Table I. Thermochemical Data of Enols 1–9

entry	enol	ΔH_f^0(ion)[a]	IE, eV	ΔH_f^0(neutral)[a] exptl	ΔH_f^0(neutral)[a] MNDO	ΔH_f^0(enol–oxo)[b]	ΔH_r[a]
1	CH_2=CHOH	758[c]	9.18[d]	−128	−146[e]	38	54
2	CH_2=C(OH)CH_3	661[f]	8.67[g]	−176	−179[e]	42	70
3	(*E*)-CH_3CH=CHOH	665[f]	8.64[h]	−169	−187[e]	23	64
4	(*Z*)-CH_3CH=CHOH	665[f]	8.70[h]	−174	−186	18	68
5	(*E*)-CH_2=CHCH=CHOH	733[i]	8.51[i]	−88	−89[i]	19[j] (−8)[k]	72
6	(*Z*)-CH_2=CHCH=CHOH	728[i]	8.47[i]	−90	−87[i]	17[j] (−10)[k]	74
7	CH_2=CHC(OH)=CH_2	761[l]	8.68[m]	−77	−73	35	61
8	HC≡CC(OH)=CH_2	944[n]	8.92[n]	83	77	33	78
9	(*Z*)-OHCH=CHOH	516[o]	8.62[o]	−316	−355	2	62

[a] kJ·mol^{-1}; the uncertainty in the ionic heats of formation is within 5–10 kJ·mol^{-1}. Standard deviations in ionization energy measurements are 2–3 kJ·mol^{-1}. [b] Positive values mean that the enol is less stable than the corresponding oxo form. [c] Reference 21. [d] Reference 13b. [e] Reference 22. [f] Reference 23. [g] Reference 13c. [h] Reference 13d. [i] Reference 13g. [j] Referred to (*E*)-2-butenal.[1] [k] Referred to the estimated[1,2] ΔH_f^0 of 3-butenal. [l] Reference 24. [m] Reference 13e. [n] Reference 13f. [o] Reference 25.

Table II. Estimated ΔH_f^0 (kJ • mol^{-1}) for Enols 10–15

entry	enol	ΔH_f^0	ΔH_f^0 (enol–keto)
10		−26	*a*
11		−59	31[b]
12		−57	33[b]
13		−27	
14	CH_3C(OH)=CHCOCH_3	(−352)	(26)[c]
15	CH_3C(OH)=CHCOOCH_3	(−524)	(35)[d]

[a] The experimental ΔH_f^0 of cyclobutanone is unknown. [b] Referred to the estimated[1,2] ΔH_f^0 of 2-cyclopenten-1-one. [c] Referred to the ΔH_f^0 of pentane-2,4-dione.[2] [d] Referred to the estimated[2] ΔH_f^0 of methyl acetoacetate.

crepancy is probably due to the known failure of MNDO[14] to evaluate correctly hydrogen bonds.

In contrast to the enol–oxo isomerism, placing the hydroxyl group onto a double bond has invariantly a *stabilizing* effect, as also predicted by high-level ab initio calculations.[17] The estimated enthalpy changes in isodesmic reactions[18] (Scheme I, ΔH_r in Table I) oscillate around 67 ± 7 kJ·mol^{-1} and show that the enolic hydroxy group can be treated as an entity in the sense of Benson's rules.[1,2] Thence we calculate the corresponding term for the O–(C_d)(H) group as −202 ± 6 kJ·mol^{-1}, which is somewhat lower than reported earlier on the basis of ionization energies of **1** and **2** (−186 kJ·mol^{-1}).[12] The revised value can be utilized for predicting the heats of formation of other enols, especially those which are at present hardly accessible by standard synthetic procedures.[9,10] (Table II).

