MODIFIED URACILS CONVERTIBLE BETWEEN CATIONS, CONJUGATED, AND CROSS-CONJUGATED MESOMERIC BETAINES. SYNTHESES, SEMIEMPIRICAL STUDY, AND X-RAY ANALYSIS

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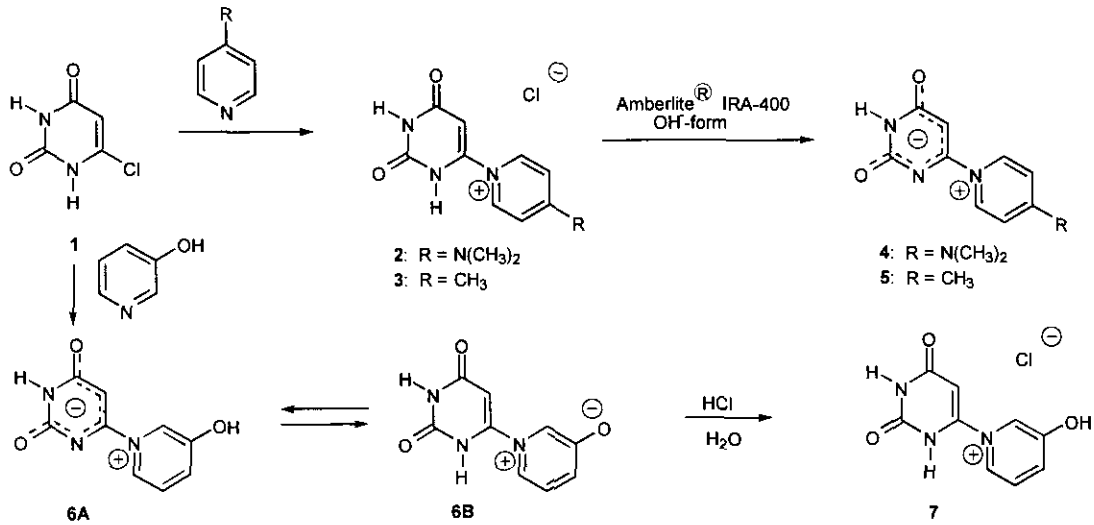
Abstract - Nucleophilic substitution on the 6-chlorouracils (**1**) and (**8**) by heteroaromatics such as DMAP, 4-methylpyridine, and 3-hydroxypyridine yielded uracilylpyridinium salts (**2**, **3**, **7**, **10**), mesomeric betaines (**4**, **5**, **6**), and a bis-betaine (**9**), respectively. A prototropic shift converts the CCMB (**6A**) into the CMB (**6B**), the dipole moments and most stable conformations of which were calculated. X-Ray crystallography was performed on the uracilylpyridinium salt (**7**).

Synthetic as well as mesomeric betaines isolated from natural sources[1] can be divided by their types of conjugation into four major classes, conjugated (CMB), cross-conjugated (CCMB), pseudo-cross-conjugated mesomeric betaines (PCCMB), and *N*-ylides.[2] Isoconjugate relationships lead to sixteen different subdivisions that are a fundamental base for the understanding of chemical and physical properties of those systems.[2] In continuation of our own work,[3] and in view of the current interest in the synthesis of modified uracils as active principles[4] as well as recently developed betaines with antiprotozoal and antibacterial activities,[5] we aimed at the preparation of uracilyl-betaines starting from 6-chlorouracil (**1**)[6] and 5-iodo-6-chlorouracil (**8**).[7] We chose heteroaromatics with different nucleophilicities for displacement of the chlorine atom, 4-(dimethylamino)pyridine, 4-methylpyridine, and 3-hydroxypyridine. The latter mentioned heteroaromatic is the well-documented partial structure of pyridinium-3-olates[8] that belong to the class of conjugated mesomeric betaines (CMB) isoconjugated with odd alternant hydrocarbon anions.

