Equilibrium between Hydroxycycloalkanones and Oxabicycloalkanols

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Hydroxycycloalkanones **1** of medium ring size (8 – 10) exist in a transannular tautomeric equilibrium with the corresponding oxabicycloalkan-1-ols **2**, which represent hemiacetals. Normally, the bicyclic structures **2** predominate in solution although their portion decreases with increasing solvent polarity. A correlation of the Gibbs reaction enthalpies ΔG (**1**→**2**) with the solvent parameters E_T (30) is presented.

Key words: Hemiacetals, Hydroxyketones, Solvent Polarity, Transannular Tautomerism

Introduction

Several examples of (substituted) hydroxycycloalkanones **1** are known, which exist in a transannular tautomeric equilibrium with the corresponding oxabicycloalkan-1-ols **2** (Fig. 1). The oxygen bridge can span six-membered [1], seven-membered [2, 3], eight-membered [2 – 7], nine-membered [8], ten-membered [8 – 10] or possibly larger rings. The equilibrium can have a considerable influence on the reactions of the tautomers, in particular on the dehydration of **2** to yield *anti*-Bredt enol ethers [11, 12]. Such enol ether functionalities are present in numerous natural products and represent a synthetic challenge [12].

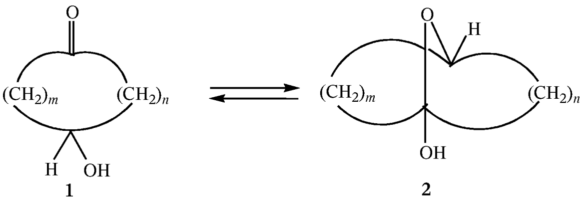

Fig. 1. Transannular tautomeric equilibrium between hydroxycycloalkanones **1** and their bicyclic hemiacetals **2** (*m, n* = 2, 3, 4, 5).

Results and Discussion

Results of an *ab initio* calculation [13] of 5-hydroxycyclooctanone (**1b**) and its energetically favored hemiacetal, 9-oxabicyclo[3.3.1]nonan-1-ol (**2b**), prompted us to report our experimental study on the hydroxyketone/hemiacetal equilibria **1a** – **1e**$\rightleftarrows$**2a** – **2e** (Fig. 2).

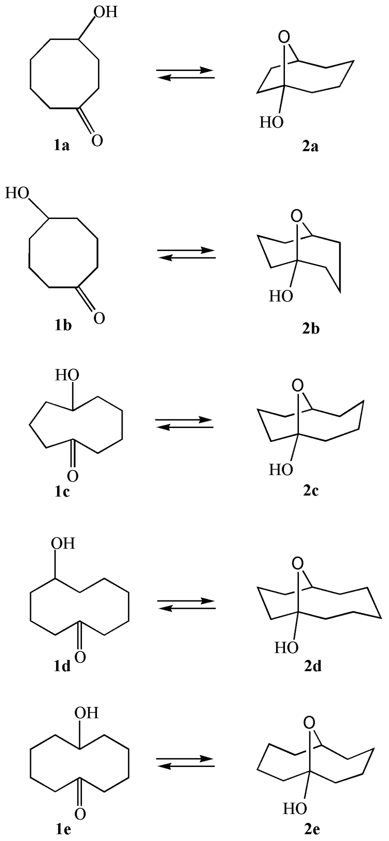

Fig. 2. Hydroxycyclooctanones **1a**, **1b**, -nonanone **1c**, and -decanones **1d**, **1e**, and their bicyclic tautomers **2a** – **2e**.

We used standard methods for the preparation of **1a/2a** [3 – 7], **1b/2b** [14], **1c/2c** [4], and **1e/2e** [10].

Table 1. ^{1}H NMR signals of the OCH groups[a] in **1a–c/2a–e** and ratios **1** : **2**.