Cyclobutenol (**10**) is estimated to be substantially less stable than **7**, and it would isomerize to the latter dienol via symmetry-allowed conrotatory ring opening.[19] By contrast, MNDO calculations predict **10** to be more stable than **7** (ΔH_f^0 (**10**) = −84 kJ·mol^{-1}). This discrepancy with the additivity-based estimate is probably due to the underestimation of ring strain in **10**, a known feature of the MNDO method.[26]

Hydroxycyclopentadienes **11**–**13** would be difficult to prepare by thermolytic methods as distinct isomers, because of rapid 1,5-suprafacial hydrogen migration across the ring.[27] The estimated ΔH_f^0 values for the isomers indicate that the dienols **11** and **12** are of comparable stability, while being more stable than the hydroxy diene **13** in which the hydroxyl is located outside the diene system (Table II). This is consistent with the stabilization of the double bonds by attachment of the hydroxy group.[17] MNDO calculations yield ΔH_f^0 (**12**) = −60 kJ·mol^{-1} in good agreement with the additivity-based prediction (Table II).

The limits of applicability of Benson's rules are crossed with the stable[20] enols **14** and **15** for which the group additivity scheme predicts substantial destabilization against pentane-2,4-dione and methyl acetoacetate, respectively (Table II). This disagreement points to a stabilizing long-range interaction in the enols, e.g., a strong intramolecular hydrogen bond, which is not taken into account by the additivity principle.[1] Further experiments are needed to clarify this point.

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Synthesis of *proximal*-Benzoguanine and a Simplified Synthesis of *proximal*-Benzohypoxanthine

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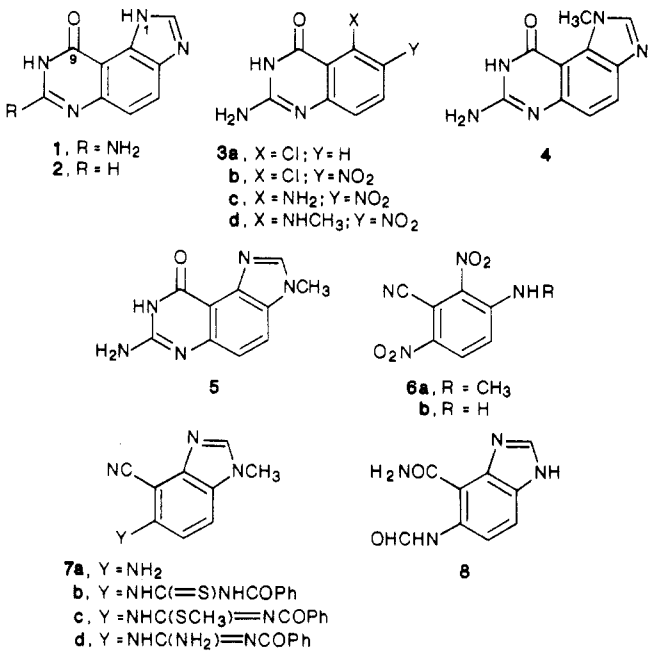
Benzo-separated purines and purine nucleosides have been used to analyze the binding domains of purine-utilizing or metabolizing enzymes.[1] These studies have produced many benzo-separated systems.[1-6] However,

Chart I



proximal-benzoguanine (**1**) has not been previously reported. The synthesis of **1** together with a simplified preparation of *proximal*-benzohypoxanthine (**2**),[3] which arose during this work, is described here.

Ring closure of 2-amino-6-chlorobenzamide[7] with chloroformamidine hydrochloride afforded **3a**. Nitration of **3a** gave **3b** which, upon amination, was converted into **3c**. Catalytic hydrogenation of **3c** in formic acid yielded a formylated derivative which, following treatment with ammonia, resulted in **1**. Due to the insoluble nature of **1**, it was characterized as its dihydrochloride.

Steric considerations of the N-1/C-9 region of **1** indicate that if enzymatic ribosylations occur, the N-3 ribonucleosides or nucleotides are likely to result. In substantiation of this conclusion, methylation of **1** was found to yield only one product. For assignment of the structure of this product, **3b** was treated with methylamine. The resultant product (**3d**) was then subjected to catalytic hydrogenation in formic acid followed by cyclization and deformylation with ammonia to produce **4**. The spectral and physical properties of **4** were found to be different from the methylation product of **1** which was, then, assumed to be the anticipated **5**.

