Tetrahedron Vol. 46, No. 2, pp. 319-324, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

REACTIVITY OF BIOLOGICALLY IMPORTANT REDUCED PYRIDINES VI. LACK OF THROUGH-RESONANCE STABILIZATION IN THE FERRICYANIDE-MEDIATED OXIDATION OF SUBSTITUTED 1-PHENYL-1,4-DIHYDRONICOTINAMIDES

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(*Received in USA* 22 *March* 1989)

Abstract: Bronsted-type analysis for the log of the reaction rates for ferricyanide-mediated oxidation for a series of 1-(4-substituted phenyl)-1,4-dihydronicotinamide and the pKa's for the corresponding component anilines produced a linear (r=0.993) relationship over the range of p-$N(CH_3)_2$ to p-CF_3. This observation is consistent with the importance of the initial electron loss in determining the reaction rate. One compound studied i.e., 1-(4-nitrophenyl)-1,4-dihydronicotinamide, was conspicuous in that it did not lie on the calculated regression line even though Hammett analysis revealed no deviation from linearity for this species. This situation was suggested to be due to steric and other restriction to planarity of the 1-phenyl substituents. These factors would preclude direct interaction of the 4-phenyl moiety with the heterocyclic pyridine nitrogen. These conclusions were based on experimental and theoretical (AM1 and MNDO) semi-empirical molecular orbital studies.

Introduction:

The mechanism by which dihydronicotinamides are converted to the corresponding pyridinium salts has been the subject of extensive investigations as these compounds represent the biochemically active partial structures in various electron-transporting coenzymes[3-5]. Two distinct chemical pathways have been forwarded as the best explanations for the amassed experimental and theoretical data. These include concerted hydride transfer[6-8] and sequential electron-proton-electron transfer[9-12]. In order to study the latter mechanism in an unambiguous fashion, strong one-electron oxidants such as the ferricyanide anion have been employed[14-17]. In the case of oxidation of 1-substituted-1,4-dihydronicotinamides by the ferricyanide ion, two mechanisms have been suggested. These include (1) a rate-determining initial electron loss followed by sequential proton and electron migrations and (2) a rapid pre-equilibrium step in which electrons are shuttled between the dihydropyridine and the dihydropyridine radical cation followed by a rate-determining proton loss and then a nonrate-determining electron loss[13]. In studying these two possibilities substituted 1-phenyl-1,4-dihydronicotinamides have been used because of their ease of preparation, their relative stability and because of the opportunity to introduce substituents into the phenyl moiety in order to study various linear free energy relationships. In the present report, the mechanistic pathways for ferricyanide-mediated oxidation of 1-phenyl-1,4-dihydronicotinamides was examined. In these studies, certain chemical proclivities were observed and could be explained using various theoretical techniques.

Materials and Methods:

Kinetic data used to generate the Bronstead relationship herein described were obtained from the literature[18,19] as were the attendent pKa's[26]. AM1[20,21] and MNDO[22,23] calculations were performed on an IBM 3084 Model K dual

processor computer operating at 15 MIPS. Both programs were obtained through the Quantum Chemistry Program Exchange (QCPE) and adapted to run on the IBM computer. Structural input was generated using the SYBYL/MOPAC interface and the geometries were found by minimizing the total molecular energy with respect to all structural variables using the standard Davidon-Fletcher-Powell optimization procedure. In rotational studies, the phenyl ring - dihydropyridine torsion angle (ϕ 17-12-1-6) was fixed at 0, 30, 60, 90, 120, 150 and 180° and the molecule was optimized at each twist angle. Energies are reported as semi-empirical heats of formation (ΔH_f, Kcal/mol) and ionization potentials were obtained using Koopman's theorem.

Results and Discussions:

The comparison of kinetic and thermodynamic data is often useful in probing the uniformity of reaction mechanism over a range of reactivities and structures. A Bronsted-type analysis was therefore attempted by correlating the rate of ferricyanide-mediated oxidation for a series of 1-(4-substituted phenyl)-1,4-dihydronicotinamides and the pKa's of their corresponding component anilines[24]. These results are collected in Figure 1. As illustrated, all of the compounds, save one, fell on a straight line (r=0.993) with a slope of 0.86. This high degree of correlation and the large positive slope are indicative of the importance to the rate of the change of the electron density on nitrogen in determining the reaction rate. In addition, since semi-empirical calculation suggest that the N-1 atomic orbital coefficient is the most important contributor to the highest occupied molecular orbital (HOMO), the information presented in the Bronsted plot is consistent with an initial rate-determining electron transfer. Other studies have in fact showed excellent correlation between the log (oxidation rates) for a series of 1-(4-substituted phenyl)-1,4-dihydronicotinamides and calculated vertical ionization potentials[18]. The only compound which significantly deviated

