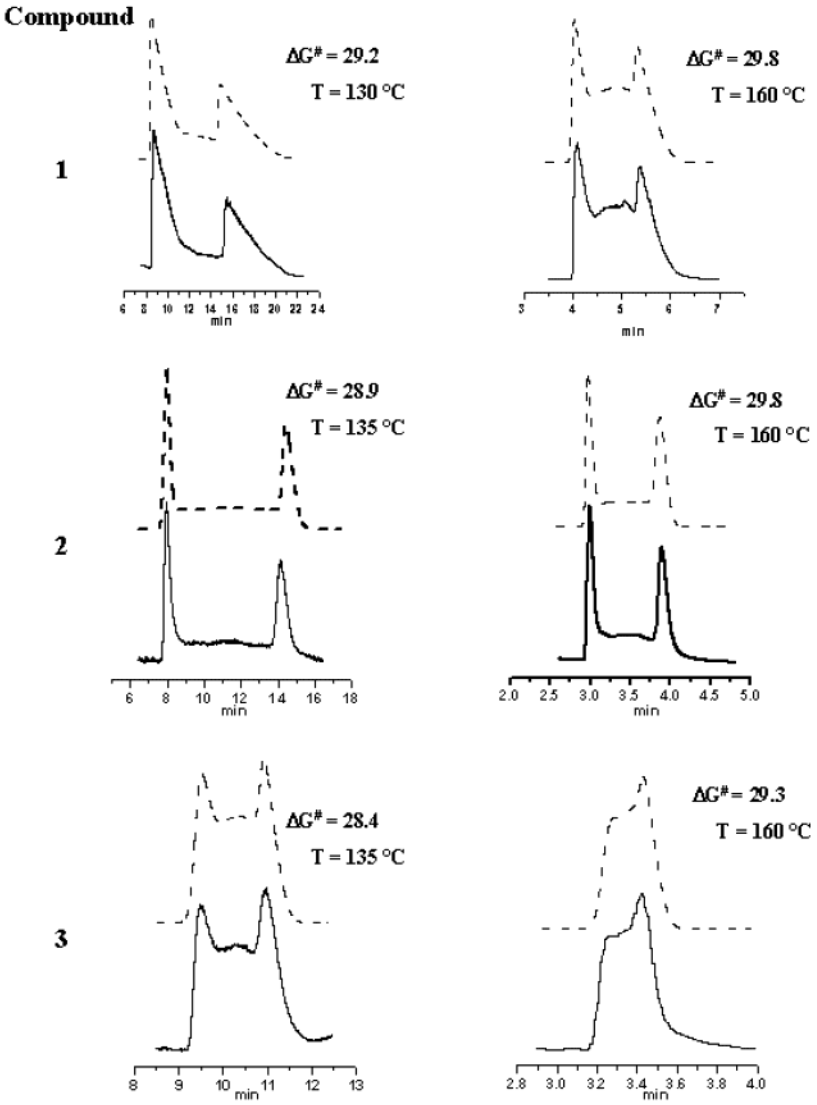
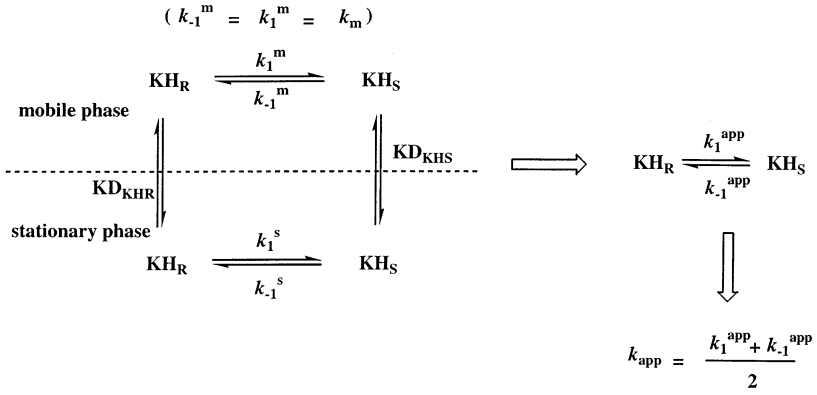


FIGURE 1. Selected dynamic high-resolution gas chromatograms of ketones **1**−**3** (simulated chromatograms, dotted lines).