Structural confirmation of **5** began with the oxidative cyanation[8] of *N*-methyl-2,4-dinitroaniline[9] to give **6a** as the only isolable product under the conditions used. Catalytic hydrogenation of **6a** in ethanol followed by reaction with triethyl orthoformate and aqueous workup formed **7a**. Adapting a method reported[10] for preparing fused 2-aminopyrimidin-4-ones, treatment of **7a** with benzoyl *iso*thiocyanate afforded **7b**. Subsequent S-methylation of **7b** with methyl iodide produced **7c** which, without full characterization, was transformed into the benzoylguanidino derivative **7d** with ammonia. Upon reaction with base, **7d** became **5** via debenzoylation, ring closure, and hydrolysis of the resultant fused 2,4-diaminopyrimidine. The **5** prepared by this method was identical in all respects with the product obtained by methylation of **1**.

While the synthesis of **5** from **6a** was being conducted, it was found that catalytic hydrogenation of **6b**[8] in formic acid gave **2** directly, possibly by ring closure of **8**. Compound **8** could have arisen from a reduction–imidazole ring closure–formylation–hydration process. No methylation studies (analogous to the **1** to **5** conversion) were carried out on **2** since its structural similarity to **1** suggested N-3 as the likely site for enzymatic ribosylation.

Experimental Section

General Methods. All melting points were obtained on a Thomas-Hoover or a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman AccuLab 3 spectrophotometer using potassum bromide disks. The ^{1}H NMR spectra were determined at 60 MHz with a Varian EM-360 spectrometer and are reported in parts per million downfield from Me_4Si as an internal standard. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), m (multiplet), and br (broad). Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

2-Amino-5-chloroquinazolin-4(3*H*)-one (3a). A mixture of 1 g (5.86 mmol) of 2-amino-6-chlorobenzamide,[7] 0.8 g (6.95 mmol) of freshly prepared chloroformamidine hydrochloride[11] and 1 g of Me_2SO_2 was heated for 1 h at 160 °C in an open flask with magnetic stirring. Water was added to the solid mass and, following warming this mixture, NH_4OH was added until neutralization was achieved. The white solid that resulted was isolated by filtration (1.15 g, 5.86 mmol, 100%), dried, and used as **3a** without purification in the next step: mp 321–325 °C dec (lit.[12] mp 321–325 °C dec); ^{1}H NMR (Me_2SO-d_6) δ 6.6 (br s, 2 H, NH_2), 7.3 (m, 3 H, Ar), 8.0 (br s, 1 H, NH).

2-Amino-5-chloro-6-nitroquinazolin-4(3*H*)-one (3b). A mixture of 29 g (0.148 mol) of **3a** and 145 mL of concentrated H_2SO_4 was cooled to −10 °C, and to this, under mechanical stirring, was added, dropwise, 5.8 mL of fuming HNO_3. The addition was done at such a rate that the reaction temperture did not exceed −10 °C. Following the addition, the mixture was allowed to warm to room temperature and was then heated on a steam bath for 10 min. At this point, the mixture was poured (with stirring) over 1 kg of ice, and the precipitated material was isolated by filtration, washed in sequence with 1 L of H_2O and 500 mL of Et_2O, and recrystallized from DMF to give the desired **3b** (34.9 g, 0.145 mol, 100%)[13] as light yellow crystals: mp >355 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.45 (d, $J_{7,8}$ = 8 Hz, 1 H, H-8), 7.85 (br s, 2 H, NH_2), 8.2 (d, $J_{7,8}$ = 8 Hz, 1 H, H-7). Anal. Calcd for $C_8H_5ClN_4O_3 \cdot {}^1/_2$DMF: C, 41.17; H, 3.09; N, 22.74. Found: C, 41.00; H, 3.05; N, 22.62.