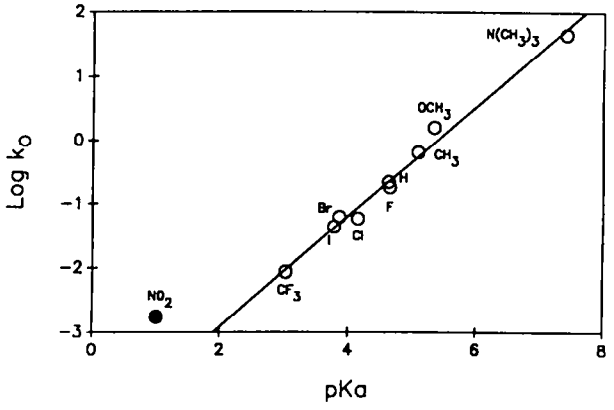
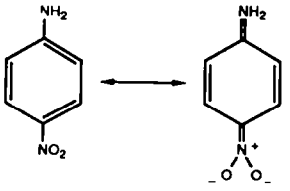
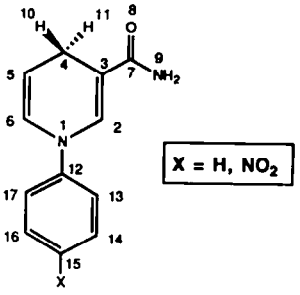


Figure 1. Correlation between Log k_o ($s^{-1}M^{-1}$) for ferricyanide-mediated oxidation of various 1-(4-substituted phenyl)-1,4-dihydronicotinamides and the pKa of the component anilines.

from the calculated regression line in the Bronsted analysis was 1-(4-nitrophenyl)-1,4-dihydronicotinamide which appears to be too reactive. The deviation from linearity for this species could be indicative of a change in the oxidative reaction mechanism for this compound. This is unlikely, however, in view of the fact that reassessment of the kinetic data using Hammett analysis produced a highly linear (r=0.9994) correlation even with inclusion of the nitro derivative[19]. A second explanation for the observed deviation could be that the basicity of 4-nitroaniline is a poor indicator of the reactivity of the substituted dihydronicotinamide. It has been shown that 4-nitroanilines and their derivatives often deviate from Hammett sigma relationships because of the ability of the nitro group to interact directly with the reaction center (amine). This through-resonance interaction is well illustrated in the effect of

substitution on the basicity of anilines where structures such as the one shown below cause the sigma values to be smaller than expected.





These effects have been compensated for by the creation of a new set of sigma values (σ) which took into account these through-resonance effects[25,26]. The observation that the oxidation of 1-(substituted phenyl)-1,4-dihydronicotinamides by ferricyanide ion correlates with σ but not σ^- and that there is deviation from linearity for the 1-(4-nitrophenyl) analog when the oxidation rates are correlated with pKa's suggest that through-resonance effects are not important with these compounds. That is to say that those factors which act to decrease the basicity of 4-nitroaniline relative to 3-nitroaniline do not operate in the case of the oxidative stability of 1-(4-nitrophenyl)-1,4-dihydronicotinamide. The reason for this may be some steric or other restrictions to planarity which would prevent the orbital overlap necessary for the indicated interaction to occur. To examine this question in detail, semi-empirical all-valence electron SCF methods including MNDO[22,23] and the AM1[20,21] approximation, were used. Numbering protocols is for the molecules are given above.

The ease with which the phenyl or 1-(4-nitrophenyl) moiety could rotate with respect to the dihydronicotinamide ring was first considered. Figure 2 gives the energy (semi-empirical heats of formation, ΔH_f) versus torsion angle profiles for the 1-phenyl-1,4-dihydronicotinamide and 1-(4-nitrophenyl)-1,4-dihydronicotinamide using the MNDO and AM1 methods, respectively. The MNDO approximation predicts an energy barrier at planarity of approximately 11.8 and 7.1 kcal/mol for the phenyl and nitrophenyl derivatives, respectively. The most stable conformation for both compounds is one in which the phenyl substituent is approximately 90° out of the plane of the dihydropyridine ring. The AM1 method paints a slightly different picture. Again, a barrier to rotation exists at planarity but it is somewhat smaller than that calculated using MNDO. These energy hills were estimated to be 2.4 and 1.8 kcal/mol for the phenyl and nitrophenyl derivatives, respectively. In addition, an energy barrier appears when the phenyl ring is perpendicular with respect to the rest of the molecule. This was predicted to be the most stable conformation by MNDO. This energy barrier is less than that observed at planarity in the case of 1-phenyl-1,4-dihydronicotinamide (1.8 kcal/mol) and greater in the case of the nitro derivative (2.9 kcal/mol). This inhibition to perpendicularity causes the lowest energy conformer to exhibit a phenyl ring twist angle of 38.7° and 33.8° for the unsubstituted and p-nitro substituted derivatives, respectively.

