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Effect of Ring Size on the Tautomerization and Ionization Reaction of Cyclic 2-Nitroalkanones: An Experimental and Theoretical Study

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Ⓢ *Supporting Information*

ABSTRACT: The keto−enol tautomerism of some cyclic 2-nitroalkanones was studied in cyclohexane. Keto−enol equilibrium constants, K_T, at 25 °C were obtained from ^{1}H NMR spectra. The relative enol content for the investigated ketones as a function of ring size decreases in the order 6 > 7 > 11 > 12 > 15. This trend apparently is different from that observed in water. Density functional theory (DFT) calculations have been performed to rationalize the effects of ring size and of the solvent on tautomerism. The acidity constants, K_a^{KH}, for the different keto tautomers were measured spectrophotometrically at 25 °C in buffered aqueous solutions. No simple correlations between K_a^{KH} and ring size was observed, and this is in agreement with a DFT analysis performed on the same compounds.
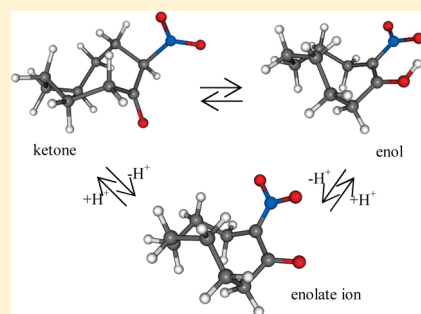
■ INTRODUCTION

The effect of ring size on kinetics and equilibria has been extensively studied in physical−organic chemistry.[1−3] In particular attempts have been made to correlate equilibrium constants for keto−enol tautomerism, K_T, of cyclic carbonyl compounds with the number of ring carbon atoms. In 1961 Gero determined the enol content in 75% methanol of some cyclic ketones by means of a modification of the Kurt Meyer titration and observed that "...a cyclic ketone with an even number of carbon atoms in the ring contains more enol than either its next higher or its next lower homolog..."[4] However, it should be underlined that the halogen titration based on the Kurt Meyer's method works only for those carbonyl compounds for which the enol content is relatively high, while it becomes unreliable when the enol content is less than about 1 ppm, leading to unacceptable high values.[5] Indeed the results obtained by Gero have been questioned in the following years by a number of Authors. For example, Allinger et al. could not detect any presence of enol in methanol for cyclohexanone, cycloheptanone, and cyclooctanone by NMR spectroscopy[6] and suggested that the conclusion of Gero should be considered unproven. Bell and Smith in 1966 reported that the enol content of cyclopentanone is higher than that of cyclohexanone in aqueous solution.[7]

Reliable results[8−10] have been obtained by the Kresge's kinetic approach based on the measurements of the forward and reverse rate constants of the tautomerization reaction. These results show that the enol content of cyclohexanone in water is two orders of magnitude higher than that of cyclopentanone and cycloheptanone. If this were the case, the relative tendency of cyclopentanone and cyclohexanone to

enolize would be in agreement with the general observation that an exo double bond to a five-membered ring is more stable than an exo double bond to a six-membered ring.[11] The ring-size effect on keto−enol tautomerism appears even less clear if a substituent is present at the position 2 of the ring. For example, the 2-benzoyl derivatives of cyclopentanone, cyclohexanone, and cycloheptanone show an enol content that increases in the order $C_6 < C_7 < C_5$ in methanol.[12] The Authors interpreted this unexpected result suggesting that the tendency to enolize depends on the ability of the ring double bond of the enol form and the substituent to lie in the same plane. Even if these results are based on UV and IR measurements, before the advent of NMR, it is reasonable to suppose that not only the size of the ring and the nature of the solvent but also the presence of a substituent should be taken into account in rationalizing the keto−enol tautomerism of substituted cyclic ketones in solution. It appears that more experimental and theoretical evidence is required before drawing firm conclusions on the complicated issue of the ring size effects on the keto−enol tautomerism of cyclic ketones. To the best of our knowledge, no previous theoretical investigations on ring-substituted ketones have been carried out with the exception of a semiempirical calculation[13] on 2-nitrocyclopentanone in a wider study on the substituent effect in cyclopentanones. These results, however, are to be intended as merely qualitative due to the relatively low accuracy of the method.

In this work we have measured the tautomeric equilibrium constants, K_T, in cyclohexane for some cyclic 2-nitroalkanones

Table 1. ^{1}H-NMR Data and Calculated K_T for the Four Investigated 2-Nitrocycloalkanones and C$_6$

ketone	δ/ppm (OH)	δ/ppm (CH)	K_T (NMR)	K_T (UV)	K_T average value
C$_6$	13.67	5.07	6.56 ± 0.20[a]	6.46 ± 0.57[a]	6.51 ± 0.57[a]
C$_7$	14.56	5.05	0.301 ± 0.009	0.304 ± 0.012	0.303 ± 0.006
C$_{11}$	15.03	4.96	0.202 ± 0.006	0.204 ± 0.010	0.203 ± 0.005
C$_{12}$	14.65	4.89	0.069 ± 0.008	0.071 ± 0.001	0.070 ± 0.003
C$_{15}$	14.67	4.92	0.045 ± 0.004	0.041 ± 0.001	0.043 ± 0.002

[a]From ref 17.

as well as their acidity constants, K_a^{KH}, in aqueous solution. In order to rationalize the experimental results, tautomerization and ionization reactions were studied theoretically, by performing preliminary molecular mechanics conformational searches to identify the most stable structures of the keto, enol, and enolate forms of the investigated compounds, followed by more accurate density functional theory (DFT) calculations. 2-Nitroalkanones represent an interesting class of substituted ketones in organic synthesis from many points of view.[14] For example, their hydrogen atom in position 2 is very acidic, with pK$_a$ values close to those of carboxylic acids,[15,16] and the dominant equilibrium in aqueous solution is between the keto form and the enolate anion without significant presence of the aci-nitro tautomer.[16] Moreover they are characterized by a relatively high enol content, depending upon the solvent used, which can be directly measured by different techniques (e.g., NMR and UV spectroscopy),[17] in different organic solvents,[17] in ionic liquids,[17] and in water.[16] For example, the value of pK$_T$, in water, for 2-nitrocyclohexanone is 1.19, exceedingly lower than that reported for cyclohexanone (pK$_T$ = 6.39)[5] which, in solution, essentially exists only in its stable keto form.

