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Near ultraviolet spectroscopic studies of 2,4-diamino-6-piperidinopyrimidine-3-oxide (minoxidil) and 2,4-diamino-6-piperidinopyrimidine (desoxyminoxidil)

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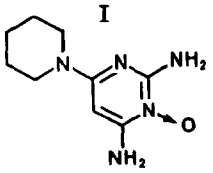
Abstract—The near u.v. spectra of 2,4-diamino-6-piperidinopyrimidine (desoxyminoxidil) and 2,4-diamino-6-piperidinopyrimidine-3-oxide (minoxidil) can be viewed as perturbed pyrimidine spectra. The u.v. properties of pyrimidine and a series of aminopyrimidines, specifically 2,4,6-triaminopyrimidine, are examined to obtain u.v. spectral assignments for desoxyminoxidil and minoxidil. Minoxidil and its desoxy counterpart have C_s symmetry, and all $\pi \rightarrow \pi^*$ absorptions are allowed $^1A' \leftarrow {}^1A'$ transitions. The two lowest energy $\pi \rightarrow \pi^*$ absorptions observed in minoxidil (262 nm, 292 nm) are tentatively assigned as very mild oxygen → pyrimidine ring charge-transfer transitions. Intensity decreases in protic solvents, and the results of simple Hückel molecular orbital calculations indicate that the 292 nm transition has more charge-transfer character than the 262 nm absorption. The protonated species of desoxyminoxidil and minoxidil have very similar u.v. spectra. This is due to the lack of oxygen-related charge transfer in protonated minoxidil, and the high probability that the positive charge resides in similar environments in the minoxidil and desoxyminoxidil molecular frameworks.

INTRODUCTION

The pyridine and pyrimidine ring systems are important as structural units in natural products and compounds of pharmaceutical interest. The chemical and physical natures of these molecules have been extensively studied [1, 2]. Among the many derivatives of these heterocyclic systems, the *N*-oxidation products of the amino pyrimidines are of particular interest, due to the complex electronic nature that exists as a result of the facile electron donating capabilities of the amino groups, and the dative bonding characteristics of the oxygen [3]. The electronic properties of these molecules have been extensively studied. For instance, thermodynamic calculations on iodine complexes of azine *N*-oxides indicate that the most basic site of the molecule is found at the oxygen atom [4]. This agrees with the drop in basicity noted on *N*-oxidation of the amino pyrimidines [5]. I.r. and NMR spectroscopy have been used to determine that an approximately linear relationship exists between the N–O stretching frequency (bond strength) and π electron density of the ring moiety, as measured by ^{15}N or ^{13}C chemical shifts [6–8]. Photoelectron [9–11] and ESR [12, 13] spectroscopy, as well as a multitude of theoretical treatments [14–19] have been employed to describe the molecular orbital arrangements in both the ground and excited electronic states of azines and the corresponding *N*-oxides.

A large portion of the spectroscopic studies of the *N*-oxides have focused on the assignment of the π electronic transition(s) that predominantly involve the oxide. Virtually all studies to data have implied that the electronic transition from the highest occupied π to lowest unoccupied π^* molecular orbital (HOMO → LUMO) involves significant transfer of charge from an oxygen p π to a parallel heterocyclic ring π^* orbital [9–15, 18, 19]. The present study involves the analysis of the near u.v. spectrum of the vasodilator minoxidil, I (2,4-diamino-6-piperidinopyrimidine-3-oxide) and desoxyminoxidil (2,4-diamino-6-piperidinopyrimidine). The data suggest that the HOMO → LUMO, $\pi \rightarrow \pi^*$, transition in minoxidil involves mild charge transfer from the oxygen atom to the pyrimidine ring. In addition, a more intense charge transfer originates from a $\pi \rightarrow \pi^*$ transition of higher energy.

I



EXPERIMENTAL

Minoxidil and desoxyminoxidil were synthesized by the Pharmaceutical Research and Fine Chemicals Divisions of the Upjohn Company. These compounds were structurally characterized by NMR, i.r., and mass spectrometry, and judged to 100% pure on the "as is" basis by HPLC. Pyrimidine was obtained from Fluka, and 2,4,6-triaminopyrimidine (97–99% pure) was obtained from Aldrich Chemical Company, and used without additional treatment.