The reason for these energy maxima can be traced to several sources. At planarity, steric interaction can occur between the hydrogens on the carbons adjacent to the pyridine ring nitrogen and the quaternary phenyl ring carbon. As shown in Figure 3, these hydrogen-hydrogen interactions provoke significant crowding at planarity as the hydrogens approach within 1.85 Å of each other. In addition, planarization causes a shortening of the C-N interannular bond as the increase orbital overlap contributes double bond character to the link. This is illustrated in Figure 4 where at planarity the p-nitro derivative has a shorter C-N bond than does the unsubstituted compound. At 90° rotation, there is no difference in the bond lengths. The observed reduction in the phenyl-dihydronicotinamide

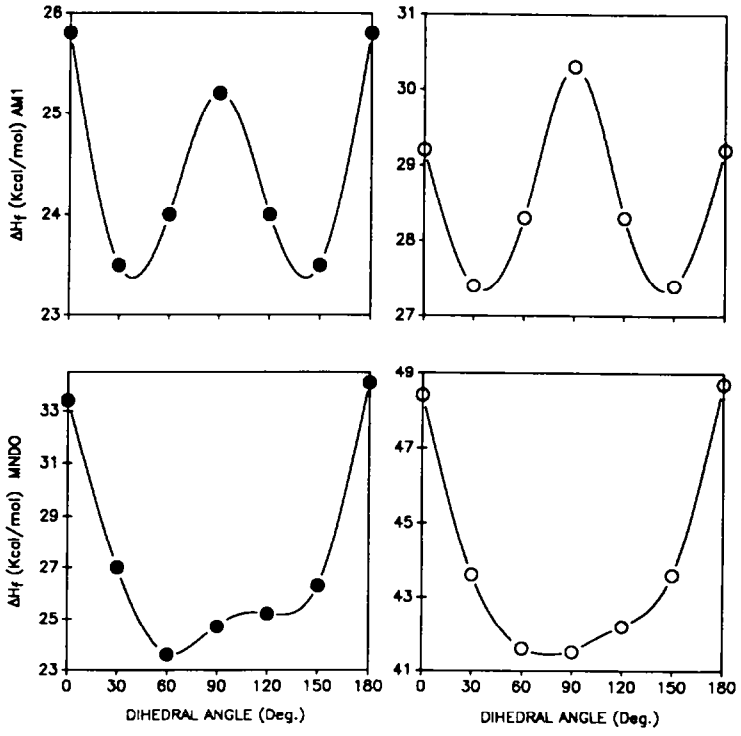


Figure 2. Energy versus torsion angle profiles for 1-phenyl-1,4-dihydronicotinamide (left panel) and 1-(4-nitrophenyl)-1,4-dihydronicotinamide (right panel) determined using either the MNDO (lower panel) or AM1 (upper panel) molecular orbital approximations.

separation distance for the 1-(4-nitro) derivative exacerbates congestion around the interacting hydrogen atoms. The energy barrier predicted by the AM1 method which occurs at phenyl ring perpendicularity can be explained based on loss of phenyl ring involvement in the HOMO. Figure 5 gives the contribution of various atomic orbitals to the HOMO as a function of torsion angle. There is little change in the contribution from the dihydropyridine dienamine system when the p-nitro phenyl ring is rotated. The contribution to the HOMO made by the pendant p-nitro phenyl ring do, however, significantly decrease the further the substituent is twisted from planarity. At 90°, there is little HOMO involvement by the phenyl ring consistent with the negligible orbital overlap. The geometry of the lowest energy conformer obtained in the case of 1-phenyl- and 1-(4-nitrophenyl)-1,4-dihydronicotinamides is therefore a compromise between steric interactions which occur at planarity and loss of orbital overlap which occurs most severely at perpendicularity. The MNDO method did not detect these orbital overlap phenomena and overestimated the steric interaction which occurred at planarity. This may be due to the general tendency of the MNDO approach to overestimate atomic repulsion within and between atoms of a molecule.

In conclusion, the apparent inability of 1-(4-nitrophenyl)-1,4-dihydronicotinamide to exert through-resonance effects is attributable to steric or other restrictions to planarity. The energy associated with planarization is not compensated for by the energy benefit associated with maximum orbital overlap. Theoretical studies indicate, however, that these systems make the best available compromise between steric crowding and orbital interactions. These findings are similar to those obtained for biphenyl and paraquat. In the biphenyl system, energy barrier at

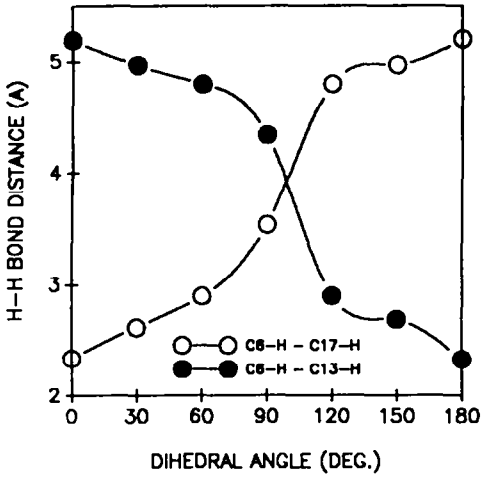


Figure 3. Interatomic (N-H) bond lengths for 1-(4-nitrophenyl)-1,4-dihydronicotinamide as a function of phenyl ring rotation.

