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Guanine hydrolysis under basic conditions to substituted imidazoles

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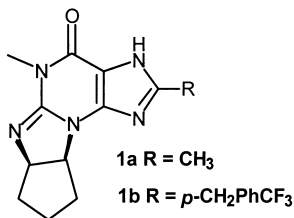
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Abstract

First base induced opening of multicyclic guanines to isolable substituted imidazoles, and possible mechanism for this observation are described. © 2000 Elsevier Science Ltd. All rights reserved.

Guanines, such as SCH 47687 (**1a**)¹ and 51866 (**1b**)² are potent phosphodiesterase (PDE) inhibitors. Guanines have been reported to be stable upon exposure to hot alkali³ and hence are often prepared by cyclizing properly substituted imidazoles or pyrimidines under basic conditions.⁴ We report here the first example of base induced hydrolysis of certain guanines to the isolation of substituted imidazoles. Note that substituted guanadines such as thymidines, 2-amino pyrimidinones, or uracil which have similar subunit as guanines, hydrolyze in base without undergoing opening of the six-member ring.^{5,6}



During the course of our work towards the preparation of **1b**, it was noticed that it was unstable to aqueous NaOH. To understand the cause of this instability, **1b** was heated in the presence of aqueous NaOH until it was consumed. Upon extractive work-up a solid was isolated. Elemental analysis and mass spectral data suggested that this solid derived from the addition of a molecule of water to **1b**. Although the TLC and HPLC suggested this solid was a single new

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entity, the 400 MHz ^1H NMR, at 25°C, appeared complex. Hence a detailed NMR,⁷ and MS⁸ study was undertaken to establish the structure of the isolated solid. Analysis of the data determined that the structure of the compound isolated from basic hydrolysis of **1b** is **2b**. The complexity of the NMR is consistent with potential intramolecular hydrogen bonding associated with this structure (Fig. 1).

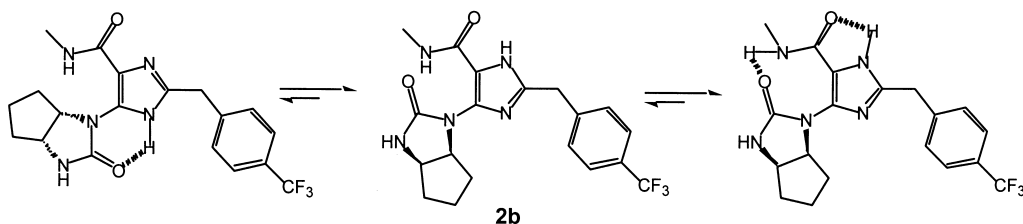
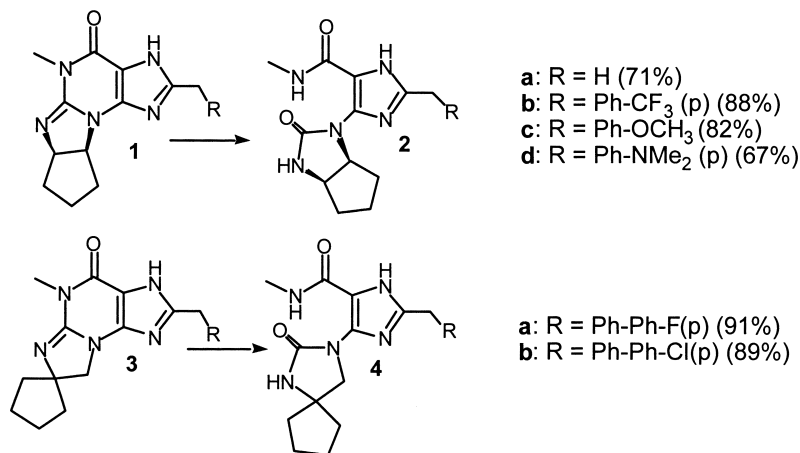


