29. NMR of Terminal Oxygen

Part 14[1])

Kinetically Stabilized Simple Enols Containing Methylated Uracil Groups: Application of a ^{17}O-NMR Test of H-Bonding

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In the crystalline *N,N'*-dimethylated uracil derivatives **2a,b**, the kinetically stabilized enol group forms an H-bond with O–C(4), as demonstrated by increased shielding of specifically labelled **2a** and **2b** in the ^{17}O-NMR spectra ($\Delta\delta(^{17}O)$(C(4)–O) = –30 ppm); absence of dilution and solvent effects show that the H-bridge is intramolecular, forming an eight-membered chelate ring. The (apparent) shielding effect $\Delta\delta(^{17}O)$ in **2a,b** is larger than that in salicylamide. The strong H-bond explains why the enols **2**, in spite of the absence of steric hindrance, are kinetically stabilized.

Introduction. – In spite of their lower thermodynamic stability, simple nonconjugated enols are often not too unstable under appropriate conditions (absence of catalysts, aprotic solvents) and can sometimes even be isolated, before being tautomerized to the more stable carbonyl compounds [2]. Even vinyl alcohol has a lifetime of several min at room temperature in MeCN solution [3]. The reason for this sluggishness of ketonisation is that the rate-determining step, *viz.* the transfer of a proton to C(α), is not a rapid reaction [4]; this contrasts with the reactions of the same enols with halogen or similar electrophiles, which are nearly diffusion-controlled [5]. Increased kinetic stability is conferred to simple enols by steric hindrance of the H-transfer: *e.g.* the hindered 1,2,2-triaryl-substituted and the equally hindered 2-mesityl-substituted enols have been isolated in crystalline form and kept indefinitely [2c]. Fluorinated enols are also known to be stabilized (thermodynamically or kinetically or both), possibly by induction [2a]; it has been established, however, that more than one electron-attracting F-atom is needed to yield enols that can be isolated. We have not found in the literature kinetically stabilized simple enols lacking both these features. H-Bonds have often considered to contribute to stabilization, but no case of an isolable enol owing its stability primarily to this factor seems to have been demonstrated.

It has recently been shown that during the acid-catalyzed hydrolysis of the bicyclic aminoacetals **1a,b** (obtained by cycloaddition reactions of uracil derivatives), the enols **2a,b** were formed [6]. They were isolated as crystalline compounds and characterized as enols (^{1}H-NMR ($CDCl_3$): 9.6 ppm; ^{13}C-NMR: 116.8 and 130.0 ppm; IR ($CHCl_3$): *ca.* 3000 cm^{-1} (br., not influenced by dilution)); enol silyl ethers were easily formed. As solids, the enols **2a,b** were stable several weeks at –20°; prolonged treatment with dilute acid at 20° transformed them into the ketones **3a,b**. Starting with the ketones **3a,b**, the enols (or

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equilibrium mixtures) could not be obtained under the same conditions, demonstrating that the latter are only kinetically and not thermodynamically stable. By the action of simple bases, these acyl cyanides **3a,b** underwent displacement reactions, not enolisation[3]).

The kinetic stability of these enols is surprising: it cannot be attributed to steric hindrance, as only one voluminous substituent, the uracilyl group is present, separated from the enol moiety by a CH_2 group. The electron attraction by one CN group cannot be considered sufficient neither[4]). It was supposed that an H-bond, demonstrated by the IR spectrum, contributes to the kinetic stabilization of the enol by slowing down its C-protonation. To test whether the H-bond is intramolecular, and, if so, which carbonyl group is the H-acceptor, we have used ^{17}O-NMR techniques.

Results and Discussion. – The carbonyl O-atoms of aldehydes and ketones show increased shielding in ^{17}O-NMR when participating in an intermolecular or intramolecular H-bond with an H-donor group [8a]. For amide O-atoms similar but smaller intermolecular shielding effects have been reported [9]. Using ^{17}O-NMR, intramolecular H-bonds in aromatic *o*-hydroxy-carbonyl compounds were demonstrated to yield shielding effects, measured as $\Delta\delta(^{17}O) = [\delta(^{17}O)(CO;\ ortho\text{-}OH)] - [\delta(^{17}O)(CO;\ para\text{-}OH)]$, of −31 ppm for salicylaldehyde [10], −40 ppm for *o*-hydroxyacetophenone [11], and −9 ppm for methyl salicylate [12]; the difference between these values has been attributed to differences in basicity of the carbonyl groups. Until now, however, intramolecular H-bond effects upon amide-type carbonyl O-atoms have not been demonstrated by ^{17}O-NMR.