The u.v. spectral data for all compounds were obtained on a Hewlett–Packard 8450A diode array spectrophotometer in 1 cm suprasil cells against the appropriate solvent blank (hexane, CCl_4, C_2H_5OH, H_2O, CH_3CN, DMSO). U.v. spectral data were obtained for minoxidil and desoxyminoxidil over a pH range of about 1.5–12.5 by dissolving the appropriate sample in an unbuffered solution of aqueous HCl or NaOH. The final solution pH was measured just after the u.v. spectrum was obtained. Spectral data were obtained at the following individual pH values, [1]. minoxidil: 1.63, 2.62, 3.79, 5.43, 6.34, 6.58, 6.72, 7.80, 8.82, 9.20, 10.24, 12.72; [2]. desoxyminoxidil: 1.65, 2.61, 3.66, 7.34, 7.50, 7.58, 7.72, 8.50, 9.00, 10.25, 12.74. The *pK* values for minoxidil and desoxyminoxidil were found to be 4.0 and 5.0, respectively;

pK_a values for minoxidil and desoxyminoxidil in 80%/20% H_2O/C_2H_5OH solutions were also obtained on a Metrohm/Brinkman Model 636 automatic titrator and yielded values of 3.7 and 4.8 respectively.

Simple Hückel molecular orbital calculations were performed on pyrimidine, 2,4,6-triaminopyrimidine (neutral and protonated), desoxyminoxidil (neutral and protonated), and minoxidil. Values for the Coulomb ($\alpha = \int \Phi_1 H \Phi_1 d\tau$) and resonance ($\beta = \int \Phi_1 H \Phi_2 d\tau$) integrals, where H is the Hamiltonian that operates on the atomic orbital wave functions of atoms #1, Φ_1, and #2, Φ_2, were varied slightly to yield results that fit the spectral data.

RESULTS AND DISCUSSION

The u.v. spectra of the aminopyrimidines and pyrimidine *N*-oxides may be viewed as perturbed benzene spectra, thus their electronic transitions can be assigned by considering how the appropriate substitutions would affect benzene spectral properties. The addition of two nitrogens to benzene, such as pyrimidine, perturbs the benzene π electron cloud to C_{2v} symmetry. The benzene e_{1g} and e_{2u} MO's of D_{6h} symmetry lose their degeneracy to form MO's a_2 and b_2 with C_{2v} symmetry. Two transitions are observed above 200 nm in hexane solution of pyrimidine, one at $\sim$ 242 nm ($\varepsilon = 3162$) and another at $\sim$ 295 nm ($\varepsilon = 400$). In a polar environment (ethanol) the weak 295 nm absorption shifts to higher energy, with a concomitant loss of vibrational fine structure. This behaviour is consistent with $n \rightarrow \pi^*$ transitions, and has been assigned as a promotion of an electron from a nitrogen lone-pair to a π^* ring MO [20, 21]. The 242 nm band, which corresponds to the 256 nm benzene absorption, does not blue-shift in polar solvent and has been assigned as a $^1B_1 \leftarrow {}^1A_1$ $\pi \rightarrow \pi^*$ transition [22]. A second $\pi \rightarrow \pi^*$ transition, $^1B_1 \leftarrow {}^1A_1$, has been observed at higher energy ($\sim$ 180 nm, $\varepsilon \sim 9 \times 10^3$) [23]. Two $^1A_1 \leftarrow {}^1A_1$ totally symmetric $\pi \rightarrow \pi^*$ transitions occur at even higher energy ($\sim$ 160 nm $\varepsilon \sim 2 \times 10^5$) [24].

The addition of amino groups to pyrimidine results in near u.v. spectra which are similar to pyrimidine. The interaction of the NH_2 lone-pair electrons, which lie above the a_2 and b_2 pyrimidine π levels results in two π MO's, one at higher energy than b_2 and one at lower energy. The same situation occurs with the pyrimidine a_2 π level. Each new set of π MO's are of the same symmetry as the original orbital, although they differ in the sign of the $2p$ π orbital of the amino nitrogen atom. The higher energy MO of each set has a node between the amino group and the pyrimidine ring, while the lower energy MO does not. The lower energy π MO of each new set is so much lower relative to the original amino lone-pair orbital, than the new higher energy π MO is above the original pyrimidine π MO (because of interaction with the π^* orbitals), that a resonance stabilization occurs. However, the final effect is a destabilization of both the π and π^* levels from which near u.v. transitions occur. Since the energies of the amino lone-pair atomic orbitals are closer to the π levels of pyrimidine than to the π^* levels, the amino pyrimidine π MO's represented in near u.v. transitions will increase in energy more than the π^* levels, thus leading to the red shift noted between pyrimidine and the amino-substituted analogs [25–29]. Lone-pair substituents that are very electronegative have lone-pair orbitals of lower energy than substituents that exhibit low electronegativity. A lower energy lone-pair orbital exhibits a weaker interaction with the vacant antibonding orbitals. Thus, substituents with high electronegativity generally produce a smaller red shift in the near u.v. transitions, than groups that are not as electronegative.