Figure 1. Potential hydrogen bonding in **2b**

The mass spectral fragmentation pattern is also consistent with this structure. No polymorph could be obtained, for either **2b**, or several other substituted imidazoles described later in this manuscript, that was suitable for X-ray crystallography. This observation could be a result of the hydrogen bonding potential in these compounds resulting in a co-crystallize in a variety of forms. The above hydrolysis is not limited to compound **1b**. Several related tetracyclic as well as spirocyclic guanines underwent similar hydrolysis to generate substituted imidazoles (Scheme 1). In all cases, the hydrolysis generated only one product. A result consistent with the mechanism proposed later in this manuscript, and based on the NMR data as well as specific rotations, i.e. the chiral guanines **1a–d** led to chiral products **2a–d**.

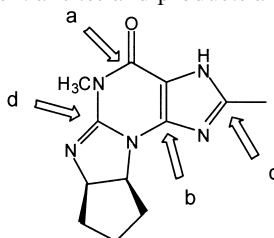


Scheme 1. Hydrolysis of guanines to substituted imidazoles: (% yield)⁹

The formation of imidazoles during the above reaction is interesting. In-process HPLC and TLC analyses, as well as analyses at the end of reactions, all of the Scheme 1 guanines indicated the formation of only the substituted imidazoles **2a–d** or **4a–b**. The hydrolysis of **1a**, under basic conditions, could have occurred at positions a, b, c, or d (Table 1). These four pathways include:

(a) 1,2 nucleophilic addition of hydroxide ion at the carbonyl carbon leading to imidazole **5**; (b) 1,4 addition of hydroxide ion at the ring carbon leading to compounds **6**, **7**, or **8**; (c) nucleophilic addition of hydroxide ion at the imine carbon leading to the pyrimidines **9**, **10**; and (d) nucleophilic addition of hydroxide ion at the guanidine carbon leading to compounds **14** and **15**, and more importantly, imidazole **2a**.

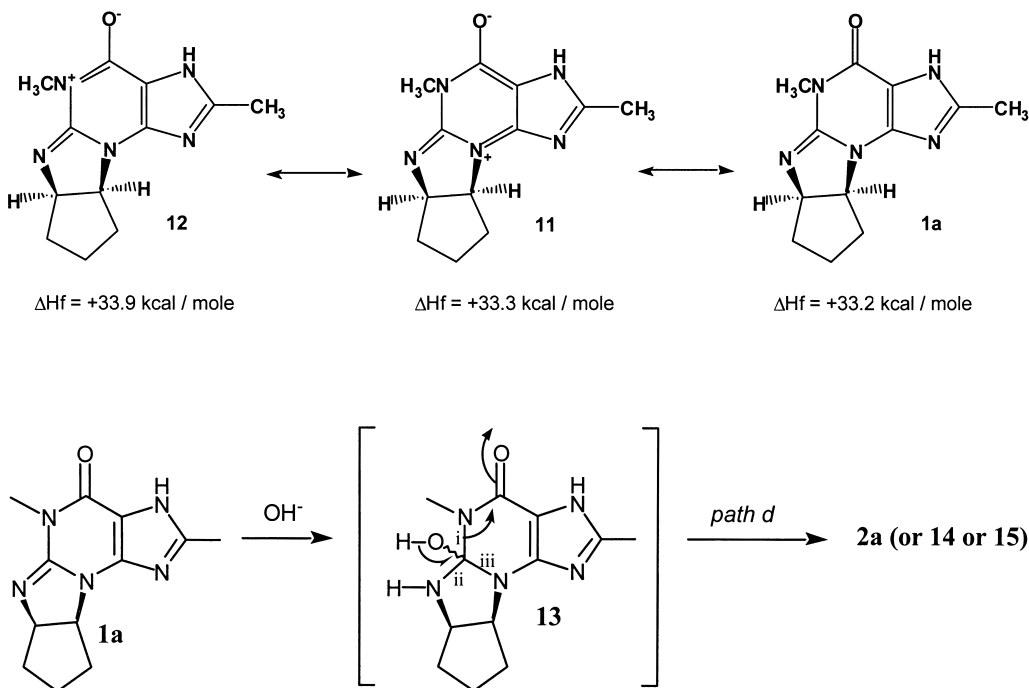
Table 1
Hydrolysis of **1a**: potential sites and products and ΔH_f values