We measured $\delta(^{17}O)$ of 2-hydroxybenzamide (= salicylamide) and compared it with the value of its 4-OH isomer and with those of the corresponding methoxy derivatives (*Table 1*). The shift difference between the 4-OH and the 2-OH compound,

Table 1. *^{17}O-NMR Shift Values* (MeCN, 40°) *of Benzamide Derivatives X-$C_6H_4CONH_2$*

X	2-OH	4-OH	2-MeO	4-MeO
$\delta(^{17}O)(=O)$[a])	289.5	307.8[b])	317.9	320.9
$\delta(^{17}O)(-O-)$[a])	86.1	81.9[c])	50.2	54.7

[a]) Line width *ca.* 200 Hz, unless, indicated otherwise. [b]) Line width 360 Hz. [c]) Line width 600 Hz.

$\Delta\delta(^{17}O)(CO) = -18$ ppm, can be attributed to intramolecular H-bonding; it is smaller than the corresponding $\Delta\delta(^{17}O)$ values for the hydroxybenzaldehydes and -acetophenones mentioned above. Still, the shift difference between the 4-hydroxy- and 4-methoxyamides, $\Delta\delta(^{17}O)(CO) = 13$ ppm, suggests that the former contains a shielding contribution coming from intermolecular H-bonding, which would diminish the effect of the intramolecular H-bond. This assumption is supported by the shift difference between salicylamide and its methyl ether, $\Delta\delta(^{17}O)(CO) = 28$ ppm[5]). Yet, for an evaluation of the

[3]) However, after treatment of **3b** with Me_3SiCl and pyridine, the ^{1}H-NMR signals of **8b** appeared.

[4]) The apparently similar case of MeC(OEt)=C(OH)CN [7] cannot be compared: as an enol ether of an α-cyano ketone it must be thermodynamically, not kinetically stabilized. Actually, it could not be transformed into the corresponding ketone or into an equilibrium mixture.

[5]) The small difference $\Delta\delta(^{17}O)(CO) = 3$ ppm between 2- and 4-methoxybenzamide might be due to a weak H-bond between NH_2 and MeO.

$\Delta\delta(^{17}O)$ values, the (deshielding) torsional effects should also be taken into account [12]. The shift value of salicylamide did not change upon dilution, showing that here the H-bond effect is purely intramolecular. It can be concluded that the ^{17}O shift differences are an excellent indicator of the presence of strong intramolecular H-bonds in hydroxyamides.

Unsubstituted uracil shows two signals in the ^{17}O-NMR spectrum, one at 336 ppm, the other at 256 ppm (in DMSO) [13] [14]. The former corresponds to that of an amide group (as in acetamide, 334 ppm) and is assigned to O–C(4). It appears at higher field than the carbonyl O-atom of aldehydes and ketones (*ca.* 550 ppm [15] [8b]), since the n-donation of the N-atom (resonance) increases the shielding of the amide O-atom. The uracil signal at 256 ppm [13] (in DMSO; 224 ppm in H_2O [14]) is comparable with that of urea (233.4 ppm in DMSO; 205 ppm in H_2O [15]), doubly shielded by resonance, and belongs to O–C(2). These peak assignments were confirmed by comparison with other nucleotide bases and by specific labelling [13]. We found for several *N,N'*-dimethyluracil derivatives containing side chains in position 5, *i.e.* for **3a,b**–**8a,b**, $\delta(^{17}O)$(O–C(4)) = 324–338 ppm (confirmed by specific labelling) and $\delta(^{17}O)$(O–C(2)) = 263–265 ppm (*Table 2*). The additional Me group at C(6) of the compounds of series **b** causes a slight shielding, $\Delta\delta(^{17}O)$ *ca.* −10 ppm for most of the shift values of O–C(4), presumably by electron donation transmitted through the double bond; the shift value of O–C(2) is practically not affected by this Me group.

