Quantum Mechanical Calculation of Stability in 2-Formyl *N*-Methyl Pyridinium (Cation) Oxime (2-PAM$^+$) Conformers

WALLY GIORDANO, JON R. HAMANN, JEROME J. HARKINS, AND
JOYCE J. KAUFMAN

Medical Research Laboratory, USAEARL, Edgewood Arsenal, Maryland; Chemistry Department, New York University, Washington Square, New York, New York; Physics Department, Research Institute for Advanced Studies (RIAS), Martin Company, Baltimore, Maryland

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SUMMARY

1. Twelve conformers of 2-formyl *N*-methyl pyridinium (cation) oxime (2-PAM$^+$) were geometrically defined and were subjected to extended Hückel molecular orbital (XHMO) quantum mechanical calculation.

2. The parameter molecular total overlap population (MTOP) was described and was shown to reflect stability and, in this study, to predict expected geometry.

3. By analyzing total energy (TE) and molecular total overlap population (MTOP), within the limitations of the conditions used and the validity of the approximations in the model chosen, the least stable isomers were found to be the two planar oxime-*trans* pairs (N_1T_- and N_3T_-); the most stable planar isomers were found to be those with oxime *syn* (*cis*), and of these the proton pair with aldoxime nitrogen vicinal to ring three (N_3S_-) was found to be slightly more stable than its ring counterpart (N_1S_-); the most stable of all conformers were found to be the aldoxime out of plane (OOP) quartet; for any rotational state the *syn* (*cis*) oxime configuration was found to be more stable than its respective *anti* (*trans*) analog; for any nonsterically hindered aldoxime-ring rotational and oxime configurational state the proton *anti* (*trans*) configurational state was found to be more stable than its proton *syn* (*cis*) analog.

4. By evaluating differences in the same parameters used above, barriers to rotation, conformation, and configuration were estimated and the energetic implications suggested were deemed significant to consider that the most stable conformers are likely to retain their identity at room temperature in slightly acidic solution (their protonated states).

5. The feasibility, implicit in an earlier study, of theoretically determining conformational stability, barriers to rotation, conformation, and configurational stereoisomerism of molecules in the free molecular state (and possibly in dilute solution) is partially and tentatively substantiated.

6. Although by using total energy (TE) alone, the expected geometry was not predictable from the three aldoxime-ring bond lengths chosen, molecular total overlap populations (MTOP's) clearly indicated that maximal stability should occur between 1.40 Å and 1.55 Å for planar conformers and very close to 1.55 Å for OOP conformers. This finding may generally imply that any molecule can have its exact geometry accurately predicted by theoretical calculations alone.

7. The use of structures derived from crystallography in the stereochemical and quantum chemical analysis of chemical reactivity in solution is suggested at least at times to be precarious.

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INTRODUCTION

In 1957, the chemical synthesis of the methiodide of 2-pyridine aldoxime (2-PAM-I) was reported (1). Two forms were described in which the more stable, higher melting point, yellow solid was tentatively identified on chemical arguments as having the *anti* configuration. This so-called B form had been tested in enzyme reactivation studies and in organophosphorus-intoxicated animals and had been found to exhibit exceptional activity (2). In 1958, considering the analogy with neostigmine, it was argued on the basis of molecular complementarity that 2-PAM-I was planar and in an *anti* configuration with the oxygen close to the 3 position in the pyridinium ring (3).

In 1961, by chemical and UV analysis, the unstable A form was designated a carbinolamine rather than an oxime (4). A year later this same group examining NMR data of stable 4-PAM-I concluded it was in the *syn* configuration and suggested the instability of the *anti* stereoisomer (5). In 1964, by base catalyzed degradation–UV studies, the A isomer was reported to be most likely a mixture of carbinolamine and *anti* oxime whereas the B isomer was *syn* (6).