■ RESULTS AND DISCUSSION

Tautomerization Reaction. ^{1}H NMR spectroscopy represents a direct method to investigate keto−enol equilibria for substantially enolizable ketones without affecting the position of the equilibrium.[5] The interconversion between the tautomers is generally a slow process compared to the inherent time scale of NMR spectroscopy so that separate resonance signals can be observed for the acidic hydrogens in the keto and the enol form.

The ^{1}H NMR spectra of 2-nitrocycloheptanone (C$_7$), 2-nitrocycloundecanone (C$_{11}$), 2-nitrocyclododecanone (C$_{12}$), and 2-nitrocyclopentadecanone (C$_{15}$), recorded soon after the solubilization of an appropriate amount of substrate in fully deuterated cyclohexane, show two main signals in the ranges 4.5−5.0 and 14.5−15.0 ppm. These signals can be assigned to the α proton of the keto form and to the hydroxylic proton of the enol form, respectively. It is well-known[17−19] that for simple ketones, the enol tautomer is relatively favored in aprotic solvents, especially if it can entail strong intramolecular hydrogen bonds, while the more polar keto tautomer is favored in polar solvents. Accordingly, the peak at low field of the enol form increases with time, while the peak at high field decreases upon transfer of neat substrate to cyclohexane solution, due to a progressive enolization. When no further changes with time are observed in the spectrum, the tautomeric equilibrium is established, and K_T can be determined from integrated peak intensities (see Figures S1−S4 in Supporting Information).

The relevant ^{1}H NMR data and the calculated K_T values are reported in Table 1. K_T have also been measured by UV−vis spectrometry using a previously reported procedure.[17] There is good agreement between the values measured by the two

techniques (Table 1). For sake of comparison, the K_T value[17] for 2-nitrocycloesanone (C$_6$) is also reported in Table 1.

The data of Table 1 show that the enol content decreases as the ring-size of 2-nitrocycloalkanones increases. This trend apparently is different from that previously observed in 75% methanol[4] and in water.[5,8−10]

DFT calculations have been used to determine the enthalpy, the entropy, and the free energy variations in the gas phase, ΔH_g, ΔS_g, and ΔG_g, for the keto−enol equilibrium as well as the differential solvation free energy contribution, $\Delta\Delta G_{solv} = \Delta G_{solv}(\text{enol}) - \Delta G_{solv}(\text{keto})$, in cyclohexane and in water. The free energy in solution, ΔG_{sol}, and the equilibrium tautomeric constant, $K_T = e^{-\Delta G_{sol}/RT}$, in both solvents have been finally obtained. In order to compare the effect of the nitro substituent on simple cyclic keto and enol tautomers, calculations have also been performed on the five-, six-, and seven-membered ring unsubstituted ketones (**unsC$_5$**, **unsC$_6$**, and **unsC$_7$**, respectively), and the results in the gas phase, in cyclohexane, and in water are reported in Tables 2 and 3, respectively, together with the

Table 2. Calculated Enthalpies, Entropies, and Free Energies Variations (at 298 K) in the Gas Phase for the Keto-Enol Tautomeric Equilibrium[a]

compound	ΔH_g	ΔS_g	ΔG_g
	Unsubstituted Cycloalkanones		
unsC$_5$	12.0	−0.2	12.0
unsC$_6$	9.5	−0.5	9.6
unsC$_7$	10.5	−2.4	11.2
	2-Nitrocycloalkanones		
C$_4$	4.7	−3.5	5.8
C$_5$	−1.0	−3.6	0.0
C$_6$	−2.8	−3.0	−2.0
C$_7$	−1.6	−3.8	−0.5
C$_8$	−1.8	−3.0	−1.0
C$_9$	−2.0	−4.3	−0.1
C$_{10}$	−3.7	−3.8	−2.5
C$_{11}$	−0.7	−2.9	0.2
C$_{12}$	0.4	−5.2	1.9
C$_{15}$	0.1	−6.9	2.1

[a]Enthalpies and free energies are in kcal/mol, entropies in cal/(mol K).

available most recent experimental tautomeric constants, K_T, in water.[5]

Calculated values in the gas phase indicate that the equilibrium is endothermic with a ΔH_g value ca. 2 kcal/mol smaller for cyclohexanone than those for cyclopentanone and cycloheptanone, whereas the entropy contributions are quite small (though they become more negative upon increasing the size of the ring) and do not have a significant influence on ΔG_g.

