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The Mills-Nixon Effect on Enol-Enol Tautomerism in β-Dicarbonyl Compounds and on Annular Tautomerism in N*H*-Pyrazoles: a Semi-Empirical Study

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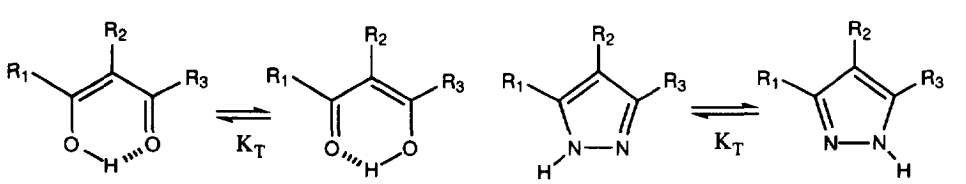
Abstract.— AM1 semiempirical calculations, both ΔH and ΔS, were carried out on the enol/enol tautomerism of 25 β-diketones and 8 β-ketoaldehydes. In the first case, $\delta\Delta G_{exp}$ was determined by Hansen (*Magn. Reson. Chem.* **1996**, *34*, 467) and his values correlate reasonably well with $\delta\Delta G_{calc}$, $\delta\Delta G_{exp}$ = - 0.23 + 0.29 $\delta\Delta G_{calc}$, r^2 = 0.83. The calculated differences in energy are linearly related to some geometrical characteristics of the ketoenol, namely the angles about the substituent on the central carbon. To check if this geometrical dependence is related to the Mills-Nixon effect, parallel AM1 calculations on the tautomerism of β-ketoaldehydes and 3(5),4-disubstituted N*H*-pyrazoles were carried out confirming the influence of the Mills-Nixon effect on the enol/enol tautomerism of β-dicarbonyl compounds.

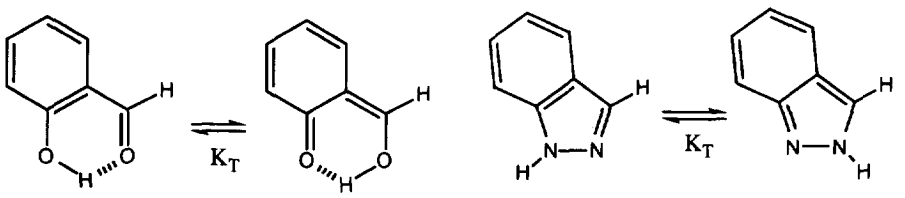
INTRODUCTION

Tautomeric studies both in alicyclic and heterocyclic compounds continue to be of prime interest. Amongst the alicyclic compounds, the β-diketones **I** are probably the reference compounds.[1-4] Reaction of hydrazine with β-dicarbonyl compounds **I** affords the corresponding N*H*-pyrazoles **II**,[5,6] whose annular tautomerism, although less representative, has been carefully studied.[7-10] We will try to demonstrate that the chemical relationship between **I** and **II** has its counterpart in a structural relationship concerning their tautomerism.



Ia **Ib** **IIa** **IIb**

There are indications in the literature that when one of the two tautomers **a** or **b** is more favoured, then it is the same for **I** than for **II**. For instance, due to the difference in energy between benzenoid and quinonoid forms, fusion to a benzene ring displaces the equilibrium towards tautomer **a** in both cases: salicylaldehyde **IIIa**[3,11] and 1*H*-indazole **IVa**.[12,13]