In order to find suitable reaction conditions for the synthesis of the target compounds, we tried an *in situ* interception of the leaving group Cl^- by stoichiometric amounts of sodium tetraphenylborate in ethyl acetate as well as by *Finkelstein*-type reaction conditions, *i.e.* sodium iodide in anhydrous acetone. However, decomposition to boron complexes and benzene occurred, and low yields were obtained, respectively, so that these approaches were abandoned. The substitution is best carried out using chlorobenzene (1 h, 132°C) as

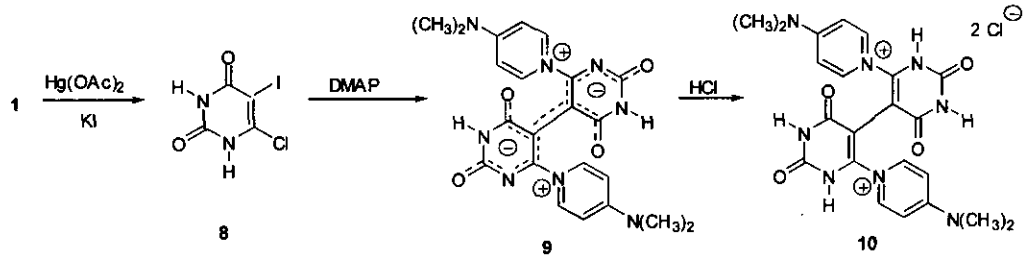
the reaction medium without any anion intercepting agent such as TMSOTf, $NaBPh_4$, $SbCl_5$, or NaI. Thus, the uracil-6-yl-pyridinium chlorides (**2**) and (**3**) were isolated in fair yields as beige solids.[9] Aqueous solutions of these salts were passed through the anion exchange resin Amberlite® IRA-400 that was previously converted into its hydroxy form. After evaporation of the elute *in vacuo*, the 6-pyridinio-2,4(1*H*,3*H*)-pyrimidinedionates (**4**) and (**5**)[9] were obtained in excellent yields and purities. Reaction of chlorouracil (**1**) with 3-hydroxypyridine was effected in chlorobenzene at reflux temperature and formed the grey mesomeric betaine (**6**) that can form two tautomers (**6A**) and (**6B**). Protonation with 15% hydrochloric acid gave the pyridinium salt (**7**), the structure of which was confirmed by X-Ray structure analysis (*vide infra*). In passing from the betaine (**6**) to the cation (**7**), the ^{1}H NMR resonance frequencies shift significantly downfield [*e.g.* $\Delta\delta$(5-H) = + 0.55 ppm].



Scheme 1

Surprisingly, the 5-iodo-6-chlorouracil (**8**) gave the bis-betaine (**9**) with excess DMAP in chlorobenzene under analogous reactions conditions (Scheme 2). The symmetric structure is reflected by eight signals in ^{13}C NMR spectroscopy. In accordance with the assigned structure, the DEPT spectra reveal substituted C-5 positions of the uracil moieties which are relatively shielded due to the delocalization of the negative charge. The EIMS spectra as well as the combustion analysis confirm that no iodine is present in the molecule. No deprotonation of **9** with Amberlite® IRA-400 could be accomplished so that a monocationic structure due to semiprotonation was eliminated from consideration. In contrast, protonation with 15% hydrochloric acid gave the corresponding salt (**10**) in nearly quantitative yield.

The mesomeric betaines (**4**), (**5**), and the bis-betaine (**9**) unambiguously are members of the class of cross-conjugated mesomeric betaines (CCMB) as even numbers of positive and negative charges are restricted to separate parts of common π-electron systems. Compound (**6**), however, can exist in two tautomeric forms that belong to distinct classes of mesomeric betaines, CCMB and CMB. The isoconjugate equivalents are



Scheme 2

even alternant hydrocarbon dianions and odd alternant hydrocarbon anions, respectively. The thermodynamically most stable type of conjugation could not be estimated *a priori*. Surprisingly, in DMSO-d_6 solution exclusively cross-conjugation is found so that **6** is observed as the CCMB 6-(3-hydroxypyridinio)-2,4(1*H*,3*H*)-pyrimidinedionate (**6A**). The charge-separation caused by cross-conjugation between the cationic and the anionic part of the molecule is in accord with characteristic downfield shifts of the pyridinium protons in ^{1}H NMR spectroscopy, and the signal of 5-H of the pyrimidine ring at 5.67 ppm. On addition of 50% of $CDCl_3$ to the DMSO-d_6 solution, however, approximately 13% of the conjugated tautomer (uracil-6-yl)pyridinium-3-olate (**6B**) is found, forming a multiplet at 7.13 ppm and an additional singlet at δ(5-H) = 5.65 ppm. Higher concentrations of $CDCl_3$ led to precipitation. Till now, very few examples of prototropic shift-induced conversions of molecules from one catagory of mesomeric betaine into an other have been presented.[10]