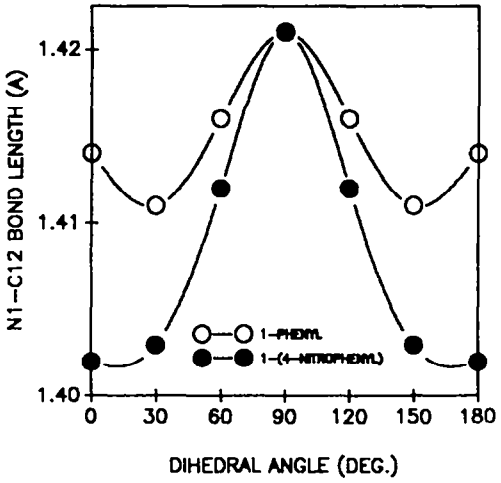


Figure 4. Interannular (N-C) bond length as a function of phenyl ring rotation for 1-phenyl and 1-phenyl and 1-(4-nitrophenyl)-1,4 dihydronicotinamide.

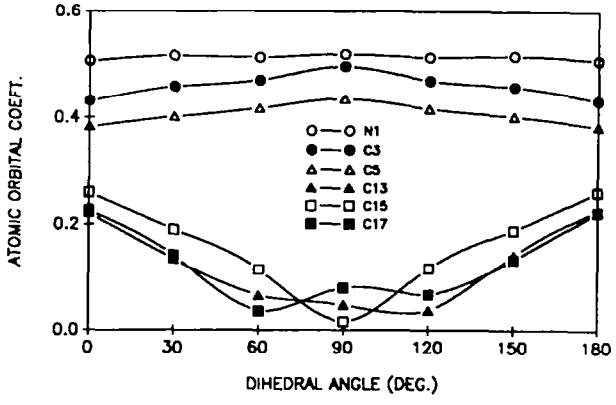


Figure 5. Atomic orbital coefficient contributions to the highest occupied molecular orbital (HOMO) as a function of phenyl ring rotation in 1-(4-nitrophenyl)-1,4-dihydronicotinamide.

planarity (ΔE^{*}) and at perpendicularity (ΔE^{90}) have been estimated using numerous experimental and theoretical methods[27-32]. A recently published account using a 6-31G split-valence basis set optimization indicated the most stable biphenyl conformation was one which expressed a twist angle of 44.7° and which was associated with a ΔE^{*} and ΔE^{90} of 3.2 and 1.65 kcal/mol, respectively[33]. In the case of paraquat the lowest energy conformer was one twisted approximately 40° with ΔE^{*} and ΔE^{90} values of 2.0 and 3.3 kcal/mol, respectively[30]. These data are in excellent agreement with experimental results and indicates that the behavior associated with these bridged ring systems extends to 1-phenyl-1,4-dihydronicotinamides. The current studies offer chemical evidence to butress theoretical results that these systems are not coplanar in solution. The chemical behavior of the p-nitro derivative is therefore consistent with its predicted geometry. In addition, when calculations (AM1) were carried out on the m-nitro derivative (1-(3-nitrophenyl)-1,4-dihydronicotinamide), the data indicated that the degree of double bond character associated with the C-N interannular connection was similar to that of the N-phenyl compound and

significantly less than that of the p-nitro system. Thus, the meta isomer, which can not manifest through resonance interactions, is more similar to the simple phenyl case than to the p-isomer where conjugative interactions can occur.

Interestingly, the relationship shown in Figure 1 clearly indicates that the reactivity of 1-(4-nitrophenyl)-1,4-dihydronicotinamide is greater towards oxidation than would be predicted based on the pKa of the component aniline. This deviation is expected if the electronic structure of the aniline is distinct from that of the aniline-containing dihydronictinamide. This is consistent with the calculated nonplanarity of the dihydronicotinamide in that planarization would allow for throught resonance interaction and corresponding deactivation of this compound. In any case, the linear relationship found between the log(reaction rates) for ferricyanide-mediated oxidation of 1-(4-substituted phenyl)-1,4-dihydronicotinamides and the pKa's of their component anilines strongly support the contention that electron removal from the HOMO largely determines the rate of ferricyanide-mediated oxidation for these compounds.

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