Hydroxy-ketone	HC–OH δ[b]	Hemiacetal	HC–O δ[b]	Solvent	Ratio **1** : **2**
1a	3.70	**2a**	4.37	C_6D_6	22 : 78
				$CDCl_3$	27 : 73
				CD_3SOCD_3	32 : 68
				CD_3OD	36 : 64
1b	3.71	**2b**	4.38	$CDCl_3$	3 : 97
				CD_3OD	6 : 94
1c	3.70	**2c**	4.08	C_6D_6	4 : 96
				$CDCl_3$	8 : 92
				CD_3SOCD_3	12 : 88
				CD_3OD	16 : 84
1d	3.75	**2d**	4.00	$CDCl_3$	24 : 76
1e	3.83	**2e**	4.07	C_6D_6	45 : 55
				$CDCl_3$	55 : 45
				CD_3SOCD_3	67 : 33
				CD_3OD	78 : 22

[a] The other signals, which belong to the CH_2 groups of **1** and **2**, strongly overlap in the region $2.7 \leq \delta \leq 1.1$ ppm; [b] in $CDCl_3$ solution; δ values in ppm relative to TMS.

Table 2. ^{13}C NMR data of the hydroxyketones **1a**,**c** – **e**[a] and the hemiacetals **2a** – **e**.

Hydroxy-ketone	Hemi-acetal	Solvent	— δ[b] — C=O	OC_qO	HCO	CH_2
1a		$CDCl_3$	217.3		70.4	40.0, 39.2, 33.3, 30.3, 28.4, 21.7
	2a	$CDCl_3$		108.1	75.6	41.4, 36.9, 36.1, 30.9, 23.6, 23.1
	2b	$CDCl_3$		93.4	72.4	36.1, 28.3, 20.7
1c		CD_3OD	220.4		71.3	44.8, 43.7, 35.4, 32.1, 24.8, 24.1, 21.3
	2c	CD_3OD		98.7	73.7	37.3, 37.2, 31.3, 28.8, 22.5, 21.2, 18.6
1d		$CDCl_3$	217.5		69.9	43.1, 40.3, 33.2, 29.6, 26.0, 23.1, 21.4, 19.1
	2d			96.2	73.6	37.6, 37.3, 32.6, 32.0, 27.8, 25.0, 21.7, 17.2
1e		CD_3OD	217.5		69.9	42.8, 34.5, 24.3, 23.9
	2e	CD_3OD		103.5	76.6	41.7, 34.6, 24.3, 23.9

[a] The portion of **1b** was too small (~3 %) for a reliable measurement; δ values in ppm relative to TMS.

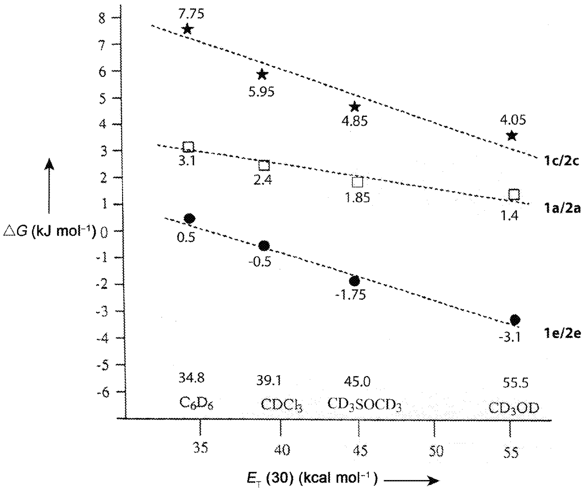

Fig. 3. Correlations of the Gibbs energies ΔG and the solvent parameters E_T (30).

The new compounds **1d/2d** were obtained by oxidation of cyclodecane-1,5-diol [15, 16] with Jones reagent (CrO_3, H_2SO_4).

The equilibria **1/2** were determined by ^{1}H and ^{13}C NMR measurements. The relevant ^{1}H NMR signals are listed together with the ratios **1/2** in Table 1. The complete sets of ^{13}C NMR signals are summarized in Table 2.

From results of measurements of the relative concentrations $c(\mathbf{1})$ and $c(\mathbf{2})$, the equilibrium constants K (Eq. 1) and the Gibbs energies ΔG (Eq. 2) were determined in various solvents at 23±3 °C.

$$K = \frac{c(\mathbf{2})}{c(\mathbf{1})} \tag{1}$$

$$\begin{aligned} \Delta G &= -RT \ln K \\ T &= 293\ \mathrm{K},\ R = 8.314\ \mathrm{J\,mol^{-1}K^{-1}} \end{aligned} \tag{2}$$

Normally, the bicyclic tautomer predominates. However, we established a strong influence of the solvent polarity on the K and ΔG values. Fig. 3 demonstrates the correlation of the ΔG values of **1a/2a**, **1c/2c** and **1e/2e** with the E_T [17] parameters of the solvents. In principle, the tautomers **1b/2b** and **1d/2d** behave similarly. However, the portion of ketone **1b** is very small (3 % in $CDCl_3$ and 6 % in CD_3OD), so that the exact concentration measurement by NMR spectroscopy proved to be difficult. The ΔG values of all systems are somewhat higher in methanol as expected. This can be taken as a hint to the additional influence of intermolecular hydrogen bonds in alcohols as solvents.