Path: a	b	c	d
5	6	9	14
-37.7 kcal	-26.9 kcal	-48.1 kcal	-41.6 kcal
	7	10	15
	-27.7 kcal	-44.6 kcal	-43.8 kcal
	8		2a
	-28.2 kcal		-46.1 kcal

Since no chemical methods were available for deciphering the precise mechanism operative for the conversion of the guanines to the imidazoles, a computational approach was applied.¹⁰ For this purpose, the simplest guanine SCH 47687, **1a**, was chosen as a model substrate. AM1 was used to calculate the heat of formation (ΔH_f) of each product arising from hydrolysis at the various positions (Table 1). The calculated heats of formation suggest that the hydrolysis products derived from pathways a and b are thermodynamically less stable relative to those obtained via pathways c and d.

The electronic structure of **1a** includes a contribution from canonical forms **11** and **12**. Contributions from resonance structures **11** and **12** could lower the susceptibility of the molecule to 1,2 or 1,4 nucleophilic addition and enhance the electrophilicity of the guanidine carbon. The proposed mechanism involves initial attack at the guanidine carbon (Scheme 2). Cleavage of bond **i-iii** would yield the products from reaction manifold **d** (Table 1). Among the three potential products **2a** was observed exclusively, suggesting the thermodynamic stability of the final products determined the cleavage pathway **i**.



Scheme 2. Proposed mechanism for hydrolysis of guanines to imidazoles

Thermodynamically stable imidazoles **2a-d**, or **9a-b**, in their imide form under alkaline reaction conditions, rule out the possibility of any further nucleophilic attack. The stability of these imidazoles was further evident in the fact that **2b** could not be converted to **1b** under acid catalyzed conditions, i.e. refluxing toluene, catalytic pTSA, several days.

In summary, hydrolysis of multicyclic guanines under basic conditions to isolable trisubstituted imidazoles, and a probable mechanism for this finding are described.