Table 3. Calculated Free Energies (at 298 K) and K_T Values in Cyclohexane and Water and, Whenever Available, Experimental K_T Constants for the Keto−Enol Tautomeric Equilibrium[a]

compound	$\Delta G_{sol(C_6H_6)}$	$K_{T(C_6H_6)}$ calc	$K_{T(C_6H_6)}$ exp	$\Delta G_{sol(H_2O)}$	$K_{T(H_2O)}$ calc	$K_{T(H_2O)}$ exp
			Unsubstituted Cycloalkanones			
unsC$_5$	12.3	9.7×10^{-10}		13.0	3.0×10^{-10}	1.12×10^{-8b}
unsC$_6$	9.7	7.8×10^{-8}		8.9	3.0×10^{-7}	4.07×10^{-7b}
unsC$_7$	11.4	4.4×10^{-9}		12.5	6.9×10^{-10}	1.00×10^{-8b}
			2-Nitrocycloalkanones			
C$_4$	6.1	3.4×10^{-5}		6.9	9.3×10^{-6}	
C$_5$	0.8	0.26		4.3	7.1×10^{-4}	
C$_6$	−0.8	3.9	6.51	1.4	9.1×10^{-2}	6.46×10^{-2c}
C$_7$	0.8	0.26	0.303	4.8	3.1×10^{-4}	
C$_8$	0.0	1.0		1.6	6.7×10^{-2}	
C$_9$	0.4	0.51		2.8	8.8×10^{-3}	
C$_{10}$	−2.0	29		−1.5	1.2×10^1	
C$_{11}$	0.7	0.31	0.203	3.0	6.3×10^{-3}	
C$_{12}$	2.3	0.021	0.070	2.9	7.5×10^{-3}	
C$_{15}$	2.5	0.015	0.043	4.9	2.6×10^{-4}	

[a]Free energies are in kcal/mol. [b]From ref 5. [c]From ref 16.

Free energies in cyclohexane, $\Delta G_{sol(C_6H_6)}$ (Table 3), are very close to gas phase values, as expected for a nonpolar organic solvent. The water solvent further favors the keto form, as expected on the basis of the higher polarity of the keto relative to that of the enol. Moreover, water seems to enhance the difference between even and odd membered rings, the latter showing an even smaller content of the enol.

As far as the corresponding nitroderivatives are concerned, preliminary conformational search highlighted that, though in principle both cis and trans isomers can be considered for the enol form when the number of ring carbon atoms is larger than 8, the cis isomer is consistently more stable, due to the formation of an intramolecular hydrogen bond between the nitro oxygen and the OH hydrogen. This interaction strongly stabilizes the enol with respect to the keto form, therefore explaining the negative values of ΔH_g for the keto−enol equilibria of the nitro derivatives up to $n = 11$, with the exception of 2-nitrocyclobutanone (Table 2).

In the enol form of 2-nitrocyclobutanone the double bond forces the four carbon atoms on the same plane, largely increasing ring strain. Moreover, this strain forbids the formation of a strong hydrogen bond due to the large distance (2.180 Å) between the nitro oxygen and the enol hydrogen (see Figure 1).
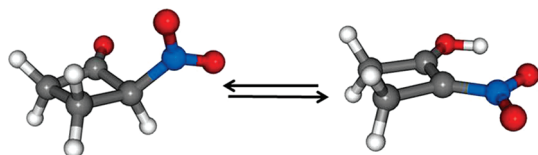
Figure 1. Structures of the keto and the enol tautomers of 2-nitrocyclobutanone.

For larger rings it is worth noting that the alternation in the relative enol content for rings with an even and an odd number of carbon atoms is generally maintained in the corresponding nitroderivatives. Indeed, at least up to $n = 10$, the ΔG_g values for compounds with an even number of ring carbon atoms are about 1 kcal/mol lower than those for compounds with an odd number of ring carbon atoms. This difference is however smaller than in the corresponding unsubstituted compounds. The exothermicity of the keto−enol equilibrium decreases as the size of the ring increases until it becomes slightly endothermic for $n > 11$ (Table 2), when the number of carbon atoms in the ring presumably allows a conformational freedom very similar to that of linear nitroketones and enols. Apparently this conformational flexibility allows the nitrocycloalkanones to adopt stable conformations with very little ring strain. To confirm this interpretation, the thermodynamic quantities for the keto−enol equilibria of 3-nitrobutan-2-one and 3-nitrohexan-2-one (Table 4) have also been calculated. Their ΔH_g values (less than 1 kcal/mol) are very close to the ΔH_g values calculated for large rings for which the alternation in the stability of enol form of even/odd membered rings is lost as well.

The entropy variations, ΔS_g, for 2-nitrocycloalkanones in the gas phase (Table 2) show a noticeable trend: ΔS_g values tend to become more negative as the ring size increases (in smaller rings a slight alternation in even/odd membered rings is again detectable, but it is too small to exclude a computational artifact). A negative entropy variation can be accounted for by considering that the double bond in the enol makes the ring more rigid, especially when the conformational freedom is higher, i.e., for larger rings. In addition, the intramolecular hydrogen bond in the enol keeps the atoms in a plane, limiting their motion and further decreasing the entropy of the enol

Table 4. Calculated Enthalpies, Entropies, and Free Energies Variations (at 298 K) in the Gas Phase and Solution for the Keto− Enol Tautomeric Equilibrium of Linear 3-Nitrobutan-2-one (l-C$_4$) and 3-Nitrohexan-2-one (l-C$_6$) and Calculated K_T Values[a]

compound	ΔH_g	ΔS_g	ΔG_g	$\Delta G_{sol(C_6H_6)}$	$K_{T(C_6H_6)}$	$\Delta G_{sol(H_2O)}$	$K_{T(H_2O)}$
l-C$_4$	0.8	−2.9	1.6	1.7	0.057	3.6	2.3×10^{-3}
l-C$_6$	1.0	−4.0	2.3	2.5	0.016	4.4	6.0×10^{-4}

[a]Enthalpies and free energies are expressed in kcal/mol and entropies in cal/(mol K).

with respect to the keto form. As a consequence of the alternation in ΔH_g and of the decrease of ΔS_g values as n increases, ΔG_g values are negative (with the exception of $n = 4$) up to $n = 11$, with a more pronounced exoergonicity for even membered rings. This alternation is less marked than in unsubstituted compounds, and it decreases as n decreases. For $n > 11$ the entropy contribution prevails, and the equilibrium becomes endoergonic. Comparison with the only existing theoretical ΔG_g value calculated at the Mindo-Forces level of theory for 2-nitrocyclopentanone[13] shows that the previous result ($\Delta G_g = -17.16$ kcal/mol) largely overestimates the presence of the enol form in the tautomeric equilibrium with respect to the presently calculated value ($\Delta G_g = -2.0$ kcal/mol).