Figure 1 A shows a simple Hückel calculation of the energy levels of the 2,4,6-triaminopyrimidine π MO's. Pyrimidine parameters (α, β) were used for the ring portion of the triamino analog. Since nitrogen is more electronegative than carbon, a slightly higher value for α was used for both ring and amino nitrogens ($\alpha N = 0.6, \alpha C = 0$). Similarly, higher β values were used for C–C ($\beta = 1.0$) than for C–N ($\beta = 0.8$) ring bonds, due to a slightly higher probability of finding electrons around a ring N. These values produced $\pi \rightarrow \pi^*$ transitions corresponding to observed pyrimidine absorptions [23, 24]. A β value of 0.2 for the C–NH_2 bond was used. This value suggests the amino groups are in resonance with the ring at a level of about 25% of the delocalization found in the ring.

The HOMO $\rightarrow$ LUMO $\pi \rightarrow \pi^*$ transition in 2,4,6-traminopyrimidine arises from promotion of an elec-

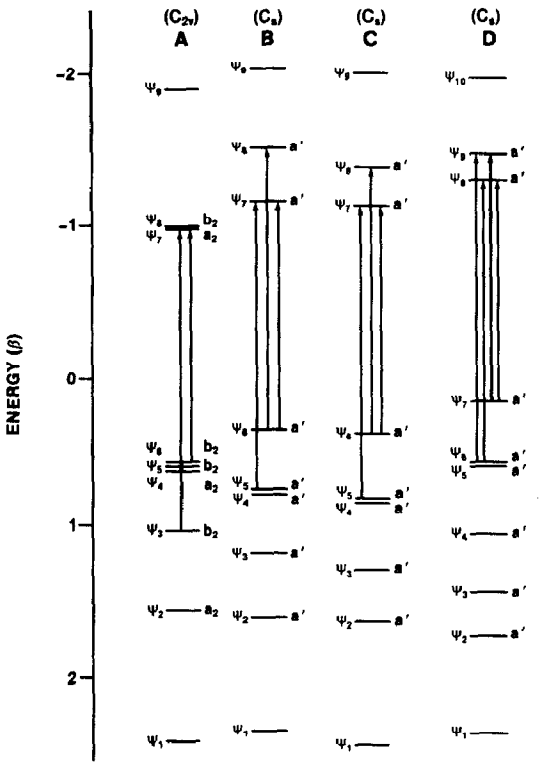


Fig. 1. Approximate MO (Ψ) energy levels and near u.v. transitions for 2,4,6-triaminopyrimidine (A), desoxyminoxidil (B), protonated desoxyminoxidil (C), and minoxidil (D).

tron from three nearly degenerate π levels of b_2, a_2 and b_2 symmetry to two nearly degenerate π^* levels of a_2 and b_2 symmetry (Fig. 1A). Two types of transitions arise, $^1B_1 \leftarrow {}^1A_1$, and $^1A_1 \leftarrow {}^1A_1$, and both are allowed. The 212 nm peak is due to the movement of an electron from a b_2 π MO to the $a_2 b_2 \pi^*$ LUMO nearly-degenerate set. This allowed transition is $^1B_1 \leftarrow {}^1A_1$ or $^1A_1 \leftarrow {}^1A_1$, depending on which LUMO π^* MO the excited electron resides in. A higher energy transition from an $a_2 \pi$ MO to the π^* LUMO set is predicted at about 172 nm.

In order to confirm that the relative ranking order of the near u.v. π MO's of 2,4,6-triaminopyrimidine did not change from those in pyrimidine, spectral data for the triamino-substituted pyrimidine were obtained at pH 1.35, well below its pK_a of 6.81. Both of the observed $\pi \rightarrow \pi^*$ transitions move 5 nm to the red (Fig. 2A). This shift corresponds to 1350 cm^{-1} and 680 cm^{-1} for the 212 nm and 272 nm bands respectively, indicating that the change in the 212 nm absorption is ~ 2 times greater than the corresponding displacement of the 272 nm transition. The site of

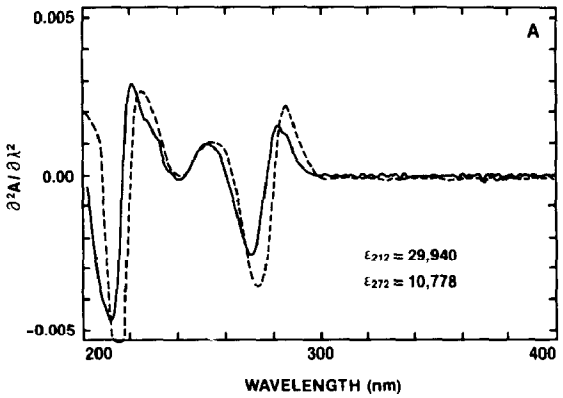


Fig. 2A. Near u.v. second derivative spectra of 2,4,6-triaminopyrimidine. The spectra are at neutral (——) and low (. . .) pH, well below the pK_a. All ε values were recorded in aqueous solution.