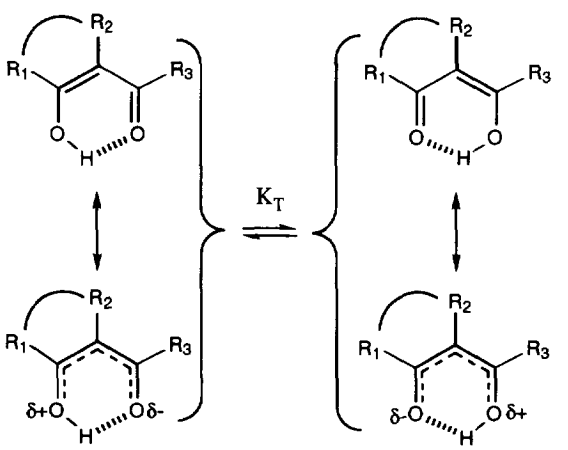


IIIa **IIIb** **IVa** **IVb**

In the case of β-dicarbonyl compounds **I**, we will not consider the equilibria with other tautomers like the diketone and the two *trans*-ketoenols,[14] but only the equilibrium between the *cis*-ketoenol tautomers **Ia** and **Ib**. This equilibrium is much more difficult to study than the keto/enol equilibrium due to the low activation barrier separating both tautomers and our discussion will be based on a recent paper by Hansen[15] where the tautomeric equilibrium constants (K_T = [**Ia**]/[**Ib**]) for 25 β-diketones were determined.

Although this paper refers to the analogies between **I** and **II**, there exists also two clear differences: i) there are only two tautomers for N*H*-pyrazoles compared with five for β-diketones; ii) β-diketones present an *intramolecular* hydrogen-bond (IMHB) while pyrazoles present only *intermolecular* hydrogen bonds and classical tautomerism.[16] The IMHB in the six-membered pseudo-ring of ketoenols was named by Gilli[1,2,17] RAHB (resonance assisted hydrogen bond) due to the delocalization of electrons.

One last aspect concerns the so-called Mills-Nixon effect.[18] We have proposed to use the observable property K_T to estimate this controversial effect.[8,10] The underlying reasoning is summarized in Scheme 1:



Ia **Ib**

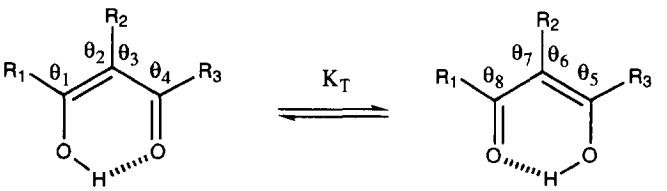
Scheme 1

If as a consequence of ring annelation (for instance R_1 and R_2 being part of a small ring) the single bond character of the C-C bond increases in the RAHB structure of a β-ketonenol this will result in a stabilization of the

tautomer which has the more single bond character in this C-C bond, that is, **Ib**. Thus, determining K_T we could verify how ring strain (as measured by the angles about R_1-C-C and C-C-R_2) affects the stability of tautomers.

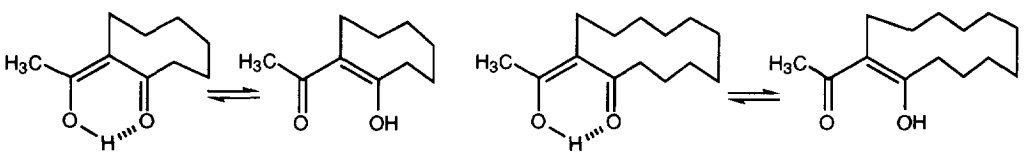
RESULTS AND DISCUSSION

Due to the size of the molecules involved in the calculations we have chosen the AM1 Hamiltonian.[19] This method much exaggerates the Mills-Nixon effect (the differences in energy are about 7 times those obtained at the 6-31G* level)[10] but it reproduces the general tendency and yields self-consistent values. Consequently, we aim at proportionality not at absolute values. We have reported in a Table (see Supplementary Material) the results we obtained for 23 of the 25 β-diketones of Bolvig and Hansen (we have used their numbering).[15] The angles θ_1 to θ_8 are defined below.



Ia **Ib**

According to AM1 calculations, tautomers **b** of compounds **20** and **21** are not chelated (no IMHB) and so these compounds have not been included in the discussion.



20a **20b** **21a** **21b**

For compounds **1**, **7** and **8**, both tautomers are identical, i.e. $\theta_1 = \theta_5$, $\theta_2 = \theta_6$, $\theta_3 = \theta_7$, $\theta_4 = \theta_8$ and thus $K_T = 1.0$ and $\delta\Delta H_f = 0.0$ kcal mol^{-1}. Consequently, we have calculated first the differences between these pairs of angles: $\theta_1 - \theta_5$, $\theta_2 - \theta_6$, $\theta_3 - \theta_7$ and $\theta_4 - \theta_8$ in order to have $\delta\theta_i = 0$ for $\delta\Delta H_f = 0$. We found that there are two classes of differences, the external ($\theta_1 - \theta_5$ and $\theta_4 - \theta_8$) and the internal ($\theta_2 - \theta_6$ and $\theta_3 - \theta_7$); therefore, we decided to calculate their average values: $[(\theta_1 - \theta_5) - (\theta_4 - \theta_8)]/2$ and $[(\theta_2 - \theta_6) - (\theta_3 - \theta_7)]/2$ (see Table).