2,5-Diamino-6-nitroquinazolin-4(3*H*)-one (3c). A mixture of 1 g (4.15 mmol) of **3b** and 10 mL of absolute 1-butanol, which had been saturated with anhydrous NH_3 at room temperature, was heated at 180 °C for 24 h in a stainless steel reaction vessel. The vessel was cooled to −20 °C for 1 h prior to opening. The resulting precipitate was isolated by filtration, washed with ab-

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solute EtOH followed by Et_2O, and then recrystallized from Me_2SO to give **3c** (0.9 g, 4.07 mmol, 98%) as yellow needles: mp >355 °C dec; ^1H NMR (Me_2SO-d_6 at 128 °C) δ 6.1 (d, $J_{7,8}$ = 8 Hz, 1 H, H-8), 6.9 (br s, 4 H, 2 NH_2), 7.9 (d, $J_{7,8}$ = 8 Hz, 1 H, H-7), 8.9 (br s, 1 H, NH). Anal. Calcd for $C_8H_7N_5O_3 \cdot {}^1/_2Me_2SO$: C, 41.54; H, 3.87; N, 26.91. Found: C, 41.75; H, 3.92; N, 26.98.

7-Aminoimidazo[4,5-*f*]quinazolin-9(8*H*)-one (*proximal*-Benzoguanine, 1). To a suspension of 4.25 g (19.2 mmol) of **3c** in 300 mL of 97% formic acid, under a stream of N_2, was added 0.89 g of 10% Pd/C. The mixture was then shaken under 52 psi of H_2 for 2 h. After filtering to remove the catalyst, the dark red filtrate was refluxed under N_2 for 2 h. The excess formic acid was evaporated in vacuo and to the residue was added 50 mL each of toluene and 97% formic acid. After refluxing this mixture for 1 h under N_2, the solvents were again removed in vacuo. To the resultant residue was added 50 mL of toluene which was then evaporated in vacuo to give a tan solid. This solid was placed in 150 mL of NH_3 saturated EtOH in a tightly sealed vessel. After being stirred overnight, the contents were transferred to a round-bottomed flask and the solvent removed on a rotary evaporator. The gray residue was dissolved in boiling 1 M HCl, decolorized with charcoal, neutralized with NH_4OH, and allowed to cool. The white precipitate that resulted was isolated by filtration, washed with H_2O, EtOH, and petroleum ether (30–60 °C), and dried to give 2.27 g (11.2 mmol, 58%) of crude **1**. A purified sample of **1** was prepared by refluxing the crude product in HCl-saturated EtOH for 24 h to give its insoluble dihydrochloride salt: mp >390 °C dec; IR 3400–3200 cm^{-1} (NH), 1650 (C=O); ^1H NMR (Me_2SO-d_6) δ 6.35 (br s, 2 H, NH_2), 7.0 (d, $J_{4,5}$ = 8 Hz, 1 H, H-4 or H-5), 7.85 (d, $J_{4,5}$ = 8 Hz, 1 H, H-4 or H-5), 8.05 (s, 1 H, H-2), 12.0 (br s, 1 H, NH). Anal. Calcd for $C_9H_7N_5O \cdot 2HCl$: C, 39.44; H, 3.31; N, 25.55. Found: C, 39.36; H, 3.48; N, 25.35.

7-Amino-3-methylimidazo[4,5-*f*]quinazolin-9(8*H*)-one (5). A mixture of 0.8 g (2.9 mmol) of **1**·2HCl, 25 mL of 2 N NaOH solution, and 1 g (7.05 mmol) of MeI was refluxed in an oil bath at 60 °C. At 10-min intervals, three 1-g portions of MeI were added and the refluxing was continued for 24 h. A precipitate formed which was isolated by filtration, washed with H_2O and EtOH, and dried to give 0.6 g of a white solid. This solid was placed in 100 mL of HCl-saturated absolute EtOH and refluxed for 24 h. The insoluble dihydrochloride which resulted was isolated by filtration to give 0.6 g (2.08 mmol, 72%) of analytically pure material: mp 306–308 °C dec; IR 3400–3200 cm^{-1} (NH), 1650 (C=O); ^1H NMR (Me_2SO-d_6) δ 3.5 (s, 3 H, CH_3), 6.9 (br s, 2 H, NH_2), 7.0 (d, $J_{4,5}$ = 8 Hz, 1 H, H-4 or H-5), 7.9 (d, $J_{4,5}$ = 8 Hz, 1 H, H-4 or H-5), 8.1 (s, 1 H, H-2), 12.6 (br s, 1 H, NH). Anal. Calcd for $C_{10}H_9N_5O \cdot 2HCl$: C, 41.69; H, 3.85; N, 24.31. Found: C, 41.38; H, 3.83; N, 24.20.