In both cyclohexane and water the solvent further favors the keto over the enol form (see Table S1 in Supporting Information). The effect in cyclohexane, as expected for a nonpolar organic solvent, is quite small with differential solvation energies of, at most, 1.3 kcal/mol and does not qualitatively change the gas phase results. Comparison with the present experimental $K_{T(C_6H_6)}$ values shows an excellent quantitative agreement (within a factor 4), well within the accuracy of the method (1 kcal/mol on $\Delta G_{sol(C_6H_6)}$).

The solvent effect becomes larger in water with differential solvation energies $\Delta \Delta G_{(H_2O)}$ between 1 and 5 kcal/mol (see Table S1 in Supporting Information), solvation free energies favoring the formation of the polar keto over the enol form (i.e., solvation free energies for the keto being significantly lower than those for the corresponding enol form). This leads to smaller $K_{T(H_2O)}$ values than in cyclohexane. As for the unsubstituted species, the enol form for odd membered rings seems to be less favored than for even membered ones, and this gives a more pronounced alternation of K_T values than in cyclohexane. Comparison with the K_T experimental value for 2-nitrocyclohexanone[16] is again well within the accuracy of the method.

Dissociation Reaction. The dissociation constants, K_a^{KH}, of the five 2-nitrocycloalkanones of Table 5 have been

Table 5. Ionization Constants in Water, pK_a^{KH}, for the Investigated 2-Nitrocycloalkanones Obtained from Eq 2

2-nitrocycloalkanone	pK_a^{KH}
C_6	6.00 ± 0.02^a
C_7	6.12 ± 0.03
C_9	5.15 ± 0.03
C_{11}	4.60 ± 0.02
C_{12}	5.60 ± 0.05
C_{15}	7.50 ± 0.07

^{a}From ref 16.

determined spectrophotometrically in aqueous solution at 25 °C by monitoring the absorbance of the enolate ions after equilibrium had been established at each pH, as previously reported for 3-nitrobutan-2-one[15] and for C_6.[16] The pHs of the different solutions were set by using hydrochloric acid or acetate, phosphate, and borate buffers of different buffer ratios. The change of the absorbance at $\lambda = 326$ nm of a 2×10^{-4} mol dm^{-3} solution of C_7 as a function of pH is reported as a typical example in Figure 2.
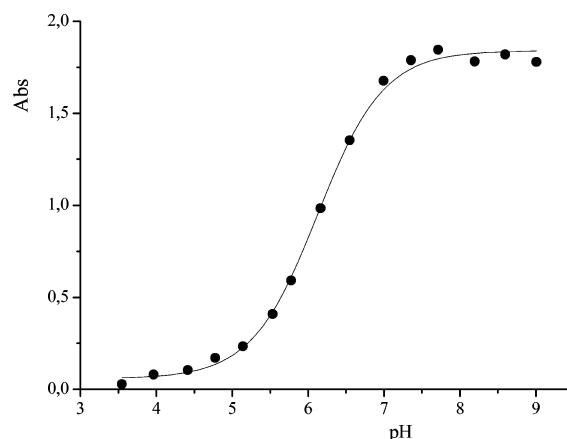
Figure 2. Plot of the absorbance, Abs, at $\lambda = 326$ nm against pH of a 2×10^{-4} mol dm^{-3} solution of 2-nitrocycloheptanone.

The total absorbance, Abs, of each solution is given by eq 1:

$$\text{Abs} = \varepsilon_{KH}[KH] + \varepsilon_{EH}[EH] + \varepsilon_E[E] \qquad (1)$$

where ε_{KH}, ε_{EH} and ε_E are the molar absorptivity of the ketone, the enol, and the enolate ion, respectively. Equation 1 can be reduced to eq 2 by taking into account that [2-nitrocycloalkanone] $= [KH] + [EH] + [E]$ and that the keto form does not absorb at the λ_{max} of the enolate ion.

$$\text{Abs} = (\text{Abs}_{min}[H^+] + \text{Abs}_{max}K_a^{KH})/$$
$$(K_a^{KH} + [H^+]) \qquad (2)$$

In eq 2 Abs_{min} and Abs_{max} are the limiting absorbances at the lowest and the highest pHs, respectively. The pK_a^{KH} values reported in Table 5 have been obtained from a best fit of experimental data to eq 2.

The experimental pK_a^{KH} of Table 5 are, in principle, "apparent" acid dissociation constants due to the deprotonation of the keto and the enol tautomers, both present in solution. However the previously determined "apparent" dissociation constants for 3-nitrobutan-2-one[15] and for C_6[16] turned out to be equal to the "true" values within the experimental error. Therefore, by considering that the enol content of the five investigated 2-nitrocycloalkanones in aqueous solution is certainly less than that of 3-nitrobutan-2-one and C_6, we can approximate the experimental K_a values, derived from eq 2, as equal to the "true" K_a^{KH} values for the dissociation reaction of the keto tautomers. The results obtained show that the acidity in water of the 2-nitrocycloalkanones of Table 5 increases in the order $C_{15} < C_7 < C_6 < C_{12} < C_9 < C_{11}$. No simple correlation apparently exists between the pK_a^{KH} and the number of the ring carbon atoms. An analogous lack of correlation was previously observed for nitrocycloalkanes.[20,21] In this case, the obtained acidity order is: nitrocyclooctane (8) > nitrocyclopentane (5) ≈ nitrocycloheptane (7) > nitrocyclobutane (4) ≈ nitrocyclohexane (6) ≫ nitrocyclopropane (3). The relatively low acidity of 3 and 4 was explained in terms of an increased angle strain when forming the corresponding nitronate ions, while the relatively higher acidity of 5, 7, and 8 as compared to that of 6 or nitrocyclododecanone was attributed to the release of torsional strain after dissociation.[21]