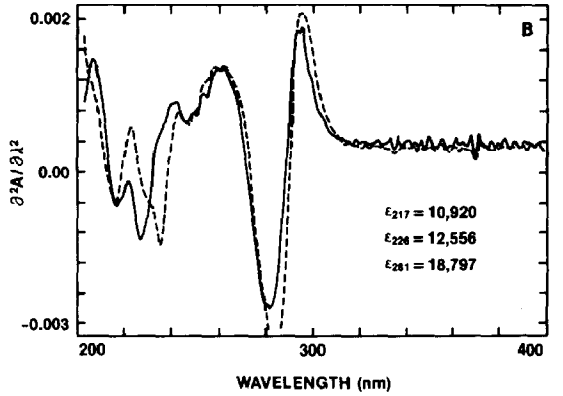


Fig. 2B. Near u.v. second derivative spectra of desoxyminoxidil. The spectra are at neutral (——) and low (. . .) pH, well below the pK_a. All ε values were recorded in aqueous solution.

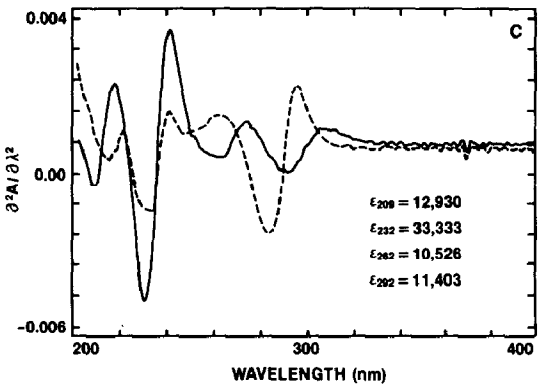


Fig. 2C. Near u.v. second derivative spectra of minoxidil. The spectra are at neutral (——) and low (. . .) pH, well below the pK_a. All ε values were recorded in aqueous solution.

protonation in 2,4,6-triaminopyrimidine at pH 1.35 is one of the ring nitrogens [28]. Figure 1A indicates the 272 nm band arises from transitions involving π MO's that have a high amino group character (Table 1A). In contrast, the 212 nm transition involves a π MO with more ring character, and would be expected to show a larger shift on protonation. The Hückel calculations indicate the spectral changes observed on protonation can be accounted for by raising the α value of the ring N's to 0.63, which is reasonable since NH+ would be more electronegative than N.

Desoxyminoxidil can be viewed as a substituted 2,4,6-triaminopyrimidine that has the 6-amino group replaced by a piperidino moiety. The amino group is more electronegative than the piperidino residue, due to the electron-releasing tendencies of the C_5H_{10} skeleton. The u.v. spectrum of desoxyminoxidil is shown in Fig. 2B, and indeed all observable $\pi \rightarrow \pi^*$ transitions exhibit a bathochromic shift when compared to 2,4,6-triaminopyrimidine. The symmetry of desoxyminoxidil is C_s [29], which leads to a slightly different qualitative picture of the MO's that is manifested by the splitting of the nearly degenerate levels of 2,4,6-triaminopyrimidine (Figs 1A, B).

The a_2 and b_2 MO's in C_{2v} symmetry correlate to a' orbitals in the C_s point group, thus all near u.v. transitions in desoxyminoxidil are allowed $^1A' \leftarrow {}^1A'$ transitions. Figure 1B illustrates how the addition of a piperidino group would be expected to shift the π MO energy levels. U.v. $\pi \rightarrow \pi^*$ transitions are observed at 217 nm, 226 nm, and 281 nm (Fig. 2B) in desoxyminoxidil. The MO diagram suggests that a higher energy absorption at ~ 180 nm should be present. Tables 1A, B indicate the π HOMO in triaminopyrimidine and desoxyminoxidil contains significant substituent character. The increased electron donating ability of the piperidino substituent is manifested in the calculations by an increase in β (more resonance) and a decrease in α (less electronegativity), compared to the corresponding values used for the 6-NH_2 group in 2,4,6-triaminopyrimidine. This increased resonance interaction of the piperidino group

over an amino substituent is manifested in the spectral data by an increase in the intensity of the lowest energy $\pi \rightarrow \pi^*$ transition in desoxyminoxidil compared to the analogous absorption in 2,4,6-triaminopyrimidine (Fig. 2A, B).

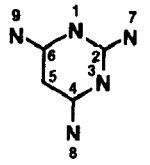
The spectral features of the protonated desoxyminoxidil (Fig. 2B) show red shifts in the 226 nm and 281 nm bands to 235 nm and 283 nm respectively. The larger red shift of the 226 nm desoxyminoxidil band is primarily due to a stabilization of the pertinent π^* MO Ψ_8 (Fig. 1B, C). When desoxyminoxidil is neutral, Ψ_8 places moderate electron density on N_3, but on protonation this density is more delocalized among N_3 and the two amino groups yielding a more stable configuration (Table 1B, C).