Acknowledgements

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7. Proton NMR spectrum of **2b** in DMSO-*d*₆ at 25°C had NH protons at δ 12.5 (imidazole), amide (CONH) protons at δ 7.71 and 8.21, and cyclic amide proton at δ 7.0 and 7.30. The remainder protons were as follows: δ 7.48, 7.69 (aromatic), δ 4.80, 4.92 (CHN), δ 4.18 (CHNH), δ 4.05 (benzylic CH₂), δ 2.72 (d~4.5 Hz, CH₃), and δ 1.60 (m, CH₂×3). NMR spectra obtained at higher temperatures (40, 65 and 80°) appeared increasingly simpler. Finally at 80°C, the complexity of the spectrum diminished significantly, and it became readily interpretable. For example, only three NH resonances appeared at δ 12.3, 8.05, and 6.90. The signals emanating from CHN proton merged at δ 4.80. These observations are consistent with hydrogen bonding and rotational isomers around N-C=O (i.e. O=C-NH-CH₃) bonds. Proton COSY and NOESY spectra in DMSO-*d*₆ at 40°C were consistent with the structure **2b**. Furthermore NH proton resonances exchanged with D₂O. ¹³C NMR spectra for **2b** was in DMSO-*d*₆ (at 50°C) was also in agreement with the proposed structure with the following resonances: δ 129.3 (=CH×2), δ 125.2 (=CH×2), δ 62.4 (CHN), δ 53.8 (CHNH), δ 34.8, 33.6, 32.0, 22.1 (all CH₂'s), δ 25.6 (CH₃), δ 159.9 (C=O), 159.6 (C=O), 144.9, 142.7, 135.0, 119.0 (all quaternary carbons), δ 127.2 (=C-CF₃), and δ 124.3 (CF₃). This structure was further confirmed by proton spectra in CDCl₃ at 25°C. Similarly, NMR data for the rest of the compounds were also consistent with the assigned structures. For example: for compound **2a** the NMR data (DMSO-*d*₆, 25°C) was as follows: ¹H NMR: δ 1.3–1.75 (m, CH₂×3); δ 2.30 (CH₃), δ 2.71 (d, J = 4.5 Hz, NHCH₃), δ 4.18 (m, CHNH), δ 4.80 (m, CHN), δ 6.19, 7.13 (br, NH). ¹³C NMR (DMSO-*d*₆, 25°C): δ 12.9 (CH₃), δ 25.5 (HNCH₃), δ 22.0, 31.8, 34.6 (CH₂×3), δ 55.9, 62.0 (CHN, CHNH), δ 120.3, 131.1, 142.5 (all quaternary carbons), 158.9 (C=O), 159.7 (C=O).
8. FABMS led to parent ion peak at 408 (M+H)⁺. Three prominent fragment ions were observed: *m/z* 377 (MH–NH₂CH₃)⁺; 351 (MH–CONCH₃)⁺; and 159 (CH₂PHCF₃)⁺. The first fragment is possible only for structure **2b** out of all possibilities listed in Table 1. The following high resolution measurements were also performed: *m/z* 408, C₁₉H₂₁O₂N₅F₃, measured 408.1630, calculated 408.1647; *m/z* 377, C₁₈H₁₆O₂N₄F₃, measured 377.1217, calculated 377.1225; *m/z* 351, C₁₇H₁₈ON₄F₃, measured 351.1429, calculated 351.1433.
9. All are unoptimized isolated yields. Isolated yields for **2a** and **2d** are low due to their water solubility. Typical experimental procedure: The guanines either as a free base or as their salts were heated at 90°C for two to six days in 10% aq. NaOH without any additional solvent. After cooling to ~5°C, the reaction mixtures were extracted with EtOAc followed by CH₂Cl₂ to separate the products. In the case of compound **2a**, the reaction mixture was carefully concentrated under vacuum (to minimize sublimation of the product) and then extracted with *i*-PrOH to isolate the product. Spirocyclic imidazoles **9a–b** were isolated by mere filtration of the cooled reaction mixture.
10. The aqueous base catalyzed hydrolysis of SCH 47687, **1a**, were investigated using the molecular mechanics and semiempirical quantum mechanics methods. The objective was to understand the mechanism of hydrolysis and provide support for the proposed pathway to the final hydrolysis product. Molecules were built using the molecular construction tools in Sybyl or Spartan. The structures then underwent a preliminary minimization using the Sybyl MAXIMIN force field. These intermediate structures were then subjected to a full geometry optimization using the AM1 (aq.) method in the Spartan program. The parameter set modifies the basic AM1 method to simulate energies in an aqueous medium. The energies reported reflect the result of these calculations. The calculations were repeated using the generic AM1 parameters (in vacuo) and the conclusions are qualitatively similar. In molecules with significant conformational flexibility the lowest energy conformations were determined in a two step procedure. Available conformations were generated using the Random Search (Saunders procedure; 1000 Monte Carlo steps) within Sybyl. The conformers generated were then minimized using the Sybyl MAXIMIN force field. The lowest energy conformation resulting from each conformational search was then subjected to a second geometry optimization using the modified AM1 (aq.) method) and these represent the reported energies of the lowest energy conformer identified. The relative energies of the imidazole tautomers of all reactants and potential products were compared. Although small energy differences between tautomers were observed in no case did this affect conclusions regarding reaction pathway or product distribution.