In principle, pK_a values can be theoretically calculated with the same approach used for pK_T. However, the evaluation of ΔG_{sol} for H^+ with the continuum solvent model turned out to

be a difficult task, making the calculation very elaborate in practice. Nevertheless, a rationalization of the pK_a values of a series of related compounds can be successfully attempted in terms of factors, such as bond polarization and/or relative stability of the protonated and deprotonated species. Both factors can be conveniently expressed by molecular descriptors, attainable at different levels of theory, which, in turn, can be used in a linear free energy relationship (LFER) analysis to estimate pK_a values.[15,16,22−48] These descriptors have been previously calculated at both low level of theory (empirical, AM1, HF/STO-3G, HF/3-21G, HF/3-21G-(d))[15,16,25,29−31,33,44−48] and Hartree−Fock (HF) or DFT methods with larger basis sets. Although, as a general rule, the highest possible computational methods have to be adopted, there are several examples where the use of HF or DFT methods with larger basis sets does not necessarily lead to significant improvements in correlations with the experimental data.[26−29,44,46] It has also been demonstrated that the atomic charge densities on the α-hydrogens, $\delta(H_\alpha)$, can be used to monitor even small variations of acidity as a function of conformational and/or configurational changes, when these changes influence the degree of polarization of the bonds involved in the dissociation process.[15,16,22,23] Thus $\delta(H_\alpha)$ values have been calculated and used to predict the pK_a of the investigated ketones as previously reported.[15,16] As a first step, we have determined the most representative conformers of the keto form of the experimentally investigated 2-nitrocycloalkanones both at the semiempirical AM1 and B3LYP/6-31G(d,p) levels of theory. Gas phase energies relative to the most stable conformer for each species, ΔE_g, and the corresponding δH_α values are reported in Table 6. The δH_α value depends on the reciprocal disposition of the C=O and C−NO$_2$ dipoles,[16] as shown in Scheme 1.

Table 6. Relative Energies in the Gas Phase, ΔE_g, and Values of δH_α for the Selected Conformations of the Investigated 2-Nitrocycloalkanones[a]

| conformers		AM1			DFT		
		ΔE_g	δH_α	$D\alpha$ (°)	ΔE_g	δH_α	$D\alpha$ (°)
C$_6$	1KH	0.0	0.1552	−2.3	0.0	0.1706[b]	112.9
	2KH	0.1	0.1617[b]	104.4	0.1	0.1551	−2.1
C$_7$	1KH	0.0	0.1608[b]	99.0	0.0	0.1557	87.9
	2KH	0.6	0.1562	−25.1	0.4	0.1611[b]	−8.9
	3KH	0.9	0.1535	24.0	2.6	0.1457	17.1
C$_9$	1KH	0.0	0.1459	44.4	0.0	0.1407	39.7
	2KH	0.2	0.1628[b]	−126.1	0.6	0.1695[b]	−130.1
C$_{11}$	1KH	0.0	0.1631[b]	150.8	0.0	0.1434	107.3
	2KH	1.3	0.1487	92.7	0.9	0.1721[b]	155.0
C$_{12}$	1KH	0.0	0.1627[b]	162.7	0.0	0.1702[b]	169.4
C$_{15}$	1KH	0.0	0.1516[b]	62.0	0.0	0.1404[b]	85.6

[a]Energies are in kcal/mol. [b]Values used for linear regression.

Scheme 1
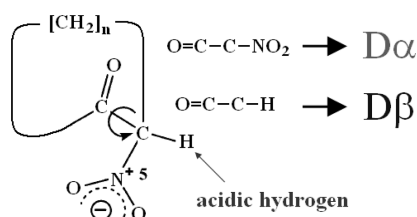
For 3-nitrobutan-2-one, which was taken as a model free of constraint, the most favorable alignment for the polarization of the C−H bond is obtained when the dihedral angle O=C−C−NO$_2$ ($D\alpha$) approaches 150° and the dihedral angle O=C−C−H ($D\beta$) is ca. 30° in module (Scheme 2).

Scheme 2. δH_α As a Function of $D\alpha$ in 3-Nitrobutan-2-one
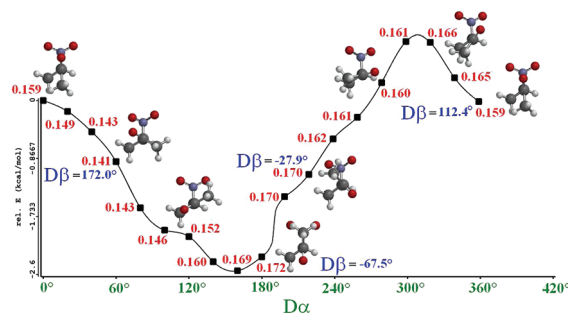
The presence of the ring in 2-nitrocycloalkanones restricts the conformational freedom and does not allow the favorable orientation of the dipoles, particularly in small rings. However, when the number of carbon atoms in the ring increases, the conformational freedom also increases, and the stable anti conformation is adopted with little ring strain.

The correlation of δH_α with the experimental pK_a values was performed by using the largest δH_α values for each ketone. The corresponding conformer, being the most acidic, is expected to lose H$^+$ better than other conformers. The very small energy difference (less than 3 kcal/mol) among the conformers ensures that a significant population of the most acidic conformer is always present and that it can easily be restored by fast conformational changes.