In order to obtain calculated MO energy level spacings that agreed with the protonated desoxyminoxidil spectral data, β values for the NH_2 groups had to be increased. This is reasonable, since protonation would generate a positive charge, predominantly in the ring, which would induce additional electron donation from the amino groups, through the π network, thus

TABLE 1A

Molecular orbitals Ψ, expressed as linear combinations of atomic orbitals, ϕ. Symmetries for the appropriate Ψ's are listed in Figure 1.

2,4,6-triaminopyrimidine



$\Psi_1 = 0.504\phi_1 + 0.468\phi_2 + 0.504\phi_3 + 0.321\phi_4 + 0.234\phi_5 + 0.321\phi_6 + 0.057\phi_7 + 0.040\phi_8 + 0.040\phi_9$
$\Psi_2 = 0.559\phi_1 - 0.559\phi_3 - 0.420\phi_4 + 0.420\phi_5 - 0.107\phi_8 + 0.107\phi_9$
$\Psi_3 = -0.177\phi_1 - 0.419\phi_2 - 0.177\phi_3 + 0.361\phi_4 + 0.603\phi_5 + 0.361\phi_6 - 0.234\phi_7 + 0.202\phi_8 + 0.202\phi_9$
$\Psi_4 = -0.136\phi_1 + 0.136\phi_3 - 0.004\phi_4 + 0.004\phi_6 - 0.694\phi_8 + 0.694\phi_9$
$\Psi_5 = -0.081\phi_1 + 0.002\phi_2 - 0.081\phi_3 + 0.002\phi_4 + 0.002\phi_5 + 0.002\phi_6 + 0.816\phi_7 + 0.0400\phi_8 + 0.400\phi_9$
$\Psi_6 = -0.080\phi_1 - 0.104\phi_2 - 0.080\phi_3 + 0.109\phi_4 + 0.313\phi_5 + 0.109\phi_6 + 0.514\phi_7 - 0.543\phi_8 - 0.543\phi_9$
$\Psi_7 = -0.411\phi_1 - 0.411\phi_3 + 0.569\phi_4 - 0.569\phi_6 - 0.084\phi_8 + 0.084\phi_9$
$\Psi_8 = -0.239\phi_1 + 0.623\phi_2 - 0.239\phi_3 - 0.283\phi_4 + 0.570\phi_5 - 0.283\phi_6 - 0.089\phi_7 + 0.040\phi_8 + 0.040\phi_9$
$\Psi_9 = 0.376\phi_1 - 0.453\phi_2 + 0.376\phi_3 - 0.417\phi_4 + 0.397\phi_5 - 0.417\phi_6 + 0.040\phi_7 + 0.036\phi_8 + 0.036\phi_9$

TABLE 1B

Molecular orbitals Ψ, expressed as linear combinations of atomic orbitals, ϕ. Symmetries for the appropriate Ψ's are listed in Figure 1.

Desoxyminoxidil*

$\Psi_1 = 0.513\phi_1 + 0.431\phi_2 + 0.440\phi_3 + 0.289\phi_4 + 0.249\phi_5 + 0.408\phi_6 + 0.052\phi_7 + 0.035\phi_8 + 0.200\phi_9$
$\Psi_2 = 0.324\phi_1 + 0.181\phi_2 + 0.593\phi_3 + 0.368\phi_4 - 0.059\phi_5 - 0.481\phi_6 + 0.039\phi_7 + 0.079\phi_8 - 0.363\phi_9$
$\Psi_3 = 0.428\phi_1 + 0.425\phi_2 - 0.016\phi_3 - 0.432\phi_4 - 0.502\phi_5 - 0.230\phi_6 + 0.186\phi_7 - 0.190\phi_8 - 0.269\phi_9$
$\Psi_4 = -0.140\phi_3 + 0.700\phi_7 + 0.700\phi_8$
$\Psi_5 = 0.216\phi_1 + 0.049\phi_2 - 0.051\phi_3 - 0.048\phi_4 - 0.138\phi_5 - 0.052\phi_6 - 0.678\phi_7 + 0.667\phi_8 - 0.136\phi_9$
$\Psi_6 = 0.302\phi_1 - 0.072\phi_2 - 0.328\phi_3 + 0.187\phi_4 + 0.495\phi_5 - 0.034\phi_6 + 0.041\phi_7 - 0.106\phi_8 - 0.707\phi_9$
$\Psi_7 = 0.402\phi_1 - 0.535\phi_2 + 0.005\phi_3 + 0.527\phi_4 - 0.509\phi_5 - 0.024\phi_6 + 0.077\phi_7 + 0.076\phi_8 + 0.024\phi_9$
$\Psi_8 = 0.068\phi_1 + 0.400\phi_2 - 0.482\phi_3 + 0.400\phi_4 + 0.085\phi_5 - 0.513\phi_6 - 0.048\phi_7 - 0.048\phi_8 + 0.408\phi_9$
$\Psi_9 = -0.379\phi_1 + 0.381\phi_2 - 0.301\phi_3 + 0.342\phi_4 - 0.387\phi_5 + 0.529\phi_6 - 0.032\phi_7 - 0.028\phi_8 - 0.264\phi_9$

*The numbering scheme in desoxyminoxidil is identical to 2,4,6-triaminopyrimidine.