The tautomerism arose our interest in calculating the most stable conformation and the dipole moment of the CCMB (**6A**) and the CMB (**6B**), respectively. According to a PM3 calculation,[11,13] the CCMB is planar [ΔH_f(PM3) = -188.56 KJmol^{-1}] with the oxygen atom at a maximum distance from the lone pair at N(1) of the pyrimidine ring. The planarity can be readily explained by charge transfers *via* intramolecular π-interactions about the pyridinium - uracilate bond. Correspondingly, as common sites for either negative and positive charge within the pyridinium-3-olate ring exist, the CMB (**6B**) adopts a nonplanar conformation with the uracil and the pyridinium ring twisted by 121.00° [ΔH_f(PM3) = -221.49 KJmol^{-1}]. Surprisingly, the CMB (**6B**) is calculated to be 32.93 KJmol^{-1} more stable than the CCMB (**6A**) that - on the other hand - unambigously predominates more than approximately 95% in DMSO-d_6 solution. The aforementioned solvent effect on the tautomeric equilibrium can be understood taking the high polarity of DMSO [E_T^N = 0.444; Z = 71.1 kcalmol^{-1}; ε_r = 46.45; $\mu/10^{-30}$ = 13.5 Cm] and the exceptionally great dipole moment of the CCMB (**6A**) ($\mu/10^{-30}$ = 49.5 Cm[14]) into consideration. On decreasing the polarity of the solvent by addition of the apolar solvent $CDCl_3$ [E_T^N ($CHCl_3$) = 0.259; Z = 63.2 kcalmol^{-1}; ε_r = 4.81; $\mu/10^{-30}$ = 3.8 Cm], the concentration of the CMB increases. In well accord, the dipole moment of (**6B**) is relatively small, 12.5 × 10^{30} Cm.[14] The most stable conformations of **6A** and **6B** are presented in Figure 1. The magnitudes and directions of the dipole moments are illustrated by arrows.[15] Obviously, prototropic transformation of the CCMB into the CMB results in dramatic changes in the polarization of the molecule.

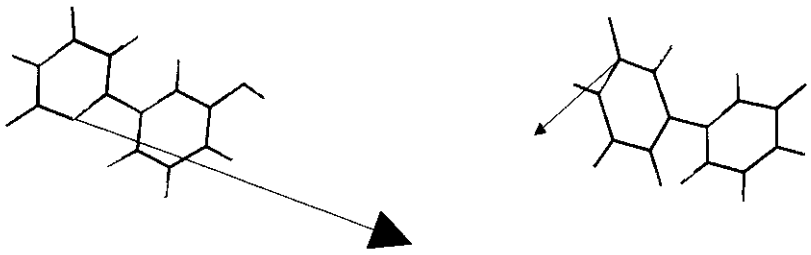


Figure 1. Most stable conformation (PM3) and dipole moment of CCMB **6A** (left) and CMB **6B** (right).

For unambiguous structure elucidation, we performed a X-Ray structure analysis of the uracil-6-yl-pyridinium chloride (**7**).[16] Monoclinic crystals were obtained by slow evaporation of a concentrated solution of **7** in 15% hydrochlorid acid. In the crystal, the salt adopts a nonplanar conformation with the 3-hydroxypyridinium ring twisted by 126.8(1)° [N(1)-C(6)-N(7)-C(8)] from the pyrimidine plane, and this finding is very similar to the calculated conformation of the CMB (**6B**). The ORTEP plot and the unit cell are shown in Figure 2 and some selected bond lengths and angles are given in Table 1. The three exchangeable protons at N(1), N(3) and O(9) form hydrogen bonds to the chloride gegenions, the bond distances and angles of which are presented in Table 2. No hydrogen bonds between different cations of **7** are detectable.