The selected δH_α values at the AM1 level of theory have been used to predict the pK_as of the corresponding conformations from the previously reported[15] eq 3:

$$pK_a = -250.0 \times \delta H_\alpha + 45.425 \quad (3)$$

A R^2 value of 0.821 was obtained when calculated, and experimental pK_a values were compared. This value shows a distinct, but quantitatively poor, linear correlation.

Nonetheless the same trend of acidity is observed for both calculated and experimental pK_a values as a function of the ring size (Figure 3 magenta dashed line compared to red line), suggesting that δH_α is indeed a good descriptor, but other factors may significantly contribute to determine the overall acidity of these compounds.

In particular, the ability of the enolate ion to assume the most stable trans disposition of NO$_2$ with respect to O$^−$ can have a relevant effect on the acidity. The dissociation process is expected to become thermodynamically favorable when this trans disposition can be obtained without appreciable torsional strain. Thus, the differential energy stability between the trans and the cis enolate ions in the gas phase ($\Delta E^g_{t−c}$) and in water ($\Delta E^w_{t−c}$), have been calculated. The most stable structures for the trans and the cis enolate ions in the gas phase were optimized at both AM1 and B3LYP levels of theory, and their hydration energies were calculated. The values of $\Delta E^g_{t−c}$ and $\Delta E^w_{t−c}$ obtained at the two levels are reported in Table 7.

To better explore the existence of a trend in the series of enolates, 2-nitrocyclooctanone, C$_8$, and 2-nitrocyclodecanone, C$_{10}$, were also included in the calculation. Interestingly, by
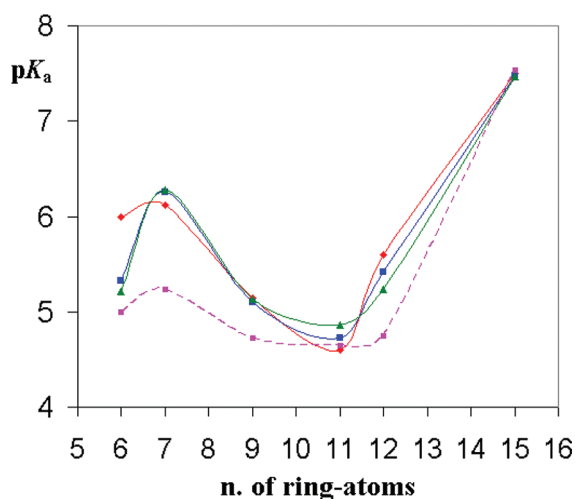
Figure 3. Experimental (red line) and calculated pK_a values from eq 3 (magenta dashed line), eq 6 (blue line), and eq 7 (green full line) as a function of ring-size.

Table 7. Calculated ΔE_{t-c} Values (kcal/mol) in the Gas Phase, ΔE^g_{t-c}, and in Water, ΔE^w_{t-c}, for the cis and trans Enolate Ions of the Investigated 2-Nitrocycloalkanones

	AM1				DFT		
	ΔE^g_{t-c}	ΔE^w_{t-c}	$\Delta\Delta E_{t-c}$		ΔE^g_{t-c}	ΔE^w_{t-c}	$\Delta\Delta E_{t-c}$
C_6	–	–		C_6	–	–	
C_7	7.69	7.81	0.12	C_7	8.84	10.42	1.58
C_8	1.23	4.07	2.84	C_8	0.26	3.36	3.10
C_9	−3.83	0.54	4.37	C_9	−9.09	−5.19	3.90
C_{10}	−7.31	−1.81	5.50	C_{10}	−11.16	−6.62	4.54
C_{11}	−8.45	−2.82	5.63	C_{11}	−14.94	−9.59	5.35
C_{12}	−2.81	3.72	6.53	C_{12}	−7.40	−2.01	5.39
C_{15}	−7.89	−3.03	4.86	C_{15}	−10.54	−2.61	7.93

increasing the number of ring carbon atoms, ΔE^g_{t-c} and ΔE^w_{t-c} values follow a trend (Figure 4a,b) similar to that observed for the experimental pK_a data. In particular the relative stability of the trans-isomer (impossible to achieve for C_6) increases on passing from C_7 to C_{11}, and starting from C_9, the trans-isomer becomes the most stable conformation.

If both δH_α and ΔE^g_{t-c} are used as descriptors in LFERs, the following equations can be obtained, where the regression coefficients have been optimized on the pK_a values of C_7, C_9, C_{11}, C_{12}, and C_{15}:

$$pK_a = -226.55 \times \delta H_\alpha + 0.05374 \times \Delta E^g_{t-c} + 42.25$$
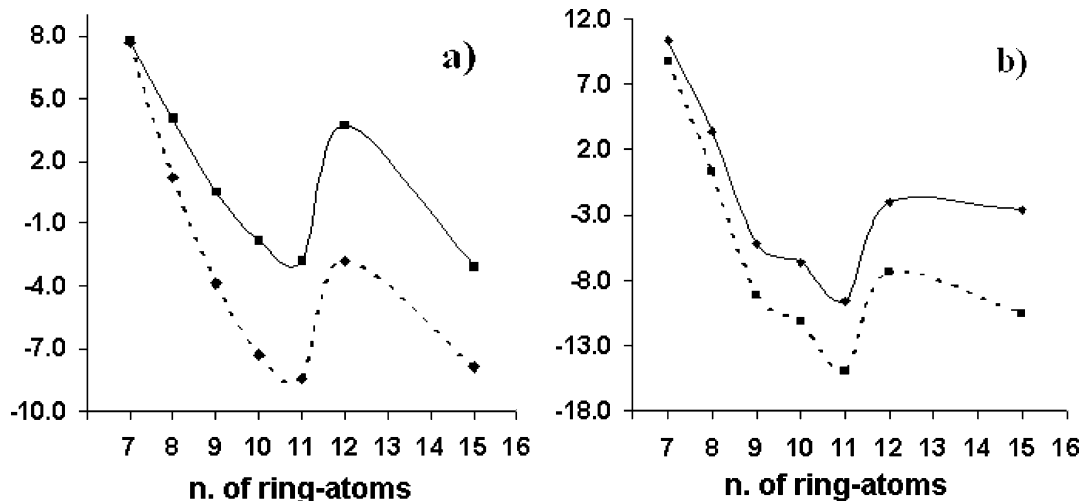$$(R^2 = 0.958; \text{ standard error} = 0.26) \tag{4}$$