An alternative synthetic route to **5** from **7b** is described later.

2-Amino-5-(methylamino)-6-nitroquinazolin-4(3*H*)-one (3d). To 5.75 g (23.9 mmol) of **3b** in a stainless steel reaction vessel was added, at room temperature, 50 mL of methylamine-saturated 1-butanol. The vessel was sealed and heated in an oil bath at 130 °C for 24 h. After cooling to room temperature and placing in a freezer for 1 h, the reaction vessel was opened, and the contents were rinsed into a beaker with absolute EtOH. The resulting solid was isolated by filtration, washed with EtOH and petroleum ether (30–60 °C), and dried to give 5.61 g (23.8 mmol, 100%) of pure **3d**: mp 300 °C dec; IR 3400–3200 cm^{-1} (NH), 1650 cm^{-1} (C=O); ^1H NMR (Me_2SO-d_6) δ 2.6 (d, J = 6 Hz, 3 H, CH_3), 6.3 (d, $J_{7,8}$ = 8 Hz, 1 H, H-8), 6.9 (br s, 2 H, NH_2), 7.9 (d, $J_{7,8}$ = 8 Hz, 1 H, H-7), 9.8 (br d, J = 6 Hz, 1 H, NH), 11.5 (br s, 1 H, NH). Anal. Calcd for $C_9H_9N_5O_3$: C, 45.96; H, 3.86; N, 29.78. Found: C, 46.05; H, 4.00; N, 29.59.

7-Amino-1-methylimidazo[4,5-*f*]quinazolin-9(8*H*)-one (4). To a suspension of 0.5 g (2.13 mmol) of **3d** in 70 mL of 97% formic acid was added, under a stream of N_2, 0.17 g of 10% Pd/C. The mixture was shaken under 52 psi of H_2 for 2 h, filtered to remove the catalyst, and then refluxed under N_2 for 2 h. After in vacuo evaporation of the excess formic acid, 35 mL each of toluene and 97% formic acid were added to the residue, and this mixture was refluxed for 1 h under N_2. The solvents were again removed in vacuo to give a tan solid to which 50 mL of NH_3-saturated absolute EtOH was added. This mixture was stirred in a sealed vessel. Isolation of the resulting precipitate by filtration followed by aqueous and ethanolic washings gave 0.4 g (1.86 mmol, 87%) of **4** after drying: mp 300 °C dec; IR 3480–3300 cm^{-1} (NH), 1650 (C=O). The analytical sample was prepared by refluxing the product in HCl-saturated EtOH for 24 h to give an insoluble dihydrochloride salt: mp 285–287 °C dec; ^1H NMR (Me_2SO-d_6)[14] δ 4.29 (s, 3 H, CH_3), 7.4 (d, $J_{4,5}$ = 10 Hz, 1 H, H-4 or H-5), 8.09 (d, $J_{4,5}$ = 10 Hz, 1 H, H-4 or H-5), 8.57 (s, 1 H, H-2). Anal. Calcd for $C_{10}H_9N_5O \cdot 2HCl$: C, 41.69; H, 3.85; N, 24.31. Found: C, 41.61; H, 3.98; N, 24.05.

