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.

Acknowledgment. We thank Dr. William J. Christ for considerable preliminary work which facilitated the present study and Ms. Ellen Salcines for assisting in obtaining the ^{1}H NMR spectrum of the dihydrochloride of **4**.

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.

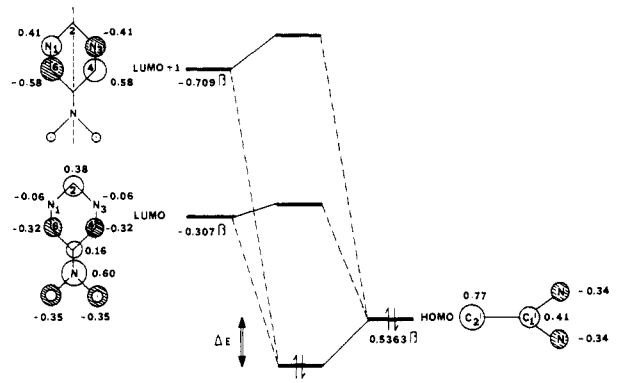
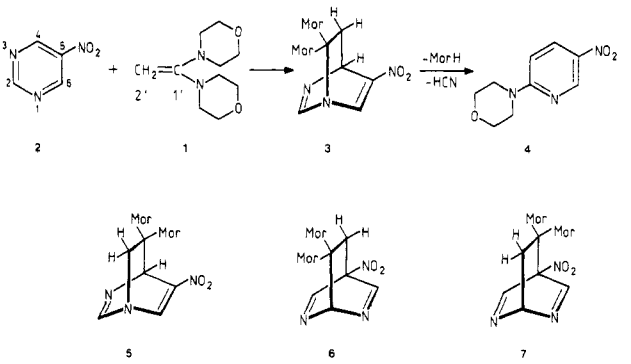


Figure 1.

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**.

(1) Ring transformation of Heterocycles with Nucleophilic Reagents. 34. For 33, see: Marcelis, A. T. M.; van der Plas, H. C.; *J. Org. Chem.* **1986**, *51*, 67.

(2) Charushin, V. N.; van der Plas, H. C. *Tetrahedron Lett.* **1982**, *23*, 3965.

(3) Charushin, V. N.; van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 373.

(4) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley and Sons: London, 1976.

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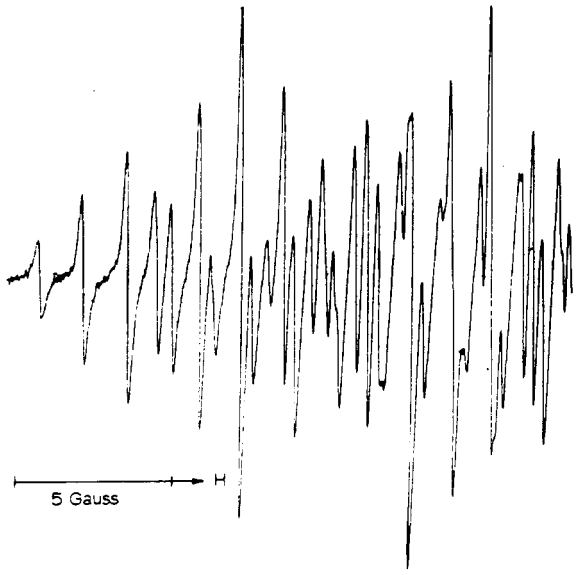
EXPERIMENT



SIMULATION

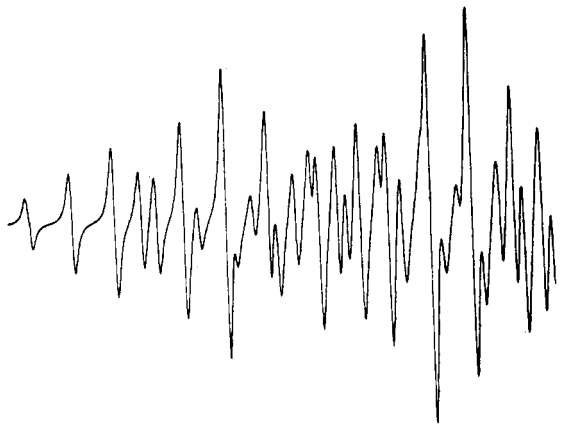


Figure 2.

Table I. Parameters Used To Simulate the ESR Spectrum of $2^{-\bullet}$ [a,b]

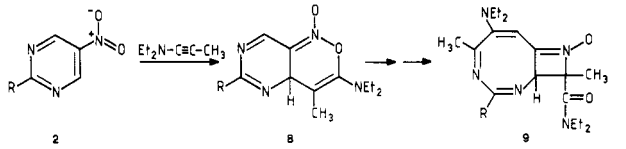
$a_N(N_1,N_3)$ = 1.40 G	$a_H(H_4,H_6)$ = 3.69 G
$a_N(NO_2)$ = 6.80 G	$a_H(H_2)$ = 8.10 G

[a] Line shape "Lorentzian". [b] Line width 180 mG.