at AM1 level and

$$pK_a = -78.30 \times \delta H_\alpha + 0.02127 \times \Delta E^g_{t-c} + 18.67$$
$$(R^2 = 0.947; \text{ standard error} = 0.29) \tag{5}$$

at B3LYP/6-31G(d,p) level.

For both relations the R^2 value is higher than that obtained from eq 3, indicating an improved quantitative agreement with the experimental data. This suggests that both descriptors should be considered to reproduce the experimental trend of acidities.

The ΔE^w_{t-c} values, obtained when hydration is taken into account, give a more realistic estimate of the trans−cis energy difference in water. Dipole moments calculated for the enolate ion of 3-nitrobutan-2-one at the B3LYP/6-31G(d,p) level of theory are 1.24 and 5.23 D for the trans and the cis isomer, respectively. These values suggest that the cis isomer can be more effectively hydrated than the trans isomer, and the overall hydration contribution $\Delta\Delta E_{t-c} = \Delta E^w_{t-c} - \Delta E^g_{t-c}$ is expected to be positive. The obtained $\Delta\Delta E_{t-c}$ values, reported in Table 7, confirm this indication. In summary it appears that, on the whole, the differential stability in water of the trans and cis enolate ions is reduced due to a better hydration of the latter isomer with increasing ring size. If ΔE^w_{t-c} values are now used in the above two-parameters linear regression analysis, the following eqs 6 and 7 are obtained at the AM1 and B3LYP/6-31G(d,p) levels of theory, respectively:

Figure 4. ΔE^g_{t-c} (dashed line) and ΔE^w_{t-c} (full line) values calculated at AM1 level (a) and at B3LYP/6-31G(d,p) level (b).

$$pK_a = -240.43 \times \delta H_\alpha + 0.09011 \times \Delta E^w_{t-c}$$
$$+ 44.20$$
$$(R^2 = 0.986; \text{ standard error } = 0.15) \tag{6}$$

$$pK_a = -75.28 \times \delta H_\alpha + 0.02933 \times \Delta E^w_{t-c}$$
$$+ 18.09$$
$$(R^2 = 0.954; \text{ standard error } = 0.27) \tag{7}$$

It appears that, in both cases, the correlation with the experimental values gives higher R^2 values than those obtained from eqs 4 and 5, as shown in Figure 3 (blue and green lines compared with the red line) and Table 8. This is particularly remarkable in the case of the AM1 level of theory.

Table 8. pK_a Values Calculated from Eqs 6 and 7

conformers		pK_a^{calc} (eq 6)	pK_a^{calc} (eq 7)
C_6	1KH	6.89	5.25
	2KH	5.32	6.41
C_7	1KH	6.24	6.67
	2KH	7.35	5.96
	3KH	6.59	7.43
C_9	1KH	9.16	7.35
	2KH	5.11	5.18
C_{11}	1KH	4.73	7.58
	2KH	8.19	5.66
C_{12}	1KH	5.42	5.13
	2KH	8.33	6.96
C_{15}	1KH	7.53	7.37
	2KH	5.05	6.25

In the light of the above results, we conclude that the acidity of the investigated 2-nitrocycloalkanones essentially depends on the following factors: (i) the reciprocal orientation of the C=O and C−NO₂ dipoles, which affects the polarity of the C−H bond. This factor is described by the term δH_α; (ii) the ability of the enolate ion to assume the trans configuration. This factor is described by the term ΔE_{t-c}: and (iii) the differential solvation of the cis and the trans enolate ions. This factor is described by the term $\Delta\Delta E_{t-c}$.

CONCLUSIONS

The keto−enol interconversion and the dissociation reaction of some 2-nitrocycloalkanones have been experimentally and theoretically investigated. The tautomerization reaction in cyclohexane was found to be shifted toward the enol tautomers for smaller rings, with an alternation in the reaction enthalpy values for even and odd membered species. The entropy factor prevails in larger rings, whose equilibrium is relatively shifted toward the keto form.

No simple correlation apparently exists between the experimental pK_a^{KH} of the investigated 2-nitrocycloalkanones and the number of the ring carbon atoms. However a definite trend can be observed if more than a single molecular descriptor of acidity, computed at either AM1 or B3LYP/6-31G(d,p) level of theory, is considered in LFER analyses.

EXPERIMENTAL SECTION

Materials. 2-nitrocycloheptanone (C_7), 2-nitrocyclononanone (C_9), 2-nitrocycloundecanone (C_{11}), 2-nitrocyclododecanone (C_{12}),

and 2-nitrocyclopentadecanone (C_{15}) were prepared and purified according to reported methods.[49,50]

Deuterated cyclohexane, acids (HCl, CH₃COOH, H₃BO₃), NaOH, and KH₂PO₄ were commercial samples of AnalaR grade and were used without furter purification. Aqueous solutions were prepared using deionized water.