TABLE 1C

Molecular orbitals Ψ, expressed as linear combinations of atomic orbitals, ϕ. Symmetries for the appropriate Ψ's are listed in Figure 1.

Protonated Desoxyminoxidil*

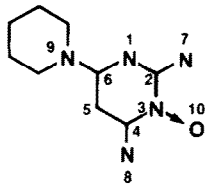
$\Psi_1 = 0.473\phi_1 + 0.448\phi_2 + 0.427\phi_3 + 0.303\phi_4 + 0.230\phi_5 + 0.382\phi_6 + 0.200\phi_7 + 0.136\phi_8 + 0.210\phi_9$
$\Psi_2 = -0.335\phi_1 + 0.129\phi_2 + 0.482\phi_3 + 0.391\phi_4 - 0.046\phi_5 - 0.491\phi_6 + 0.093\phi_7 + 0.282\phi_8 - 0.390\phi_9$
$\Psi_3 = 0.236\phi_1 + 0.433\phi_2 + 0.038\phi_3 - 0.403\phi_4 - 0.367\phi_5 - 0.247\phi_6 + 0.424\phi_7 - 0.394\phi_8 - 0.244\phi_9$
$\Psi_4 = 0.017\phi_1 + 0.005\phi_2 - 0.496\phi_3 + 0.005\phi_4 - 0.006\phi_6 + 0.602\phi_7 + 0.624\phi_8 - 0.017\phi_9$
$\Psi_5 = -0.589\phi_1 - 0.047\phi_2 + 0.141\phi_3 - 0.033\phi_4 - 0.214\phi_5 + 0.108\phi_6 + 0.528\phi_7 - 0.368\phi_8 + 0.395\phi_9$
$\Psi_6 = -0.136\phi_1 + 0.060\phi_2 + 0.243\phi_3 - 0.165\phi_4 - 0.673\phi_5 - 0.001\phi_6 - 0.119\phi_7 + 0.328\phi_8 + 0.562\phi_9$
$\Psi_7 = -0.331\phi_1 + 0.537\phi_2 - 0.001\phi_3 - 0.535\phi_4 + 0.415\phi_5 + 0.007\phi_6 - 0.266\phi_7 + 0.265\phi_8 - 0.007\phi_9$
$\Psi_8 = 0.067\phi_1 + 0.388\phi_2 - 0.417\phi_3 + 0.395\phi_4 + 0.077\phi_5 - 0.516\phi_6 - 0.168\phi_7 - 0.171\phi_8 + 0.428\phi_9$
$\Psi_9 = 0.356\phi_1 - 0.387\phi_2 + 0.288\phi_3 - 0.347\phi_4 + 0.362\phi_5 - 0.522\phi_6 + 0.123\phi_7 + 0.110\phi_8 + 0.295\phi_9$

*The numbering scheme in desoxyminoxidil is identical to 2,4,6-triaminopyrimidine.

TABLE 1D

Molecular orbitals Ψ, expressed as linear combinations of atomic orbitals, ϕ. Symmetries for the appropriate Ψ's are listed in Figure 1.

Minoxidil



$\Psi_1 = 0.425\phi_1 + 0.447\phi_2 + 0.527\phi_3 + 0.327\phi_4 + 0.211\phi_5 + 0.291\phi_6 + 0.154\phi_7 + 0.112\phi_8 + 0.109\phi_9 + 0.236\phi_{10}$

$\Psi_2 = 0.499\phi_1 + 0.094\phi_2 - 0.433\phi_3 - 0.268\phi_4 + 0.100\phi_5 + 0.476\phi_6 + 0.028\phi_7 - 0.152\phi_8 + 0.262\phi_9 - 0.397\phi_{10}$

$\Psi_3 = -0.196\phi_1 - 0.382\phi_2 - 0.619\phi_3 + 0.435\phi_4 + 0.446\phi_5 + 0.256\phi_6 - 0.358\phi_7 + 0.408\phi_8 + 0.196\phi_9 - 0.154\phi_{10}$

$\Psi_4 = 0.187\phi_1 - 0.234\phi_2 - 0.025\phi_3 - 0.211\phi_4 + 0.024\phi_5 + 0.241\phi_6 - 0.370\phi_7 - 0.335\phi_8 + 0.247\phi_9 + 0.727\phi_{10}$