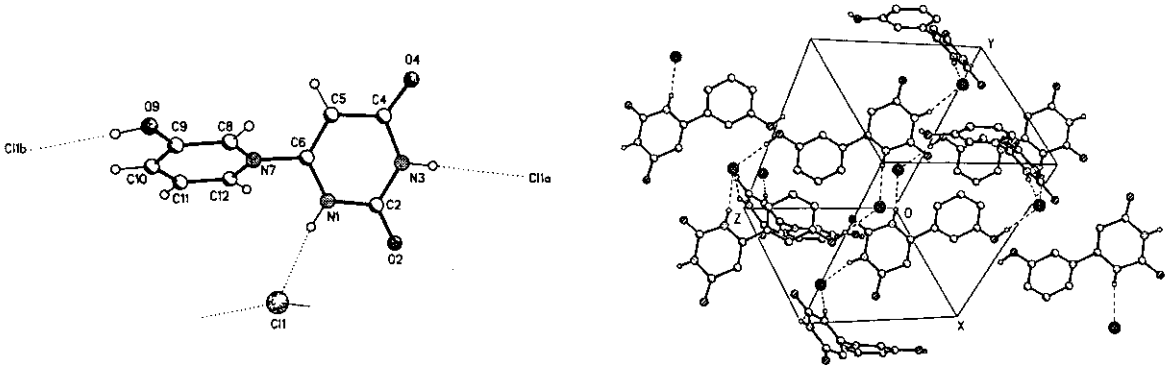


Figure 2

Table 1. Atom Nos. / Selected bond lengths [pm], bond angles [°], and torsion angles [°] of **7**.

N(1)-C(2)	137.43(13)	N(1)-C(2)-N(3)	114.32(9)	C(6)-N(1)-C(2)-O(2)	177.92(10)
C(2)-N(3)	137.61(14)	C(2)-N(3)-C(4)	127.11(9)	N(3)-C(4)-C(5)-C(6)	0.25(15)
N(3)-C(4)	138.83(14)	N(3)-C(4)-C(5)	114.80(9)	O(4)-C(4)-C(5)-C(6)	-179.77(11)
C(4)-C(5)	145.30(15)	C(6)-C(5)-C(4)	117.83(10)	C(4)-C(5)-C(6)-N(7)	179.68(9)
C(5)-C(6)	133.37(15)	C(5)-C(6)-N(7)	121.59(9)	C(5)-C(6)-N(7)-C(8)	-54.15(13)
C(6)-N(7)	144.59(13)	C(8)-N(7)-C(6)	118.55(8)	N(1)-C(6)-N(7)-C(8)	126.81(10)
C(9)-O(9)	133.85(13)	N(7)-C(8)-C(9)	119.25(10)	N(7)-C(8)-C(9)-O(9)	178.36(9)
N(7)-C(12)	135.95(14)	O(9)-C(9)-C(8)	116.91(10)	C(8)-C(9)-C(10)-C(11)	-0.37(18)

Table 2. Hydrogen bonds of **7**: Distances [pm] and angles [°].

D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
N(1)-H(1)···Cl(1)	85.0(11)	231.4(11)	315.50(9)	170.1(12)
N(3)-H(3)···Cl(1)#1	85.3(12)	259.1(12)	335.46(10)	149.6(12)
O(9)-H(9)···Cl(1)#2	85.6(13)	218.6(13)	304.28(9)	178.6(14)

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9. Selected physical and spectroscopic features (melting points are uncorrected, NMR spectra were measured in DMSO-d_6 unless otherwise noted; values are given in ppm downfield from TMS): **2**, yield: 41% from **1**, mp > 300°C (EtOH, H_2O), ^{1}H NMR: δ = 3.30 (s, 6H), 5.97 (s, 1H, H/D exchangeable), 7.17 (d, J = 8.1 Hz, 2H), 8.42 (d, J = 8.1 Hz), 11.53 (s, 1H, H/D exchangeable); **3**, yield 39 % from **1**, mp 275°C (EtOH, H_2O), ^{1}H NMR: δ = 2.72 (s, 3H), 6.10 (s, 1H), 8.63 (d, J = 6.6 Hz, 2H), 9.21 (d, J = 6.6 Hz, 2H), 11.25 (s, 1H); **4**: yield 95% from **2**, mp > 300°C (H_2O), ^{1}H NMR: δ = 3.53 (s, 6H), 5.53 (s, 1H), 7.05 (d, J = 8.1 Hz, 2H), 8.76 (d, J = 8.1 Hz, 2H), 9.75 (s, 1H); **5**: yield 95% from **3**, > 279°C (decomp, H_2O), ^{1}H NMR: δ = 2.68 (s, 3H), 5.75 (s, 1H), 8.03 (d, J = 6.6 Hz, 2H), 9.32 (d, J = 6.6 Hz, 2H), 10.17