Instruments. The ¹H NMR spectra were recorded with a 300 MHz spectrometer operating at 7.1 T. Chemical shift (δ) are given in parts per million relative to TMS.

The UV−vis spectra were recorded with a UV−vis spectrophotometer with a spectral resolution set to 0.333 nm. The spectrophotometer was provided with a thermostatted cell holder. A pH meter was used for the pH measurements of the samples.

¹H NMR Measurements. Tautomeric equilibrium constants, K_T, have been determined at 25 °C in deuterated cyclohexane by ¹H NMR from the peak area ratios for the acidic hydrogens of the enol and the keto tautomers, following a previously reported procedure.[16] Catalytic amounts of triethylamine were added to speed up the establishment of the equilibria. The constancy of the total intensities of the two hydrogen signals during tautomerization was checked with respect to the intensity of the signal due to the aromatic protons of pyrene, used as a standard.

UV−vis Measurements. Ionization equilibrium constants, K_a^{KH}, have been determined at 25 ± 0.1 °C spectrophotometrically at the λ_{max} of the enolate ion. The spectra were registered at $2 \leq pH \leq 9$ in acetate, phosphate, and borate buffers of different buffer ratios. The lowest values of pH (2−3) were obtained by adding HCl to the aqueous solution of the ketone. The concentration of the substrate was kept constant at 2×10^{-4} mol dm⁻³, and the pH of the solution was measured before and after each experiment.

Computational Details. The keto−enol equilibrium was theoretically studied by performing DFT calculations on the keto and enol tautomers in cyclohexane and in water. More in detail, preliminary conformational searches in the gas phase on all the keto and enol species were carried out through MACROMODEL 9.0,[51] using a Monte Carlo multiple minimum algorithm and MMFF94s as force field and conjugate gradient with Polak−Ribiere first derivatives method as minimization algorithm. For each species, 1000 conformations were minimized. All the conformers within 15 kJ/mol from the global minimum were then optimized at the M06-2X/6-311++G(d,p) level of theory using the Jaguar 7.5 quantum chemistry package.[52] This functional[53] has been parametrized for nonmetals and main group thermodynamics and kinetics and is thus expected to give a greater accuracy (within 1 kcal/mol) than other usually employed functionals (generally within 2 kcal/mol). Frequency calculations were performed on the global minimum for each compound to verify the correct nature of the stationary point and to estimate zero-point energy (ZPE) and thermal corrections to thermodynamic properties. All structures were reoptimized in solution using the Poisson−Boltzmann (PB) continuum solvent method implemented in Jaguar, representing the solvent as a layer of charges at the molecular surface (i.e., the contact surface between the van der Waals envelope of the solute and a probe solvent molecule), serving as a dielectric continuum boundary, thus accounting for detailed molecular shape.[54] Though this method was found to give good quantitative estimates of solvation free energies, even in the more difficult to model polar solvent, it still relies on simplifications, and optimizations in such environment might decrease the accuracy of the results, in particular in a water solvent (geometries in cyclohexane are very close to gas phase ones). The calculated ΔG_{sol} values in water are thus expected to have an accuracy within 2 kcal/mol.

The ionization reaction of the investigated 2-nitrocycloalkanones was theoretically studied by performing molecular modeling calculations with the computer program SPARTAN '04. Conformational searches, based on the molecular mechanics force field MMFF, of ketones and cis- and trans-enolate ions were performed using the implemented Monte Carlo algorithm, setting the initial temperature to 5000 K and taking conformers within 40 kJ/mol from the minimum energy structure of each species. The conformations within 3 kcal mol⁻¹ in energy from the global minimum were reoptimized at AM1

semiempirical level. Ketones were grouped according to the syn or anti disposition assumed by the C=O and C−H bonds (H being the acidic hydrogen) and only the most stable structure in each group was further optimized using B3LYP/6-31G(d,p) level of theory. Similarly, only the most stable among the conformers of the cis- and trans-enolates were also optimized at the B3LYP/6-31G(d,p) level. For these conformers hydration energies, based on the SM5.4 model of Cramer and Truhlar, were estimated.

The variation of δH_α as a function of the dihedral angle, $D\alpha$, for the rotation around the OC−CNO$_2$ bond was also investigated for 3-nitrobutan-2-one, used as a molecular model free of ring strain, by using the dedicated algorithm implemented in SPARTAN. To this aim, an energy scan at the B3LYP/6-31G(d,p) level of theory was performed on the whole angle range, 0°−360°, with steps of 20°.

Regression Analyses. The acidity of the investigated ketones was rationalized by correlating pKa values to δH_α and $\Delta E^{g/w}_{t-c}$ by linear regression. The obtained results were analyzed according to the F- and t-tests, to exclude casualness (index F) and to quantify the statistical weight of each of the two descriptors (index T and factors t_1 and t_2). Linear regression analyses, F- and t-tests were performed by the dedicated functions implemented in the Microsoft Office Excel 2003 program. Probability related to the t-Student distribution in the t-test was set to 0.1. In all the considered cases a T value of 2.9 was obtained. Regressions corresponding to eqs 4−7 led to the following index F, factor t_1 and factor t_2: (i) 0.04, 6.7, 2.1; (ii) 0.01, 11.7, 4.1; (iii) 0.05, 5.8, 1.1; and (iv) 0.05, 5.8, 1.3, respectively.

ASSOCIATED CONTENT

⑤ Supporting Information

^{1}H NMR spectra of the 2-nitrocycloalkanones; calculated solvation free energies for the keto and enol species and differential solvation free energies ($\Delta\Delta G$) in cyclohexane and water; Cartesian coordinates of the optimized species in gas phase and in water. This material is available free of charge via the Internet at http://pubs.acs.org.

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