These "external" and "internal" angles are linearly related, Eq. (1), thus one angle is sufficient to describe a ketoenol, for instance the "internal" one, $\theta_{int} = [(\theta_2 - \theta_6) - (\theta_3 - \theta_7)]/2$.

$$\theta_{ext}\{[(\theta_1 - \theta_5) - (\theta_4 - \theta_8)]/2\} = 0.67\pm0.02\ \theta_{int}\{[(\theta_2 - \theta_6) - (\theta_3 - \theta_7)]/2\},\ n = 25,\ r^2 = 0.98 \qquad (1)$$

We have calculated for these equilibria not only the differences in heat of formation, $\delta\Delta H_f$, but also the changes in entropy, $\delta\Delta S$, in order to calculate $\delta\Delta G$ at 298 K. In most studies, $\delta\Delta H_f$ is used since it is assumed

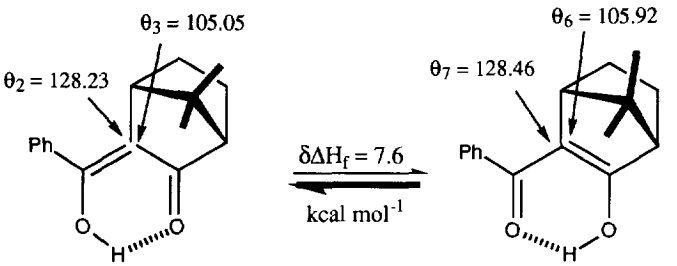
that the changes in entropy do not affect the "relative" results, the only results one could expect from semiempirical calculations. This is actually the case for the 25 ketoenols as eq. (2) shows.

$$\delta\Delta G_{calc} = 0.20\pm0.10 + 0.95\pm0.04\ \delta\Delta H_f\ ,\ n = 25,\ r^2 = 0.97 \qquad (2)$$

We can now plot $\delta\Delta G_{calc}$ in function of θ_{int} (see, Fig. 1). The result, Eq. (3), is acceptably correct.

$$\delta\Delta G_{calc} = 0.28\pm0.02\ \theta_{int},\ n = 25,\ r^2 = 0.89 \qquad (3)$$

What is important is that $\delta\Delta H_f$ increases when θ_{int} increases, i.e. that tautomer **a** becomes more stable when θ_2 (and θ_7) are greater than θ_3 (and θ_6), exactly what is expected from the Mills-Nixon empirical rule. This is illustrated in Scheme 2 for the camphor derivative **18**:



18a **18b**

Scheme 2

We can now turn towards the problem of experimental $\delta\Delta G$ values from ref. 15. We have selected the values (mole fractions of tautomer **a**) obtained from ^{13}C NMR since they are the most complete. We have transformed the mole fractions into ΔG by means of $\Delta G = -RT \ln K_T$, $K_T = [\mathbf{a}]/[\mathbf{b}]$ and T = 298 K. The problem arises with three compounds, **18**, **19** and **24**, for which the amount of tautomer **b** is so small that Bolvig and Hansen represented them by mole fraction ~ 0.[15] Since in some cases they have measured mole fractions up to 0.92 we have supposed that these mole fractions are 0.07 or less.

We can now represent $\delta\Delta G_{exp}$ against $\delta\Delta G_{calc}$ [Fig. 2 and Eq. (4)]. Concerning compounds **18**, **19** and **24** (black points in Fig. 2) we have assumed that they have small amounts of **b** tautomers: **18**, 4% ($\delta\Delta G_{exp}$ = 1.96 kcal mol^{-1}), **19**, 7% ($\delta\Delta G_{exp}$ = 1.57 kcal mol^{-1}) and **24**, 17% ($\delta\Delta G_{exp}$ = 0.95 kcal mol^{-1}), only the last value is inconsistent with a population of 0.07 or less.