Increasing solvent polarity causes in all cases decreasing ΔG values, that means decreasing portions of hemiacetal components **2**. We attribute this effect to the higher polarity of the hydroxyketones **1**. Polar solvents provide a better solvation of these tautomers. Although the correlation coefficients for the linear relations are between 0.92 and 0.99, linearity of the correlations is not stringent. Further solvents have to be included in the study.

Conclusion

Cyclooctanones, -nonanones and -decanones **1a**–**1e** with hydroxy groups in 4-, 5- or 6-position show a transannular tautomerism to the corresponding hemiacetals **2a**–**2e**. The oxabicycloalkan-1-ols **2a**–**d** represent the major components in the equilibria although their portion decreases with increasing solvent polarity. As an exception, 6-hydroxycyclodecanone (**1e**), in benzene still the minor component, is the predominating tautomer in chloroform, dimethylsulfoxide and methanol. In large-ring hydroxyketones, with 12- and 15-membered rings, the transannular tautomerism does not play a role [18, 19]. The compounds studied here exhibit correlations between the Gibbs reaction enthalpies ΔG (**1**→**2**) and the solvent parameters E_T (30).

Experimental Section

The ^{1}H and ^{13}C NMR spectra were obtained on Bruker AM 400 and ARX 400 instruments. A Finnigan MAT 95 spectrometer served for the FD MS measurement. The elemental analysis was obtained in the microanalytical laboratory of the Institute of Organic Chemistry of the University of Mainz.

Compounds **1a/2a** [3–7], **1b/2b** [14], **1c/2c** [4] and **1e/2e** [10] were obtained according to the literature.

*5-Hydroxycyclodecanone (**1d**)/11-oxabicyclo[5.3.1]undecan-1-ol (**2d**)*

To cyclodecane-1,5-diol [15, 16] (7.75 g, 45.0 mmol), dissolved in 200 mL of acetone, Jones reagent (2.0 g, 20 mmol CrO_3, 3.5 mL conc. H_2SO_4, 15 mL ice water) was slowly added with stirring at 0–5 °C. After stirring for 1 h, the mixture was filtered and the filtrate evaporated. The residue was dissolved in CH_2Cl_2, and the solution was washed with water and dried (Na_2SO_4). Column chromatography (4 × 80 cm^2 SiO_2, petroleum ether (b. p. 40–70 °C)/diethyl ether) gave 2.04 g (40 %) of an oil, which solidified in the refrigerator at 5 °C to a wax. The yields were higher when 1.5 equivalents of diol for 1 equivalent of Jones reagent were used, but the purification was then more difficult. – ^{1}H NMR ($CDCl_3$): δ = 4.00 (m, 1H, 7-H, **2d**), 3.75 (m, 1H, 5-H, **1d**), 2.70–22.0 (m, 4H, 2-H, 10-H, **1d**), 2.01–1.05 (m, 28H, 3-H, 4-H, 6-H, 7-H, 8-H, 8-H, 9-H of **1d** and 2-H, 3-H, 4-H, 5-H, 6-H, 8-H, 9-H, 10-H of **2d**). According to the integration of the ^{1}H NMR spectrum, the ratio **1d** : **2d** amounts to 24 : 76 (in $CDCl_3$). – ^{13}C NMR signals: see Table 2. – MS (FD): *m/z* (%) = 170 (100) $[M]^{+\cdot}$. – $C_{10}H_{18}O_2$ (170.25): calcd. C 70.55, H 10.66; found C 70.91, H 10.38.

Measurement of the tautomeric equilibria

The ^{1}H NMR signals of the methine protons *H*C(OH) in **1a**–**e** and *H*CO in **2a**–**e** are well separated, so that repeated signal integration furnished reliable concentration ratios $c(\mathbf{2})/c(\mathbf{1})$. An independent determination by ^{13}C NMR spectroscopy was possible by the inverse-gated decoupling method [20].

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