To prepare the ^{17}O-enriched uracil derivatives mentioned above, we started by specific labelling of O–C(4) in *N,N'*-dimethyluracil and in *N,N'*,6-trimethyluracil; this was achieved by heating them with $H_2{}^{17}O$ in strongly acid solution, following the methods known for uracil and thymine labelling [13] [14]. The label enters by nucleophilic addition/elimination of $H_2{}^{17}O$ to a carbonyl group, preferentially that of the amide-type position 4, leaving that of the less electrophilic urea-type position 2 untouched. These labelled compounds were transformed into [^{17}O]-**2a** and -**2b**, respectively, and then into the compounds [^{17}O]-**3a,b** to [^{17}O]-**8a,b**, by the reactions described before [6].

For O–C(2) and O–C(4) of uracil, shielding effects of $\Delta\delta(^{17}O) = -8$ ppm and −32 ppm, respectively, have been reported when H-bonds are formed with H-donating solvent molecules (H_2O *vs.* MeCN) [11] [9] [16]. It could thus be expected that ^{17}O shift values would allow the detection of intramolecular H-bonds in uracil derivatives also. In the enols **2a** and **2b**, the signals for O–C(4) appear at 305 and 295 ppm, respectively. They are at *ca.* 30 ppm higher field than those of the corresponding ketones **3a,b** and of the other uracil derivatives **4a,b**–**7a,b**, and also of the silyl ethers **8a,b** (*Table 2*). On the other hand, the O–C(2) signal, at 265 ppm in **2b**, remains practically invariable in all compounds examined. The shielding effect on O–C(4) of **2a,b** ($\Delta\delta(^{17}O) \approx -30$ ppm) is interpreted as the result of an H-bridge between the enolic OH and O–C(4). Comparison of this $\Delta\delta(^{17}O)$ effect with that of salicylamide and related compounds (see above) indicates the H-bond in **2a,b** to be strong.

Enol **2b** gives a further signal at 74 ppm, which must belong to the enol group: tertiary alcohols are found at *ca.* 60 ppm [17a], the conjugated ester enols R–C(OH)=CH–COOEt at 124, 109, and 96 ppm for R = Me, Ph, and CF_3, respectively [18], simple enol ethers at *ca.* 80 ppm [17b], and intramolecularly H-bonded phenols at *ca.* 95 ppm [18]. The scarcity of comparable data does not allow to identify the effect of H-bonding upon the signal of an enol group.

Whether the bridge between the enolic OH and O–C(4) is inter- or intramolecular was tested by a dilution experiment with **2a** using ^{1}H-NMR: between 0.01M and 0.15M the

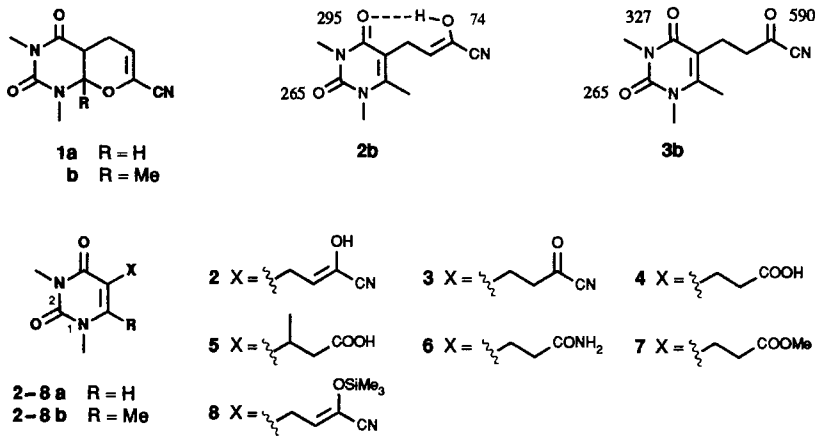

Table 2. *^{17}O-NMR Shift Values* (MeCN, 40°; δ [ppm]) *of Methylated Uracil Derivatives* **1** *and* **2–8**. ^{17}O-Enriched groups are marked by *.