$$\delta\Delta G_{exp} = -0.24\pm0.09 + 0.30\pm0.03\ \delta\Delta G_{calc},\ n = 25,\ r^2 = 0.80 \qquad (4)$$

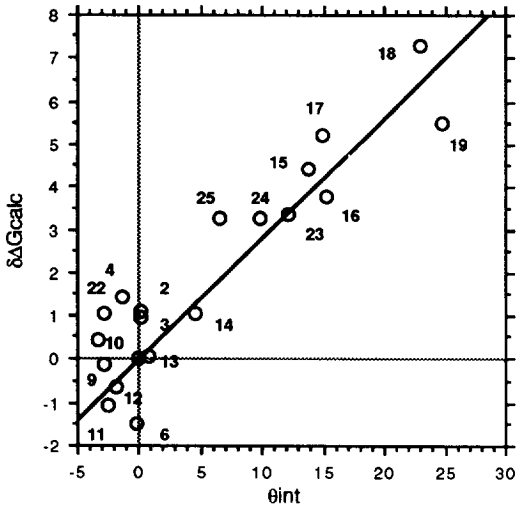


Figure 1. Plot of $\delta\Delta G_{calc}$ (in kcal mol^{-1}) for ketoenol tautomerism vs θ_{int} (in °)

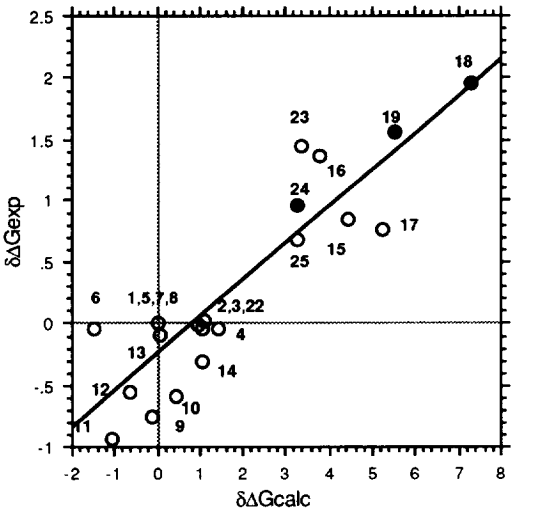
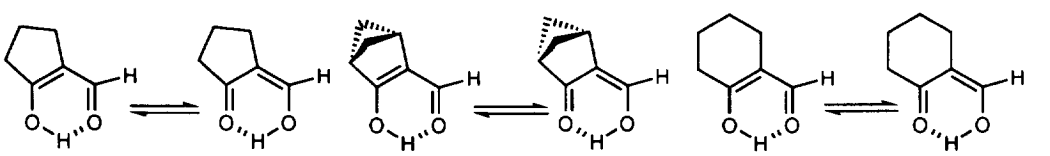


Figure 2. Plot of $\delta\Delta G_{exp}$ (in kcal mol^{-1}) vs $\delta\Delta G_{calc}$ (in kcal mol^{-1})

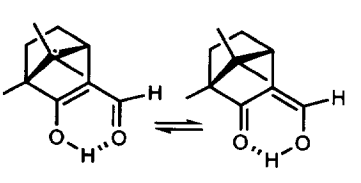
In eq. (3) we have neglected the electronic and steric effects of R_1 and R_3 (see formulae **Ia** and **Ib**) which certainly affects K_T; nevertheless, inclusion of $\delta(\sigma)$ and $\delta(E_s)$ parameters[20] does not significantly improve the models. We feel authorized to conclude that ring-strain effects are the dominant factor in what this collection of β-diketones are concerned.

Comparison between β-diketones and pyrazoles.