3-(Methylamino)-2,6-dinitrobenzonitrile (6a). To a solution of *N*-methyl-2,4-dinitroaniline[9] (3.33 g, 16.9 mmol) in 250 mL of MeOH, which was vigorously stirred and heated at 55 °C, was added a solution of potassium ferricyanide (30 g, 91.1 mmol) in 150 mL of H_2O and of potassium cyanide (5.2 g, 79.9 mmol) in 30 mL of H_2O separately and dropwise such that the addition of both solutions was completed simultaneously. After further stirring for 6 h at 55 °C, the reaction mixture was poured into 1 L of ice water. The resulting precipitate was isolated by filtration, washed with H_2O, and allowed to dry to give 1.6 g (7.2 mmol, 43%) of crude **6a** which was purified by recrystallization from EtOH: mp 168–170 °C; IR 2250 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ 2.92 (d, J = 4 Hz, 3 H, CH_3), 7.21 (d, $J_{4,5}$ = 10 Hz, 1 H, H-4 or H-5), 8.02 (br s, 1 H, NH), 8.28 (d, $J_{4,5}$ = 10 Hz, 1 H, H-4 or H-5). Anal. Calcd for $C_8H_6N_4O_4$: C, 43.25; H, 2.72; N, 25.22. Found: C, 43.62; H, 2.79; N, 24.82.

5-Amino-1-methylbenzimidazole-4-carbonitrile (7a). In a hydrogenator bottle was placed 1 g (4.5 mmol) of **6a**, 30 mL of absolute EtOH, and a catalytic amount of 10% Pd/C. After shaking for 2 h under 52 psi of H_2, the catalyst was removed by filtration and the filtrate refluxed for 2 h after 10 mL of triethyl orthoformate was added. The solvents were removed by distillation and to the residue was added 25 mL of H_2O. After refluxing this new mixture for 2 h, the solvent was evaporated in vacuo and the residue dissolved in absolute EtOH. Petroleum ether (60–110 °C) was added to cause a gummy material to form. The mixture was transferred to another flask and evaporated to dryness to give a yellow-organge gum. When H_2O was added to the gum accompanied by scratching of the flask, a yellow-tan solid formed, which was isolated by filtration and sublimed at 170 °C/1 mmHg to give 0.16 g (0.92 mmol, 20.4%) of **7a**: mp 172–175 °C; IR 2250 cm^{-1} (CN); ^1H NMR (Me_2SO-d_6) δ 3.72 (s, 3 H, CH_3), 5.77 (br s, 2 H, NH_2), 6.68 (d, $J_{6,7}$ = 8 Hz, 1 H, H-6 or H-7), 7.49 (d, $J_{6,7}$ = 8 Hz, 1 H, H-6 or H-7), 8.0 (s, 1 H, H-2). Anal. Calcd for $C_9H_8N_4$: C, 62.78; H, 4.68; N, 32.54. Found: C, 62.62; H, 4.72; N, 32.52.

5-[(*N*-Benzoyl(thiocarbamoyl))amino]-1-methylbenzimidazole-4-carbonitrile (7b). To a stirred suspension of 0.5 g (2.9 mmol) of **7a** in 10 mL of H_2O was added, dropwise, 0.5 g (3.06 mmol) of benzoyl isothiocyanate. Stirring was continued at room temperature for 24 h. The resulting precipitate was isolated by filtration, washed with H_2O, and dried to give 0.96 g (2.86 mmol, 98.6%) of **7b** as a light yellow solid which was recrystallized from ethanolic DMF: mp 210–211 °C dec; ^1H NMR (Me_2SO-d_6) δ 3.89 (s, 3 H, CH_3), 7.42–8.1 (d over m, 7 H, Ar), 8.42 (s, 1 H, H-2). Anal. Calcd for $C_{17}H_{13}N_5OS$: C, 60.83; H, 3.90; N, 20.86. Found: C, 60.65; H, 3.98; N, 20.82.