Simple HMO calculations using standard parameters[5] indicate the presence of a low-lying LUMO (E_{LUMO} = $\simeq 0.3072\beta$) with the orbital coefficients depicted in Figure 1. The next unoccupied level (LUMO + 1) is found at considerably higher energy and displays a nodal plane through C_2 and C_5 (see Figure 1).

(5) The Hückel parameters used to calculate the FMO coefficients and energies of 1 and 2 were taken from: Streitwieser, A. *Molecular Orbital Theory for Organic Chemists*; Wiley: New York, 1961. $\alpha_N = \alpha_c + 1.5\beta$; $\alpha_O = \alpha_c + 1.0\beta$; $\alpha_N = \alpha_c + 0.7\beta$ instead of $\alpha_N = \alpha_c + 0.5\beta$ (as suggested by Streitwieser) was found to give better results. One of the referees suggested to use the consistent set of parameters published by Van Catledge, F. A. *J. Org. Chem.* **1980**, *45*, 4801. The ΔE values then obtained are $\Delta E_{2,2'/5,1'} = 0.20$; $\Delta E_{1,2'/4,1'} = 0.61$, and $\Delta E_{1,1'/4,2'} = 0.77$. These values are in nice agreement with our results and confirm the trend $\Delta E_{1,1'/4,2'} > \Delta E_{1,2'/4,1'} > \Delta E_{2,2'/5,1'}$.

Scheme II



Experimental verification of the calculated LUMO coefficients was achieved by studying the ESR spectrum (see Figure 2) of the radical-anion $2^{-\bullet}$, generated via electrochemical reduction (cf. Experimental Section). Simulation of the experimental spectrum (see Figure 2) was accomplished with the hyperfine coupling constants compiled in Table I. These data confirm the qualitative correctness of the LUMO coefficients derived by HMO calculation. Thus the large LUMO coefficient at C_2 in **2** is nicely substantiated by the large value of aH_2 in the radical-anion.[6] This may seem to enforce the prediction that a Diels–Alder-type cycloaddition between **2** and electron-rich olefins will occur across C_2 and C_5 but this prediction is refuted by the exclusive N_1,C_4 addition observed experimentally!

The reason for this uncommon failure of the simple HOMO/LUMO argument becomes clear upon further analysis of the frontier orbital interaction diagram depicted in Figure 1. Within the framework of first-order perturbation theory the total stabilization energy (ΔE) can be written as the sum of the HOMO/LUMO and HOMO/(LUMO + 1) perturbation energies:[4]

$$\Delta E \sim \frac{2(c_{1'}a_x + c_{2'}a_y)^2}{E_{HOMO} - E_{LUMO}} + \frac{2(c_{1'}b_x + c_{2'}b_y)^2}{E_{HOMO} - E_{(LUMO+1)}} \quad (1)$$

In eq 1 $c_{1'}$ and $c_{2'}$ are the HOMO coefficients of 1 at $C_{1'}$ and $C_{2'}$. The labels x and y indicate the atoms in **2** across which addition occurs, while a and b stand for the LUMO and LUMO + 1 coefficients at these positions. For addition across C_2, C_5 the second term in (1) vanishes ($b_x = b_y = 0$). The largest stabilization for this mode of addition is gained if $C_{2'}$ approaches C_2, while $C_{1'}$ approaches C_5. This gives

$$\Delta E_{2,2'/5,1'} \sim \frac{2(0.38 \times 0.77 + 0.16 \times 0.41)^2}{0.843} = 0.30$$

For addition across N_1,C_4 the two possible modes of addition lead to

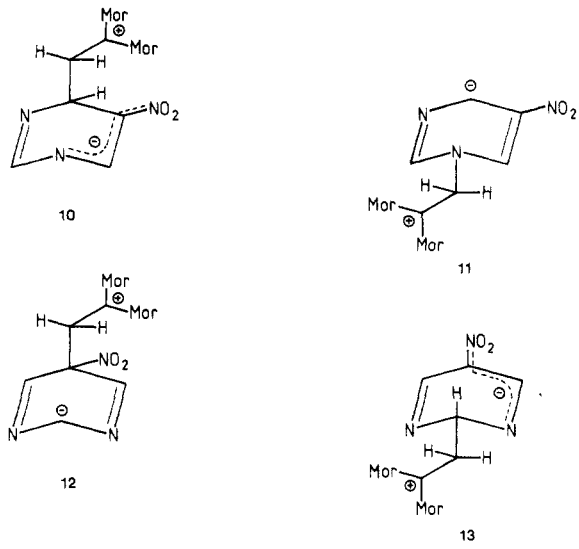
$$\Delta E_{1,2'/4,1'} \sim \frac{2(-0.06 \times 0.77 - 0.32 \times 0.41)^2}{0.843} + \frac{2(-0.41 \times 0.77 - 0.58 \times 0.41)^2}{1.245} = 0.0746 + 0.492 = 0.57$$

$$\Delta E_{1,1'/4,2'} \sim \frac{2(-0.06 \times 0.41 - 0.32 \times 0.77)^2}{0.843} + \frac{2(-0.41 \times 0.41 - 0.58 \times 0.77)^2}{1.245} = 0.174 + 0.607 = 0.78$$

The two latter stabilization energies are much larger than that for addition across C_2,C_5 because of the very important contribution from the second term, i.e., from HOMO/(LUMO + 1) interaction. The ring-localized nature of LUMO + 1 allows stronger interaction with HUMO than can be achieved between HOMO and the diffuse LUMO notwithstanding the smaller energy gap separating the latter two.