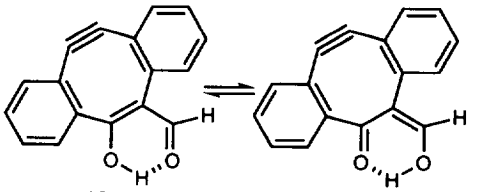
Since we have recently shown the tautomerism of NH-pyrazoles **II** is a benchmark for the study of the Mills-Nixon Effect we have studied, at the same level of calculations, the corresponding β-ketoaldehydes **26-33**:



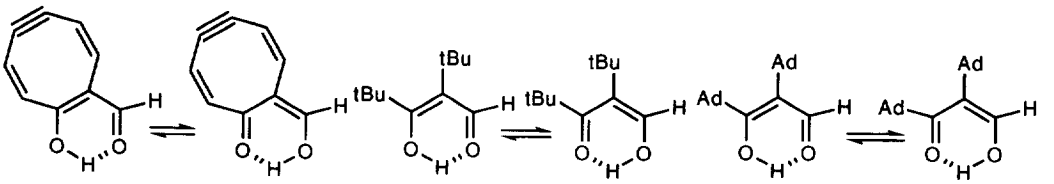
26a **26b** **27a** **27b** **28a** **28b**



29a **29b**

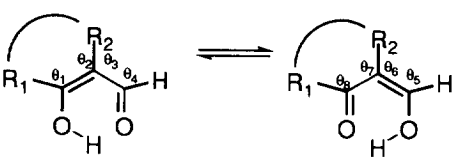


30a **30b**



31a **31b** **32a** **32b** **33a** **33b**

In this series, we also find the problem that several **b** tautomers do not exist, according to the AM1 calculations, as chelated RAHB structures: **30b**, **31b**, **32b** and **33b**. For the remaining four compounds we have obtained the results of Table 1:



a **b**

No	$\theta_1(\theta_8)$	$\theta_2(\theta_7)$	$\theta_3(\theta_6)$	$\theta_4(\theta_5)$	θ_{int}	ΔH_f	$\delta\Delta H_f$	$\delta\Delta G_{calc}$	$\delta\Delta H_f$[a]
26a	112.71	110.56	123.08	116.02		-79.63			
26b	109.04	109.91	124.21	123.91	-13.41	-84.46	-4.83	-4.98	-2.83
27a	104.38	102.20	129.00	116.38		-7.31			
27b	101.01	101.32	129.58	124.82	-27.53	-19.60	-12.29	-12.02	-5.84
28a	123.94	121.04	115.17	115.21		-91.48			
28b	119.20	119.37	118.14	122.61	3.55	-91.67	-0.19	-0.21	-0.02
29a	108.63	106.33	126.27	116.26		-65.47			
29b	105.19	105.53	126.99	124.44	-20.70	-74.45	-8.98	-8.75	-4.12

[a]Data of the corresponding N*H*-pyrazoles from ref. 10.

We have tried two correlations imposing the condition that for symmetric compounds: $\theta_{int} = \delta\Delta H_f = \delta\Delta G = 0.0$. In these conditions, eqs. (5) and (6) are found:

$$\delta\Delta G_{calc} \text{ (ketoaldehydes)} = 0.42\pm0.02\ \theta_{int},\ n = 4,\ r^2 = 0.986 \quad (5)$$

$$\delta\Delta H_f \text{ (ketoaldehydes)} = 2.07\pm0.07\ \delta\Delta H_f \text{ (}N\textit{H}\text{-pyrazoles)},\ n = 4,\ r^2 = 0.995 \quad (6)$$

Both equations show that β–ketoaldehydes are more sensitive to angular strain than both β-diketones [Eq. (4), slope 0.074] and pyrazoles [Eq. (6), slope 2.07].

Conclusions

We have proved: i) that there is a structural relationship between β-dicarbonyl compounds and N*H*-pyrazoles in what tautomerism is concerned; ii) that the Mills-Nixon effect is useful to predict the dominant tautomer in both systems.

On the other hand, we have failed in two respects: i) we have been unable to calculate β-dicarbonyl compounds **20**, **21**, **30**, **31**, **32** and **33** since according to AM1 calculations the corresponding tautomers **b** are not chelated (no RAHB); ii) we have not been able to reproduce the experimental result[15] for β-diketone **24**.

COMPUTATIONAL DETAILS

AM1 calculations[19] have been performed with the MOPAC 6.0 program.[21] All the structures have been fully optimized using the EF minimization algorithm and the PRECISE keyword. The minimum nature of the structures obtained have been confirmed by analyzing the force constant matrix.

Supplementary material

A Scheme with the formulae of Hansen's 25 β-diketones (both tautomers), and a Table with the AM1 calculations (geometries and energies) for β-diketones **1**-**33**.

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