7-Amino-3-methylimidazo[4,5-*f*]quinazolin-9(8*H*)-one (5) from 7b. To a mixture of 0.5 g (1.49 mmol) of **7b** in 22 mL of 0.1 N NaOH solution was added 0.26 g (1.83 mmol) of MeI. This mixture was stirred for 24 h and then acidified to pH 6 (litmus) with glacial AcOH. The resulting precipitate was isolated by filtration, washed with H_2O and EtOH, and dried to give a crude yield of 0.38 g (1.09 mmol, 73%) of 5-[(*N*-benzoyl-*S*-methyl(isothiocarbamoyl))amino]-1-methylbenzimidazole-4-carbonitrile (**7c**) as a light yellow solid which was recrystallized from MeOH and used directly in the next step without complete characterization: mp 186 °C; ^1H NMR (Me_2SO-d_6) δ 3.83 (s, 3 H, CH_3), 3.9 (s, 3 H, CH_3), 7.35–8.02 (d over m, 7 H, Ar), 8.46 (s, 1 H, H-2).

To a solution of 50 mL of DMF containing 2% NH_3 was added 2 g (5.72 mmol) of **7c**, and this mixture was heated at 120 °C for 2 h in a stainless steel reaction vessel. After 1 h in the freezer, the vessel was opened and the odor of methanethiol noted. The solution was evaporated to dryness under reduced pressure and the resulting residue was recrystallizerd from aqueous DMF to

(14) The ^1H NMR spectrum of the dihydrochloride of **4** was obtained on a JEOL FX90Q spectrometer using Me_4Si as an internal standard.

give 0.54 g (1.69 mmol, 28.5%) of 5-(*N*-benzoylguanidino)-1-methylbenzimidazole-4-carbonitrile (**7d**) which was used directly in the next step without complete characterization: mp >365 °C with darkening beginning at 300 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.96 (s, 3 H, CH_3), 7.39–8.10 (d over m, 7 H, Ar), 8.4 (s, 1 H, H-2).

A suspension of 0.2 g (0.63 mmol) of **7d** in 5 mL of 1 N NaOH solution was refluxed for 3 h and then acidified to pH 6 with AcOH. After the precipitate was isolated by filtration, washed with H_2O, and dried, it was suspended in 50 mL of HCl-saturated EtOH and refluxed for 2 h. The resulting precipitate was obtained by filtraton, washed with absolute EtOH, and dried to give 0.13 g (0.6 mmol, 98%) of a product whose NMR, IR, TLC, and mmp characteristic indicated it to be identical with the dihydrochloride of **5** obtained by methylation of **1**.

Imidazo[4,5-*f*]quinazolin-9(8*H*)-one (*proximal*-Benzohypoxanthine, 2). A mixture of 4 g (19.2 mmol) of **6b**,[8] 300 mL of 97% formic acid, and 0.89 g of 10% Pd/C (added under a stream of N_2) was shaken under an initial pressure of 50 psi of H_2. When the pressure dropped to 40 psi, the mixture was filtered to remove the catalyst and the filtrate refluxed for 10 h under N_2. The excess formic acid was then evaporated in vacuo and to the residue was added 100 mL of a 1:1 mixture of toluene and 97% formic acid. This new mixture was refluxed for another 10 h under N_2 and the solvents were again removed in vacuo. The solid residue was placed in 250 mL of NH_3-saturated EtOH and stirred for 28 h in a sealed vessel. The contents were transferred to a flask and evaporated to dryness on a rotary evaporator. The residue was then recrystallized from H_2O to give 1 g (5.37 mmol, 28%) of **2** as white needles: mp >400 °C dec (lit.[3] mp >320 °C); IR 1650 cm^{-1} (C=O); ^{1}H NMR (Me_2SO-d_6) δ 7.43 (d, $J_{4,5}$ = 8 Hz, 1 H, H-4 or H-5), 8.05 (d, $J_{4,5}$ = 8 Hz, 1 H, H-4 or H-5), 8.1 (s, 1 H, H-2 or H-7), 8.14 (s, 1 H, H-2 or H-7). Anal. Calcd for $C_9H_6N_4O$: C, 58.07; H, 3.25; N, 30.09. Found: C, 57.89; H, 3.34; N, 30.11.