(s, 1H), ^{13}C NMR: δ = 27.61, 87.51, 127.80, 140.40, 157.21, 159.12, 162.11, 166.24, IR: 3102.5, 2987.5, 1674.9, 1627.1 cm^{-1}; **6**: yield 45% from **1**, > 117°C (decomp, EtOH, H_2O), ^{1}H NMR of **6A**: δ = 5.67 (s, 1H), 7.96 (dd, J = 8.6/5.9 Hz, 1H), 8.06 (ddd, J = 8.6/2.4/1.2 Hz, 1H), 8.89 (d, J = 2.4/1.3 Hz, 1H), 8.91 (ddd, J = 5.9/1.3/1.2 Hz, 1H), 10.06 (br s, 1H), OH not detectable; ^{1}H NMR signals of **6B** in DMSO-d_6/$CDCl_3$: δ = 5.65 (d, J = 1.5 Hz, 1H), 7.13 (m, 4H); **7**: yield 100% from **6**, > 252°C (decomp, EtOH, H_2O), ^{1}H NMR: δ = 6.22 (s, 1H), 7.06 (br s, OH), 8.13 (dd, J = 8.8/5.9 Hz, 1H), 8.35 (ddd, J = 8.8/2.0/0.5 Hz, 1H), 8.78 (d, J = 5.9 Hz, 1H), 8.88 (dd, nonresoluted, 1H), 11.53 (br s, 1H), 11.67 (br s, 1H); **9**: yield 31% from **8**, mp > 300°C (EtOH, H_2O), ^{1}H NMR: δ = 3.32 (s, 6H), 7.07 (d, J = 8.1 Hz, 2H), 8.41 (d, J = 8.1 Hz, 2H), 10.35 (s, 1H), ^{13}C NMR : δ = 40.25, 92.23, 106.56, 140.51, 156.26, 156.42, 156.83, 162.32; **10**: yield 95% from **9**, mp > 300°C (EtOH, H_2O), ^{1}H NMR: δ = 3.32 (s, 6H), 7.29 (d, J = 8.1 Hz, 2H), 8.39 (d, J = 8.1 Hz, 2H), 12.08 (s, 1H), ^{13}C NMR: δ = 40.38, 103.71, 107.58, 140.52, 145.08, 148.81, 159.69.

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11. Calculations were carried out using MOPAC 6.0[12] on a CONVEX 3440. The structures were first optimized with the default gradient requirements and subsequently refined with the options EF DMAX = 0.1, GNORM = 0.1, SCFCRT = 1×10^{-6}. The absolute minima were proved with a force calculation.
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14. Given is the total moment (Σ) in Cm, the vectorial sum of the dipole moments on the x, y, and z axes: [x-axis, C(2)-N(1), y-axis, rectangular on x and z, origin C(2); z-axis, rectangular to the uracil-plane]; **6A**: 14.834, 0.248, 0.004, Σ = 14.836 Debye; **6B**: -1.296, 1.650, -3.116, Σ = 3.757 Debye.
15. The following program was used for the illustration: StrukEd, Bruker-Franzen Analytik GmbH, Fahrenheitstrasse 4, D-28359 Bremen, Germany, Version 950801.
16. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-108450. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Some crystal data of **7**: $C_9H_8N_3O_3Cl$; M = 241.63; space group $P2_1/n$ (no. 14); dimensions 0.50 x 0.25 x 0.20 mm^3, a = 7.8856(4), b = 14.0523(5), c = 9.4706(4) Å; β = 104.029(2)°; V = 1018.14(8) Å^3, D_c = 1.576 MG m^{-3}, Z = 4, μ(MoKα) = 0.370 mm^{-1}; T = 123(2) K; F(000) = 496, 15661 reflections were collected in a Nonius KappaCCD diffractometer ($2\Theta_{max.}$ = 56.4°, $-10 \le h \le 10$, $-18 \le k \le 17$, $-12 \le l \le 12$), 2505 symmetry independent reflections (R_{int} = 0.0295) were used for the structure solution (direct methods)[17] and refinement (full-matrix least-squares on F^2,[18] 154 parameters, 3 restraints), non-hydrogen atoms were refined anisotropically, H atoms localized by difference electron density, aromatic hydrogen atoms were refined using a riding model, other free; wR2 = 0.078 [R1 = 0.028 for 2801 $I > 2\sigma(I)$].
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