(6) As indicated by the McConnell relation, the large coupling constant corroborates with the high spin density.

Scheme III



In conclusion, the regiospecificity of the present reactions appears to be a clear-cut example of superjacent orbital control.[7] It has been reported[8] that 5-nitropyrimidine (2) and some of its 2-substituted derivatives give with 1-(diethylamino)prop-1-yne the 2:1 adducts 9. This reaction has been proposed to involved the 4 + 2 cycloadduct 8, which after rearrangement and addition of a second molecule of the propyne yields 9. The regioselectivity of the cycloaddition leading to 8 would appear to constitute a "normal" HOMO/LUMO controlled situation since C_4 (C_6) and the nitro group oxygen carry large LUMO coefficients (cf. Figure 1).

Stereospecificity. The various FMO interaction energies calculated above do not only predict an exclusive regiospecific addition of the enamine across N_1,C_4—as observed—but also indicate that a considerable preference should exist for the $N_1,C_{1'}/C_4,C_{2'}$ mode over the $N_1,C_{2'}/C_4,C_{1'}$ mode, since the former provides both stronger HOMO/LUMO and stronger HOMO/(LUMO + 1) interaction. The experimental observation that only the product 4 derived from 3 is formed fully corroborates the predicted regiospecificity of the addition process.

Concluding Remarks

While the results discussed above nicely demonstrate that FMO perturbation theory correctly predicts the observed course of the cycloaddition between 2 and electron-rich olefins, it should be noted that this does not automatically imply that the cycloaddition occurs in a concerted manner.

The presence of strongly electron-withdrawing and electron-donating substituents not only induces a highly polar character in the transition-state for a concerted pathway but might even stabilize a zwitterionic structure sufficiently to make it an actual reaction intermediate. Experimental support for the possible existence of a zwitterionic intermediate is the fact that the reaction of 2 with 1 occurs readily and in good yield in the polar solvent ethanol but poorly in an apolar solvent. As usual the most stable transition state in a concerted pathway also sets the stage for formation of a stable zwitterionic intermediate as may be seen upon comparison of the mesomeric option available to the zwitterions 10 – 13 depicted in Scheme III, that are related to 3, 5, 6, and 7, respectively. Consideration of the stability of such zwitterions, i.e., 10 > 11 and 13 > 12, readily leads to prediction of regioselectivity. However, prediction of the correct regioisomers 10 or 13 cannot easily be achieved on this basis.

Experimental Section

The radical anion of 2 was measured on a Varian 4502-10A; X band. The electrolysis was performed with a 10^{-4} M solution of 2 in dimethylformamide with tetra-*n*-butylammonium iodide as a supporting electrolyte, 10 μA at −1.45 V. The cell used in these experiments was deoxygenated in a glovebox.

Registry No. 1, 14212-87-4; 2, 14080-32-1; $2^{-\cdot}$, 34515-84-9.

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New Syntheses of 2-Fluoroisovanillin and 5-Fluorovanillin

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The addition of fluorine to give the three different positional isomers on the aromatic ring of the neurotransmitter norepinephrine has provided new drugs with very selective actions on the adrenergic nervous system.[1] We have been interested in the synthesis of new drug molecules incorporating fluorine into the aromatic ring and have thus investigated the synthesis of potential fluorinated aldehyde precursors.

A previous report of the synthesis of 5-fluorovanillin (1) involved a photochemical–Schiemann reaction of 5-aminovanillin (2).[1] This reaction gave 1 in low yields (10–12%) and involved a tedious chromatographic step. Since the reaction also does not lend itself to the preparation of significant quantities of 1, we sought a method for preparation of 1 that would be amenable to large scale reactions and be carried out in a minimum number of steps. We now report a new method for the formation of 1. During this investigation, a new route to 2-fluoroisovanillin (3) was also discovered. The synthetic pathways for the formation of 1 and 3 are outlined in Scheme I.

Our first attempt at the formation of 1 involved treatment of 2-fluoro-6-methoxyphenol[2] (4) with hexamethylenetetraamine (HMTA) and trifluoroacetic acid. This is a modification of the Duff reaction[3] and under these mild reaction conditions, a high para regioselectivity has been observed.[4] However, upon completion of the reaction, the major product of the reaction was 2-fluoro-3-hydroxy-4-methoxybenzaldehyde (2-fluoroisovanillin, 3) (75%), rather than 1. Compound 3 had previously been formed in 4% yield by partial demethylation of 2-fluoroveratraldehyde.[5,6]

The second approach to 1 involved the oxidation of a *N,N*-dimethylbenzylamine. Phenols are easily aminomethylated by reaction with formaldehyde and a secondary

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