SCHEME 3. Equilibria Occurring during Chromatography, Where *k* Represents Rate Constants and KD Represents Distribution Constants



tween the peaks of the separated enantiomers. The process of reversible enantiomerization becomes progressively faster with increasing temperature and the peak interference increases accordingly. Peak-form analysis through the iterative comparison of simulated and experimental chromatograms (see Figure 1 and Experimental Section) was performed in terms of the discontinuous plate model.[28,29] The obtained k_{app} values are reported in Table 1.

For ketone **1**, the independence of enantioselectivity (and the associated $\Delta G^{\#}$ values) on the adopted gas chromatographic experimental conditions has been as-

TABLE 1. Chromatographic and Kinetic Results Obtained by DHRGC of Ketones 1−3

	compd **1** (column 25 m)			compd **1** (column 50 m)			compd **2** (column 50 m)			compd **3** (column 50 m)		
T (° C)	α^a	$k_{app}{}^{b,c}$ (min^{-1})	$\Delta G^{\#}$ (kcal/mol)	α^a	$k_{app}{}^{b,c}$ (min^{-1})	$\Delta G^{\#}$ (kcal/mol)	α^a	$k_{app}{}^{b,c}$ (min^{-1})	$\Delta G^{\#}$ (kcal/mol)	α^a	$k_{app}{}^{b,c}$ (min^{-1})	$\Delta G^{\#}$ (kcal/mol)
130				1.92	0.038	29.19[d]			28.8[e]			28.2[e]
135				1.87	0.051	29.32[d]	1.93	0.087	28.89[f]	1.18	0.165	28.37[f]
140	1.70	0.101	29.13[f]	1.87	0.092	29.31[f]	1.81	0.099	29.14[f]	1.15	0.230	28.45[f]
145				1.63	0.114	29.39[f]	1.78	0.121	29.34[f]	1.12	0.271	28.67[f]
150	1.56	0.178	29.3[f]	1.61	0.162	29.46[f]	1.69	0.149	29.53[f]	1.12	0.351	28.81[f]
155				1.55	0.199	29.64[f]	1.64	0.199	29.64[f]	1.10	0.408	29.03[f]
160	1.46	0.358	29.49[f]	1.34	0.250	29.80[f]	1.54	0.261	29.76[f]	1.10	0.454	29.28[f]

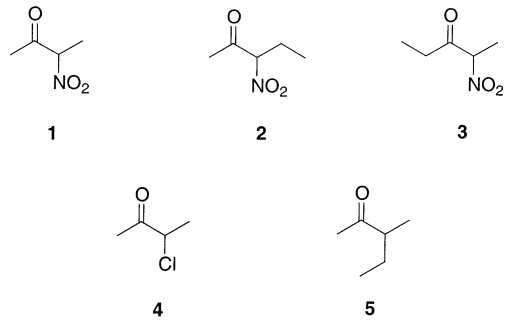
[a] α: chromatographic enantioselectivity factor. [b] k_{app}: apparent rate constant. [c] Values ±0.001 min^{-1}. [d] Values ±0.02 kcal mol^{-1}. [e] Extrapolated value. [f] Values ±0.01 kcal mol^{-1}.

TABLE 2. Eyring Activation Parameters for the Enantiomerization of Ketones 1−3

compd	$\Delta H^{\#}$ (kcal mol^{-1})	$\Delta S^{\#}$ (cal mol^{-1} K^{-1})
1[a]	21.7 ± 2.0	−18 ± 5
1[b]	21.7 ± 0.5	−19 ± 2
2[b]	14.8 ± 0.3	−35 ± 1
3[b]	13.4 ± 0.3	−37 ± 1

[a] Column length: 25 m. [b] Column length: 50 m.

CHART 1



certained at 140, 150, and 160 °C by means of two capillary columns of different length (25 and 50 m) containing the same CSP. As one can see from the values of α, $\Delta G^{\#}$ (Table 1), $\Delta H^{\#}$, and $\Delta S^{\#}$ (Table 2), the differences of the results obtained by the two columns are quite small, pointing to a negligible effect of the column geometry on thermodynamic (α) and kinetic ($\Delta G^{\#}$) data. On the other hand, it is very significant that the chromatogram obtained at 130 °C for racemic chloroketone **4** (Chart 1) does not show any evidence of a plateau between the resolved peaks of the two enantiomers (α = 1.39). This fact clearly indicates that replacement of the (polar) chloro substituent of compound **4** with the nitro group (compound **1**) strongly promotes the $R \rightleftharpoons S$ interconversion of the enantiomers at this temperature.

