Synthesis of Self-Complementary Betainic Guanine Model Compounds

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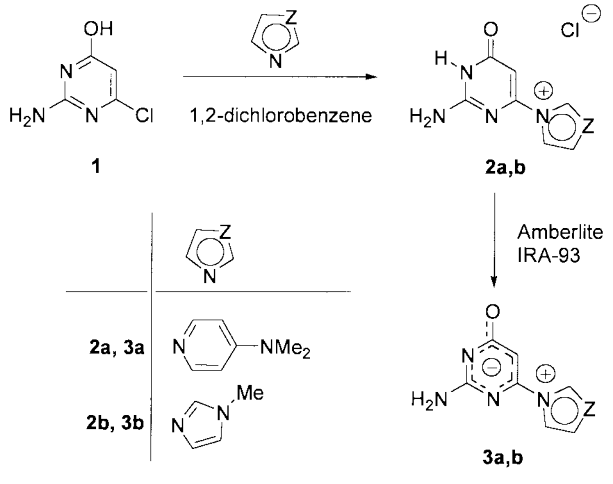
Reaction of 4-(dimethylamino)pyridine and 1-methylimidazole, respectively, on 2-amino-4-chloro-6-hydroxypyrimidine resulted in the formation of pyrimidine-heteroarenium salts. These could be deprotonated using anion exchange resin to yield pyridinium-pyrimidinolates as model compounds for biologically highly important betainic guanines present in RNA. As proved by ESIMS, these cross-conjugated mesomeric betaines are self-complementary and form homo-intermolecular dimers.

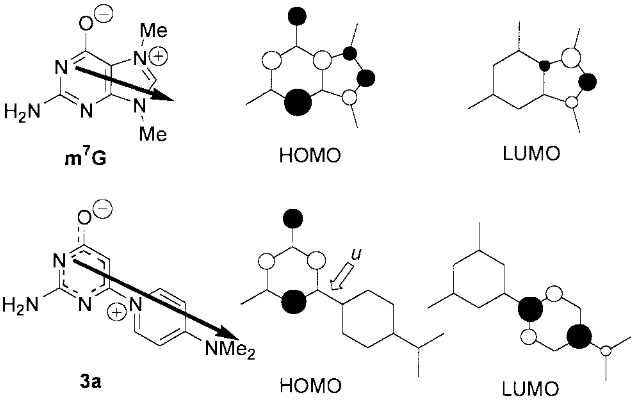
During the recent years, much interest has been paid to naturally occurring mesomeric betaines due to the biological and pharmacological activities of this class of compounds. Whereas dozens of betainic alkaloids have been isolated from biological sources,[1] only few natural betainic nucleobases are known to date.[2] Among these, 7-methylguanine, a conjugated mesomeric betaine (CMB), plays by far the most important biological role. Identified as modified nucleobase present in transfer RNA,[3] it was also identified as 5'-terminal capping structure of messenger RNA (mRNA).[4] Numerous efforts has been devoted to the elucidation of its biological function. Obviously, it is involved in the molecular recognition of the mRNA to the binding protein on the surface of the ribosome prior to the initiation of translation.[5] Among the extraordinary properties of 7-methylguanine and model compounds, its self-complementary at physiological pH, its mutagenicity, and its properties to induce base mispairing are worth-mentioning.[6] In general, mesomeric betaines are divided into four major classes (conjugated, cross-conjugated, pseudo-cross-conjugated, ylidic).[7] Nothing is known to date about the influence of the type of conjugation on molecular recognition and biological activity. In continuation of our work on mesomeric betaines[8] we present here our first results of a systematic investigation on self-complementary guanine model compounds and their base-pairing properties.

Nucleophilic substitution of 4-(dimethylamino)pyridine and 1-methylimidazole, respectively, on 2-amino-4-chloro-6-hydroxypyrimidine **1** in boiling 1,2-dichlorobenzene resulted in the formation of the (2-amino-4-oxopyrimidin-6-yl)heteroarenium chlorides **2a,b** in 75% and 82% yield, respectively. Deprotonation of **2a,b** in aqueous ethanol using Amberlite® IRA-93 in its hydroxy form gave the yellow colored mesomeric betaines 2-amino-6-[4-(dimethylamino)pyridinio]pyrimidin-4-olate **3a** and 2-amino-6-(3-methylimidazolio)pyrimidin-4-olate **3b** in nearly quantitative yields, respectively. On deprotonation, the resonance frequencies of 5-*H* of the pyrimidine moiety shifts characteristically from δ = 6.14 ppm (**2a**) to 5.57 ppm (**3a**) and the NH-signal at 11.85 ppm (DMSO-d_6) disappears. According to the NMR spectra, the salts **2a,b** exist as single NH-tautomers.