	X	Series **a** (R = H)		Series **b** (R = Me)	
		$\delta(^{17}O)$(O–C(4))[a])	$\delta(^{17}O)$(O–C(2))[a])	$\delta(^{17}O)$(O–C(4))[a])	$\delta(^{17}O)$(O–C(2))[a])
1		381.3	284.0[b])	378.7	284.2[c])
		382.0*		378.2*	
2	$CH_2CH{=}C(OH)CN$	304.8*		295.3	265.3[d])
				294.7*	
3	$CH_2CH_2C(O)CN$	335.4*		326.6	264.7[e])
				326.9*	
4	CH_2CH_2COOH	332.1*		324.6	263.3[f])
				324.5*	
5	$CH(Me)CH_2COOH$	334.0	263.6[f])	331.4	263.3[f])
6	$CH_2CH_2CONH_2$	334.4*		335.1	263.8
7	CH_2CH_2COOMe	338.2	264.3[g])	327.7	263.4[h])
8	$CH_2CH{=}C(OSiMe_3)CN$	337.5	265.2[i])	327.3	264.8[j])

[a]) Line width: *ca.* 200 Hz for **1a**, [^{17}O]-**1a**, [^{17}O]-**2a**, **3a**, **6b**, and **7a**; *ca.* 300 Hz for **1b**, [^{17}O]-**1b**, **2b**, [^{17}O]-**2b**, **3b**, **5b**, and **7b**; *ca.* 400 Hz for [^{17}O]-**3b**, [^{17}O]-**4a**, **4b**, **5a**, **6a**, and **8a**; > 500 Hz for **8b**. [b]) $\delta(-O-) = 79.6$. [c]) $\delta(-O-) = 101.6$. [d]) $\delta(OH) = 73.6$. [e]) $\delta(CO) = 589.6$. [f]) Signal of COOH hidden under O–C(2). [g]) $\delta(CO) = 354.2$; $\delta(-O-) = 138.0$. [h]) $\delta(CO) = 354.3$; $\delta(-O-) = 137.6$. [i]) $\delta(OSi) = 70.8$. [j]) $\delta(OSi) = 71.5$.

^{1}H-NMR signal at 9.58 ppm (in $CDCl_3$) did not change its position, confirming the intramolecular character of the bridge. Changing the solvent to better H-bond acceptors did not much affect the signal neither: We found for **2b** 9.66 ppm in $CDCl_3$, 9.78 ppm in (D_6)acetone, and 10.07 ppm in (D_6)DMSO, demonstrating that the intramolecular H-bridge, rather strong, is not replaced by an intermolecular bridge to a solvent molecule.

The intramolecular H-bond of the enolic OH to O–C(4) forms an 8-membered chelate ring, a not very familiar feature. There are, of course, formally eight-membered rings containing two H-bonds, as in the carboxylic acid dimers and in the nucleotide base

pairs, but they present a different geometry. *Dreiding* models show that the chelate ring of **2** can be formed without strain; it is not coplanar with the uracil ring. It must, however, be assumed that the ring forms and opens rapidly on the NMR time scale; otherwise the protons CH_2–C(4) of the side chain would be diastereotopic.

To test whether other potentially H^+-donating groups, notably COOH or $CONH_2$, equally form intramolecular H-bonds with O–C(4) of uracil, we measured $\delta(^{17}O)$ of derivatives containing the side chains CH_2CH_2COOH (**4a,b**), CH(Me)CH_2COOH (**5a,b**) and $CH_2CH_2CONH_2$ (**6a,b**). In none of these compounds, significant shielding effects upon O–C(4) were observed (*Table 2*), *i.e.* H-bonds are absent or very weak. It is proposed that the particular strength of H-bonding of the enol group in **2** is due to the increased rigidity of its side chain.

In conclusion, our measurements confirm the existence of a strong H-bond in the enols **2** and specify its character as a 8-membered chelate. H-Bonds often have been supposed to contribute to the stabilization of enols; **2** is the first case in which, in the absence of significant steric hindrance, an enol ows its kinetic stability primarily to H-bonding.

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Experimental Part

General. IR Spectra (cm^{-1}): *Perkin-Elmer 1420.* ^{1}H-NMR Spectra (δ, in ppm): *Bruker-WH-250* spectrometer. Mass spectra (*m/z* (rel. %)): *Nermag-R-10-10C* spectrometer.