The values of the Gibbs free energy of activation, $\Delta G^{\#}$, for enantiomer interconversions of compounds **1**−**3** at the different temperatures are similar, being equal to 29.0 ± 0.8 kcal mol^{-1}. However, an Eyring plot of $\Delta G^{\#}/T$ vs $1/T$ shows that the presence of an additional methyl group in the isomeric nitropentanones **2** and **3** with respect to 3-nitrobutan-2-one **1** produces a significant decrease in the enthalpy and entropy of activation (see Table 2). This is in agreement with the higher conformational freedom of ketones **2** and **3** than that of ketone **1**. However, the conformational freedom is largely lost in the TS of the $R \rightleftharpoons S$ interconversion, as $\Delta S^{\#}$ values for the three ketones are highly negative.

An even more negative $\Delta S^{\#}$ value (about −59 cal mol^{-1} K^{-1}) has been recently reported in a study of the stereointegrity of thalidomide[17] and was attributed to an enantiomerization mechanism involving charge separation in the TS of the keto−enol tautomerization. Interestingly, the higher enantiomerization barrier of thalidomide ($\Delta G^{\#}$ = 36.8 kcal mol^{-1} at 200 °C) is due to an entropy effect as the enthalpy of activation ($\Delta H^{\#}$ = 10.0 kcal mol^{-1}) is lower than those of compounds **1**−**3**. It is now well-established[7,20,23] that rate constants measured by DHRGC depend on the particular CSP used. The chiral stationary phase leads to different values for the forward ($k^s{}_1$) and backward ($k^s{}_{-1}$) reactions. In addition, the enantiomerization barrier in the stationary phase can be higher or lower than that in the mobile phase. Either the chiral selector or the inert matrix in which it is dispersed can be responsible for this effect.

To approach this problem, the concept of the retention increment has been put forward.[25] Application[14] of this concept to the enantiomerization barrier of Troger's base (one example of configurational enantiomerization) has revealed only marginal differences between the effects of the chiral selector and the inert matrix on the stereoinversion process. Moreover, the small differences observed are mainly entropic in origin (about 6% for $\Delta S^{\#}$). A similar effect of the stationary phase on the enantiomerization of our nitroketones should result in small deviations from the activation parameters reported in Table 2, and this small effect can probably be neglected when relative activation parameters for ketones **1**−**3** are compared. The residence time of the enantiomers in the gas phase is usually low when the retention factors are relatively high. Thus the contribution of the gas phase to the overall rate of enantiomerization has commonly been neglected.[12,17,26] However, in consideration of the low retention factors (1.5−11.0) observed in the present work, this contribution might in principle be appreciable for ketones **1**−**3** and the measured rate constant, k_{app}, strictly would be an averaged value that brings contribution from the process occurring in both phases. Nevertheless, the gas phase is virtually apolar while the liquid phase is semipolar due to the presence of the modified cyclodextrin and polysiloxane OV-1701 moieties. It is well-known that

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SCHEME 4. Keto−Enolization Mechanism via Hydrogen [1,3] Sigmatropic Shift

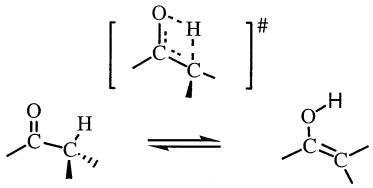

TABLE 3. Ab Initio Activation Energy Barriers for Enolization of Ketones 1−5 via Hydrogen [1,3] Sigmatropic Shift.

compd	$\Delta E^{\#}$ (kcal mol^{-1})
1	50.1
2	50.7
3	50.1
4	59.7
5	62.3

keto−enol tautomerizations are subject to general acid−base catalysis[30] and that they occur in preference in protic media. Consequently the apolar mobile gas phase is likely not to give a significant contribution to the observed kinetic process.

Ab initio calculations suggest that the enolization of simple carbonyl compounds via direct hydrogen transfer (i.e. [1,3] sigmatropic shift, Scheme 4) in the gas phase is unlikely to occur at ordinary experimental temperatures, as the corresponding activation barrier is >70 kcal mol^{-1}.[11] To check if this is a difficult process for nitroketones too, ab initio calculations of structures and energies for compounds **1**−**5** and the corresponding transition states for the intramolecular enolization have been carried out.