$\Psi_5 = 0.372\phi_1 + 0.105\phi_2 + 0.151\phi_3 - 0.004\phi_4 - 0.214\phi_5 - 0.135\phi_6 - 0.782\phi_7 + 0.030\phi_8 - 0.338\phi_9 - 0.188\phi_{10}$

$\Psi_6 = -0.247\phi_1 + 0.019\phi_2 + 0.312\phi_3 + 0.158\phi_4 + 0.283\phi_5 + 0.011\phi_6 - 0.093\phi_7 - 0.772\phi_8 + 0.032\phi_9 - 0.358\phi_{10}$

$\Psi_7 = 0.193\phi_1 - 0.098\phi_2 - 0.296\phi_3 + 0.093\phi_4 + 0.490\phi_5 + 0.017\phi_6 + 0.141\phi_7 - 0.133\phi_8 - 0.728\phi_9 + 0.216\phi_{10}$

$\Psi_8 = 0.368\phi_1 - 0.529\phi_2 - 0.008\phi_3 + 0.541\phi_4 - 0.447\phi_5 - 0.028\phi_6 + 0.209\phi_7 - 0.214\phi_8 + 0.020\phi_9 + 0.002\phi_{10}$

$\Psi_9 = -0.162\phi_1 - 0.323\phi_2 + 0.434\phi_3 - 0.321\phi_4 - 0.204\phi_5 + 0.592\phi_6 + 0.116\phi_7 + 0.116\phi_8 - 0.376\phi_9 - 0.126\phi_{10}$

$\Psi_{10} = 0.363\phi_1 - 0.437\phi_2 + 0.364\phi_3 - 0.396\phi_4 + 0.368\phi_5 - 0.439\phi_6 + 0.108\phi_7 + 0.098\phi_8 + 0.174\phi_9 - 0.077\phi_{10}$

increasing substituent-ring resonance. Indeed, the intensity of the 272 nm transition, which involves large substituent contributions, increases (Fig. 2B). The MO calculations reveal a relative drop in ground state electron density at N_1, relative to N_3, or protonation, suggesting the proton favors N_1, although it probably spends considerable time on N_3 as well [30]. The proximity of the piperidino group, and its strong electron donating capacity, to N_1 accounts for the increased basicity at this site.

Minoxidil has C_s symmetry [29], and a near UV spectrum similar to desoxyminoxidil, as might be expected. The presence of an electronegative oxygen atom, however, induces several spectral changes, as shown in Fig. 2(B, C). Photoelectron spectroscopic studies of *N*-oxides of pyridine and pyrimidine indicate the π HOMO contains significant oxygen character [9–11], suggesting the $2p\pi$ oxygen atomic orbital is higher in energy than the HOMO of the non *N*-oxidized analogs. ESR studies of various heterocyclic *N*-oxide cation radicals have revealed high electron density on the oxygen $2p\pi$ orbital [13]. Conversely, analogous ESR studies on anion radicals show little electron density on the π oxygen orbitals [12]. Since cation and anion radicals may closely approximate the ground and first excited states respectively of the neutral *N*-oxide, the ESR studies indicate the π HOMO $\rightarrow \pi^*$ LUMO transition to be an oxygen $\rightarrow$ ring intramolecular charge transfer. Various molecular orbital calculations confirm this assignment [14, 18, 19].

The photoelectron, ESR, and MO studies suggest the π HOMO $\rightarrow \pi^*$ LUMO transition in minoxidil is probably an oxygen $\rightarrow$ ring π charge transfer. This assignment would depend on the energy of the $2p\pi$ oxygen orbital with respect to the energy of the π HOMO in desoxyminoxidil. If the oxygen atomic orbital is higher in energy than the desoxyminoxidil HOMO, the minoxidil π HOMO $\rightarrow \pi^*$ LUMO transition is an oxygen $\rightarrow \pi^*$ ring transition. However, if the desoxyminoxidil HOMO is higher in energy than the oxygen $2p\pi$ orbital, the π HOMO $\rightarrow \pi^*$ LUMO transition in minoxidil is a π HOMO $\rightarrow \pi^*$ ring transition, analogous to desoxyminoxidil except for the presence of some oxygen character in the MO's, and the major π oxygen $\rightarrow \pi^*$ ring charge transfer would be at higher energy.