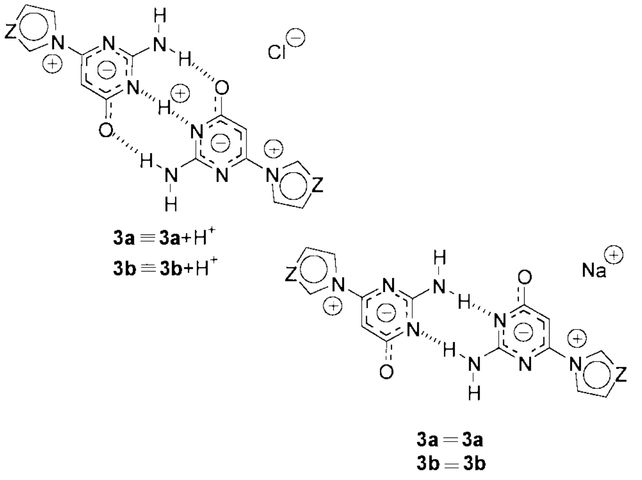
Scheme 1.

In contrast to the naturally occurring 7-methylguanine (m^{7}G) which is a conjugated mesomeric betaine (CMB), the planar compounds **3a,b** are cross-conjugated (CCMB). Nevertheless, the geometry of the binding site of m^{7}G and **3a,b** as well as the HOMO in the pyrimidine rings are closely related and make **3a,b** excellent model compounds for the study of charge-effects on the molecular recognition of this biologically important compound. Thus, as a consequence of the charge-separation in the ground state which is due to the characteristic union ("u") of the molecule to a nodal position of the HOMO of the anionic fragment, the betaines **3a,b** possess a high permanent dipol moment that differs in size and direction from the natural analogue 7-methylguanine.[9] The results of PM3 calculations are given in Scheme 2.[10–12]



Scheme 2.

In order to elucidate the base-pairing properties of the betaines **3a,b** and of their cationic precursors in comparison to 7-methylguanine, we performed electrospray ionization mass spectrometry (ESIMS) of aqueous solutions in MeCN at fragmentor voltages between 0 and 100 V. The extremely mild ES ionization technique enables the detection of charged species and their hydrogen bonded associates. As expected, the mass spectrum of e.g. **3a** displays peaks at *m/z* = 232.1 (**3a**+H$^+$; 14%) and 254.1 (**3a**+Na$^+$, 8%). The homo-intermolecular associate between two semiprotonated betaines **3a≡3a**+H$^+$ forms the base peak at *m/z* = 463.3 (100%) at fragmentor voltages between 0 and 30 V (Scheme 3). A dimeric, non-protonated betaine **3a=3a** was detected as sodium adduct at *m/z* = 485.2 (5%). As shown in Scheme 3, three hydrogen bonds are possible in **3a≡3a**+H$^+$ forming a centrosymmetric dimer, whereas the betaine dimerizes to **3a**=**3a** through two hydrogen bonds. Analogous results were obtained in ESIMS experiments of the imidazolium derivative **3b** and its precursor **2b**.[13]

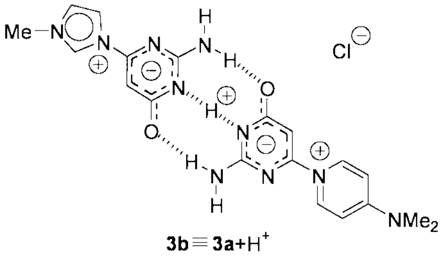


3a≡3a+H$^+$
3b≡3b+H$^+$

3a=3a
3b=3b

Scheme 3.

Furthermore, a 1:1-mixture of the pyridinium compound **3a** and the imidazolium derivative **3b** in water form hydrogen-bonded dimers **3a≡3b**+H$^+$ which are detectable by ESIMS in MeCN (*m/z* = 423.3; 100%) (Scheme 4).



3b≡3a+H$^+$

Scheme 4.

It is apparent, that all dimerizations presented here and in our previous paper on uracils[14] result in coupling or cancelling of the permanent dipole moments of the monomeric species, so that molecular recognition of the model nucleobases seems to be dependent on the type of conjugation. These results gain insight into the important biological function of 7-methylguanine and encourage the design of novel nucleobase receptor molecules.

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References and Notes

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9 μ(m^{7}G) = 9.2 D, μ(**3a**) = 18.0 D.

10 PM3 calculations[11] 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 = 0.05, GNORM = 0.01 and SCFCRT = 1×10^{-15}. The absolute minima were proved with a force calculation.

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13 Peaks were found at *m/z* = 192.1 (**2b**), 383.1 (**2b≡3b**), 405.2 (**3b**=**3b**+Na$^+$).

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