^{17}O-NMR Spectroscopy. ^{17}O-NMR Spectra were recorded on a *Bruker-WH-360* spectrometer, equipped with a 10-mm probe, at 48.8 MHz, in the *Fourier* transform (FT) mode without lock. System control, data acquisitions, and data managements were performed by an *Aspect-2000* microcomputer. Instrumental settings: spectral width 50000 Hz (1025 ppm), 2 K data points, pulse width 33 μs, acquisition time 20 ms, preacquisition delay 5 μs, 1.4–2.3M scans, sample spinning (27 Hz). An even number (28–32) left-shifts (LS) were applied to the FID signal; the latter was zero-filled to 8 K words and exponentially multiplied with a 100-Hz line-broadening factor (LB) before being subjected to the FT. Chemical shifts $\delta(^{17}O)$ are reported rel. to $\delta(^{17}O)(H_2O)$ (= 0.0 ppm); dioxane ($\delta(^{17}O)$ = 0 ppm) was used as an external standard; downfield shifts are positive. The general reproducibility of chemical shift values is *ca.* ± 1 ppm (± 0.2 ppm within the same series).

Substrates. 1,3-Dimethyl[O^4-^{17}O]uracil and 1,3,6-Trimethyl[O^4-^{17}O]uracil were prepared by exchange: the corresponding unlabelled uracils were heated in sealed tubes for 15 h at 100° with $H_2{}^{17}O$ (10.2%, *ca.* 50 fold excess) and catalytic amounts of $SOCl_2$. The enriched compounds [^{17}O]-**1a,b** to [^{17}O]-**8a,b** were prepared from the enriched uracils as previously described [6].

3-(1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-[O^4-^{17}O]dioxopyrimidin-5-yl)propanamide ([^{17}O]-**6a**). A soln. of [^{17}O]-**3a** (90 mg) in CH_2Cl_2 (10 ml) at 0° was saturated with NH_3 gas and kept 10 min at r.t. After evaporation, the resulting solid was washed with CH_2Cl_2: 85 mg of [^{17}O]-**6a**. M.p. 192–194°. IR (KBr): 3380*vs*, 3200*s*, 1692*vs*, 1660*vs*, 1615*vs* (br. since associated with other bands at 1625–1610), 1335*s*, 783*s*, 765*s*, 750*s*. ^{1}H-NMR (CD_3CN): 7.33 (*t*, *J* = 0.7, H–C(6)); 6.25 (br., NH); 5.76 (br., NH); 3.38 (*s*, Me–N(1′)); 3.32 (*s*, Me–N(3′)); 2.61 (*m*, CH_2(3)); 2.44 (*m*, CH_2(2)). EI-MS: 213 (0.5, (^{18}O)M^+), 212 (1.4, (^{17}O)M^+), 211 (6, M^+), 194 (10), 166 (74), 153 (11), 111 (23), 110 (19), 97 (47), 95 (10), 83 (19), 82 (100), 69 (43), 68 (17), 61 (27), 59 (58), 58 (94), 57 (40), 56 (89).

3-(1,2,3,4-Tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidin-5-yl)propanamide (**6b**) was prepared as described for [^{17}O]-**6a**. M.p. 227–229°. IR (KBr): 3410*vs*, 3310*s*, 3205*s*, 1690*vs*, 1660*vs*, 1625vs, (br. since associated with other bands at 1636–1610), 1350*s*, 775*s*, 750*s*. ^{1}H-NMR (CD_3CN): 6.24 (br., NH); 5.63 (br., NH); 3.47 (*s*, Me–N(1′)); 3.34 (*s*, Me–N(3′)); 2.76 (*m*, CH_2(3)); 2.37 (*s*, Me–C(6′)); 2.34 (*m*, CH_2(2)). EI-MS: 225 (1, M^+). 208 (2), 207 (2), 180 (9), 167 (7), 153 (2), 112 (12), 110 (17), 97 (47), 96 (23), 95 (20), 84 (32), 82 (30), 72 (35), 69 (38), 68 (24), 61 (27), 59 (77), 57 (11), 56 (100).

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