It has been observed that the intensity of a charge transfer transition is a function of solvent properties [31, 32]. Solvent systems that diminish the charge gradient between the donating and receiving atoms induce a smaller charge transfer, and a concomitant reduction in the absorption intensity of that transition. It has been determined that the oxygen atom in pyridine and pyrimidine *N*-oxides is the location of the highest negative charge [4, 13, 14, 16, 18, 19]. This suggests that the intensity of the charge transfer transition should decrease in solvents that reduce the charge differential in the N–O bond by decreasing either the positive character of the nitrogen, or the negative oxygen environment. In aprotic solvents that hydrogen bond with the 2,4-amino groups of minoxidil, the intensity of the 262 nm band increases slightly and the 292 nm absorption weakens. In these solvents, the amino groups become more electropositive and are stronger electron donors to the pyrimidine ring. This results in a decreased positive environment at N_3, and a diminished oxygen $\rightarrow$ ring electron transfer. However, the increased electronic contribution from the amino substituents increases resonance between them and the ring, resulting in an increased $\pi \rightarrow \pi^*$ transition moment for the absorption involving the amino groups. Thus, the behavior of the two low energy minoxidil $\pi \rightarrow \pi^*$ bands in aprotic polar solvents suggests that the 292 nm peak has oxygen $\rightarrow$ ring charge transfer character, and the 262 nm transition involves predominantly $NH_2 \rightarrow$ ring resonance.

Although the exact energy of the oxygen $2p\pi$ orbital relative to the desoxyminoxidil orbitals is not known, it has been shown to lie in the vicinity of the π HOMO in

pyridine [14, 15], at approximately 0.6 β. Pyrimidine π MO's are lower in energy than pyridine MO's, but as previously discussed, the higher energy desoxyminoxidil π MO's are raised substantially due to the presence of the amino and piperidino substituents, resulting in a red shift of the π HOMO → LUMO transition, compared to pyridine. Since oxygen is more electronegative than an amino group, its $2p\pi$ lone-pair orbital should be lower in energy. This suggests that the oxygen $2p\pi$ orbital is below the π HOMO in desoxyminoxidil. The MO calculations for desoxyminoxidil indicate the HOMO energy to be about 0.3 β, with the next two occupied MO's at about 0.7 β (Fig. 1B). If the energy of the oxygen $2p\pi$ atomic orbital is about 0.6 β, the three highest energy occupied desoxyminoxidil π MO's would rise in energy and the oxygen $2p\pi$ orbital would decrease to about 1.0 β (Fig. 1D, Table 1D). The MO calculations that come the closest to matching the minoxidil spectral data indicate the HOMO → LUMO $\pi \rightarrow \pi^*$ transition (292 nm) to contain more oxygen → ring electron transfer than the 262 nm absorption. The calculations also indicate that neither the 262 nm nor 292 nm transitions involve a large transfer of charge from oxygen. This is supported by the fact that the intensities of the 262 nm and 292 nm peaks are comparable to the 272 nm $\pi \rightarrow \pi^*$ transition in 2,4,6-triaminopyrimidine (Fig. 2A, C), and are only about half as intense, compared to the higher energy $\pi \rightarrow \pi^*$ transition (232 nm), as the oxygen → ring charge transfer band in pyridine *N*-oxide and pyrimidine *N*-oxide are to their higher energy $\pi \rightarrow \pi^*$ ring transition [18]. The MO with the most electron density on the oxygen atom is Ψ_4 (Table 1D), thus the strongest oxygen → ring charge transfer should be from $\Psi_4 \rightarrow \Psi_8$. The calculations suggest this transition should occur at approximately 168 nm.

The near u.v. spectrum of protonated minoxidil is very similar to that of protonated desoxyminoxidil. This behavior is typical of *N*-oxides [12, 33, 34], and results from the fact that the positive charge resides in both minoxidil and desoxyminoxidil ring systems in a similar fashion, namely, distributing itself primarily between the two ring nitrogens. The oxygen → ring charge transfer in protonated minoxidil is not observed due to the probable hybridization of the oxygen $2p$ orbitals to a quasi-sp^3 configuration, when hydrogen is bonded to the oxygen atom.

CONCLUSIONS

The near u.v. spectra of desoxyminoxidil and minoxidil can be viewed as perturbed pyrimidine spectra. Both desoxyminoxidil and minoxidil have C_2 symmetry, and their observed $\pi \rightarrow \pi^*$ absorptions are allowed $^1A' \leftarrow {}^1A'$ transitions. The piperidino and amino substituents participate in molecular electronic resonance, as evidenced by the considerable intensity enhancements when these groups are present. The two lowest energy $\pi \rightarrow \pi^*$ bands in minoxidil are assigned as very mild oxygen → pyrimidine ring intramolecular charge transfer transitions, with the 292 nm absorption exhibiting more charge transfer character due to intensity decreases when switching from protic to aprotic solvents, and from the results of simple Hückel MO calculations.

Near u.v. data of the protonated species of desoxyminoxidil and minoxidil are very similar. This is due to the lack of oxygen-related charge transfer in protonated monoxidil, and the high probability that the positive charge resides in similar environments in the minoxidil and desoxyminoxidil molecular frameworks.

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