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Registry No. 1, 103884-21-5; 1·2HCl, 103884-30-6; **2**, 53449-52-8; **3a**, 50440-85-2; **3b**, 103884-19-1; **3c**, 103884-20-4; **3d**, 103884-23-7; **4**, 103884-24-8; **4**·2HCl, 103884-31-7; **5**, 103904-06-9; **5**·2HCl, 103884-22-6; **6a**, 103884-25-9; **6b**, 26808-08-2; **7a**, 103884-26-0; **7b**, 103884-27-1; **7c**, 103884-28-2; **7d**, 103884-29-3; 2-amino-6-chlorobenzamide, 54166-95-9; chlorformamidine hydrochloride, 29671-92-9; *N*-methyl-2,4-dinitroaniline, 2044-88-4; benzoyl isothiocyanate, 532-55-8.

Frontier-Orbital Interactions in the Reaction of 5-Nitropyrimidine with Electron-Rich Olefins. An Example of Superjacent Orbital Control[1]

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In a previous paper it has been reported that the electron-rich olefin 1,1-dimorpholinoethene (**1**) reacts with the electron-poor 5-nitropyrimidine (**2**) in a Diels–Alder reaction with inverse electron-demand.[2,3] In this reaction the 1,4-cycloadduct **3** is postulated as intermediate, being formed by linking $C_{1'}$ and $C_{2'}$ of the olefin to N_1 and C_4, respectively, of the pyrimidine ring. Loss of morpholine and hydrogen cyanide leads to the formation of 2-morpholino-5-nitropyridine (**4**). Neither NMR evidence for the intermediary existence of the cycloadduct **3** has been obtained nor any indication for the formation of isomeric morpholinonitropyridines, excluding the cycloadducts **5**, **6**, or **7** as intermediates.

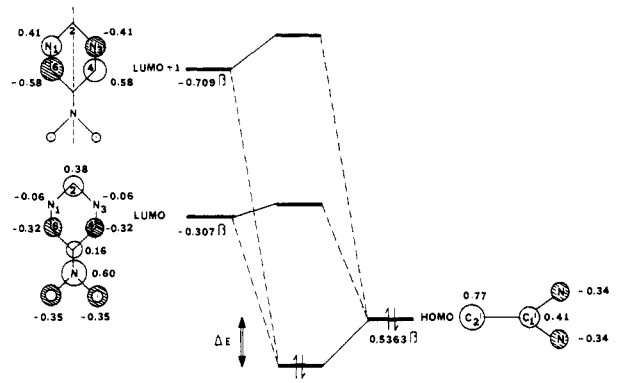
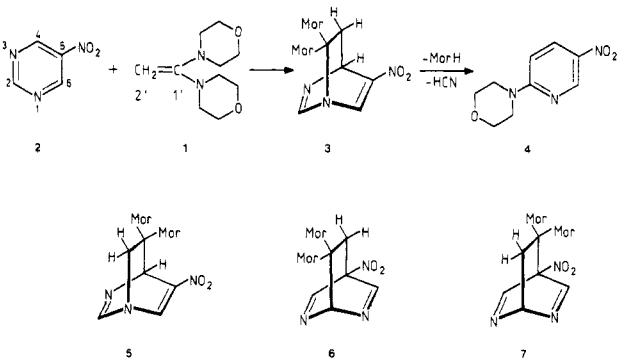


Figure 1.

Scheme I



In order to get a better understanding why the 1,4-cycloaddition takes place *regiospecifically*, i.e., addition across C_4 and N_1 of the pyrimidine ring and not across C_2 and C_5, and why the formation of adduct **3** is favored to **5**, we calculated the stabilization energy ΔE, resulting from interaction between the frontier molecular orbitals of **1** and **2** upon approach in various orientations expected to lead to formation of **3**, **5**, **6**, or **7**.

Results and Discussion

Regiospecificity. It is well established that the outcome of [2π + 4π] cycloaddition reactions can, in general, be predicted by consideration of the HOMO and LUMO coefficients in the "electron-rich" and the "electron-poor" reactant, respectively.[4] Since 5-nitropyrimidine (**2**) evidently constitutes the electron-poor reactant, the problem to predict the regiospecificity of the present reaction seemed limited to finding the two position (i.e., 1,4 (= 3,6) or 2,5) with the largest LUMO coefficients in **2**.

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