The ab initio DFT (nonlocal density functional of the Becke and Perdew model) calculations have been performed on compounds **1**−**5** with the 6-31G** basis set. The choice of the DFT approach was dictated by the necessity of taking into account the electronic correlation effects, more pronounced in the TS than in the keto form,[11] and of keeping the calculation times reasonably low. The obtained $\Delta E^{\#}$ values of Table 3 suggest that, even for nitroketones **1**−**3**, the intramolecular hydrogen transfer is a very unlikely mechanism for the "spontaneous" enolization reaction under the experimental conditions adopted for the DHRGC measurements.

However, it is apparent that the nitro-substituent in compounds **1**−**3** lowers $\Delta E^{\#}$ by some 11 kcal mol^{-1} with respect to the methyl group in compound **5**. This is in agreement with the strong π-acceptor effect ($\sigma_R = 0.15$) of the NO_2 group (for a detailed discussion of electronic effects on $\Delta E^{\#}$ of enolization of simple ketones see ref 11).

It is also interesting to note that while the fluoro-substituent increases[11] (with respect to CH_3) the activation barrier to enolization, the chloro-substituent (**4**) slightly decreases the same barrier, and this can probably be accounted for by the reduced π-donor effect of Cl (σ_R-Cl: −0.18) relative to F (σ_RF: −0.31).

In conclusion the experimental kinetic results and the above calculations point to a stepwise mechanism of

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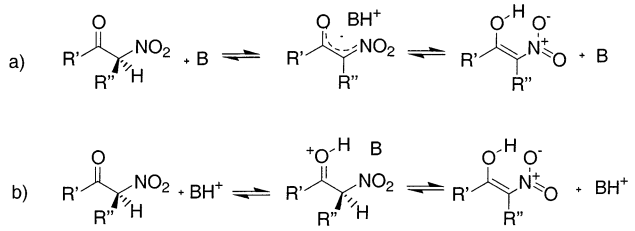
SCHEME 5. Base- and Acid-Catalyzed Mechanisms of Enolization



racemization via enolization of **1**−**3** (Scheme 5) with base [*a*] and/or acid [*b*] catalysis in the DHRGC conditions.

In Scheme 5, B and BH^+ can be a basic or acid group of the stationary phase or a second molecule of ketone (or its conjugate base).[31] It is noteworthy that the mechanism of Scheme 5 is in agreement with the highly negative $\Delta S^{\#}$ values observed in the DHRGC experiments and with a TS with large charge separation.[14,17,32,33]

3. Experimental Section

Materials. 1, **2**, and **3** were synthesized and purified following described procedures;[34] 3-chlorobutan-2-one **4** and 3-methylpentan-2-one **5** were commercial samples.

Gas Chromatography. The measurements were performed on a gas chromatograph equipped with a flame-ionization detector. Two commercial fused silica capillary columns (25 m × 0.25 mm i.d. and 50 m × 0.25 mm i.d.) coated with 0.25 μm OV-1701 containing 30% 6-*O*-[(*tert*-butyldimethyl)silyl-2,3-di-*O*-acetyl-β-cyclodextrin] were used. Helium was used as a carrier gas.

Computer Simulation. The calculations were performed on a personal computer. Use was made of the program Auto-DHPLC-y2k (Auto-Dynamic HPLC), which is an improved version for PC of the program SIMUL[29] implemented with a novel control on peaks asymmetry and a Simplex algorithm for automatic fitting of experimental data.

Ab initio Calculations. Molecular Mechanics and DFT ab initio methods as implemented in the Titan 1.0.1 package were used throughout this work. Preliminary conformational searches on ketones **1**−**5** were carried out with the MMFF Force Field. All the rotatable bonds were explored. Low-energy structures found within 3 kcal mol^{-1} and their TS on enolization pathway were optimized at the SCF level with the 6-31G** basis set. Lowest energy structures of **1**−**5** and their TS were identified as minima or first-order saddle points by calculating harmonic vibrational frequencies at the DFT BP/6-31G** level.

Acknowledgment. We thank MIUR, Italy for financial support (Faculty Research Projects and Contract 2001033797_004).

Supporting Information Available: Calculated structures of ketones **1**−**5** and their transition states in PDB format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) Preliminary kinetic measurements carried out on the keto−enol interconversion of 2-nitro-cyclohexanone in aprotic apolar solvents, such as cyclohexane or carbon tetrachloride, show quite clearly that a basic catalyst (e.g. triethylamine) is necessary for the tautomerization to take place. On the contrary, acid species (e.g. trifluoroacetic acid) apparently inhibit the tautomerization process.

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