In an analysis previously reported this year[1] as the first of a series of theoretical treatises on the stereochemical and quantum chemical considerations of the same pyridine aldoximes, the basis for evaluating multiple stereochemical states of 2-PAM was laid. At that time it was argued that as a start the exact conformation, including rotations about the ring-aldoxime bond, and *syn-anti* configurations of the oxime as well as the oxime proton, had to be included in a thorough, although not exhaustive, quantum mechanical evaluation. It was noted that inasmuch as crystallography of the solid state does not necessarily describe the state in solution and that, since X-ray analysis of solutes is not practical nor have other powerful physical tools been capable of defining the exact stereochemistry or quantum chemistry, a theoretical approach was both timely and necessary (7).

With the problem thus defined, the following initial study was undertaken (7). The rotameric states of 2-PAM were categorized and subjected to the most modern and appropriate semiempirical quantum mechanical calculation known (8). The ensuing energetics, their implications and limitations, were analyzed.

METHODOLOGY AND GEOMETRY

A. The extended Hückel molecular orbital (XHMO) calculation has been described previously (8). Essentially, for this initial study the following conditions were used:

1. The 52 valence shell electrons alone were treated without explicit inclusion of electron-electron interaction or nuclear-nuclear interaction. The molecule was thus assumed to be formally positive.

2. The basis set consisted of Slater type orbitals (STO) with shielding coefficients (μ) as described previously (see, e.g., ref. 9)

$$X_{\mathrm{STO}}\,(r,\theta,\phi) = Nr^{n-1}\exp\,(-\mu r)Y_l^m(\theta,\phi)$$

where N is a normalizing constant. The X_{STO} for pyridinium nitrogen was chosen as that having a four electron valance state.

3. The overlap integrals (S_{ij}) between these STO's were calculated as described by Mulliken *et al.* (10). The pyridinium nitrogen was assigned four electrons for this calculation.

4. The one-center integrals making up the diagonal elements of the Hamiltonian matrix (H_{ii}) were set equal to the appropriate valence state ionization potentials (VSIP) (11, 12) [see Table 1]. The VSIP of the pyridinium nitrogen was chosen as that of the neutral state.

5. The resonance integrals or nondiagonal elements (H_{ij}) of the Hamiltonian matrix were constructed according to the following formula (13):

$$H_{ij} = 0.5(H_{ii} + H_{jj})S_{ij}(2 - |S_{ij}|)$$

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[1] W. Giordano and J. R. Hamann. Submitted to *J. Pharm. Sci.*

TABLE 1

Valence state ionization potentials (VSIP) used as diagonal elements (H_{ii}) in the Hamiltonian matrix

These values were chosen from values previously derived (12). Nitrogen used was that in the neutral valence state.

Atom	Atomic orbital	Valence state ionization potentials (VSIP) (electron volts)
H	1S	−13.60
C	2S	−19.52
	2P	−9.75
N	2S	−25.58
	2P	−12.38
O	2S	−32.30
	2P	−14.61

It should be noted that special attention must be given formulas of this type in order to minimize the effects of transformational non-invariances.

B. The input geometry consisted of 12 conformers in which the following arbitrary numbering system and assignment of positions and designations was made. A conformer with the aldoxime nitrogen planar and vicinal to carbon three (ring) is designated N_3 (see Fig. 1). Likewise N_1 implies that this nitrogen is planar and vicinal to the pyridinium nitrogen (ring). A 90-degree rotation of the aldoxime nitrogen in either direction from any planar position is an equivalent position and puts the nitrogen a maximum distance from the plane of the ring. The designation used was N ↑. This was the only out-of-plane nitrogen position studied and was chosen to most likely demonstrate the effect of this rotation. Other out of plane (OOP) positions are reserved for later studies. For each of the above positions the aldoxime oxygen was set either *syn* (same side) or *anti* (opposite side) with respect to the aldoxime carbon's proton (H_7) and designated O_s or O_t, respectively (see Fig. 1). Likewise the aldoxime oxygen's proton (H_9) was set on the same side (*syn* or *cis*) or opposite side (*anti* or *trans*)

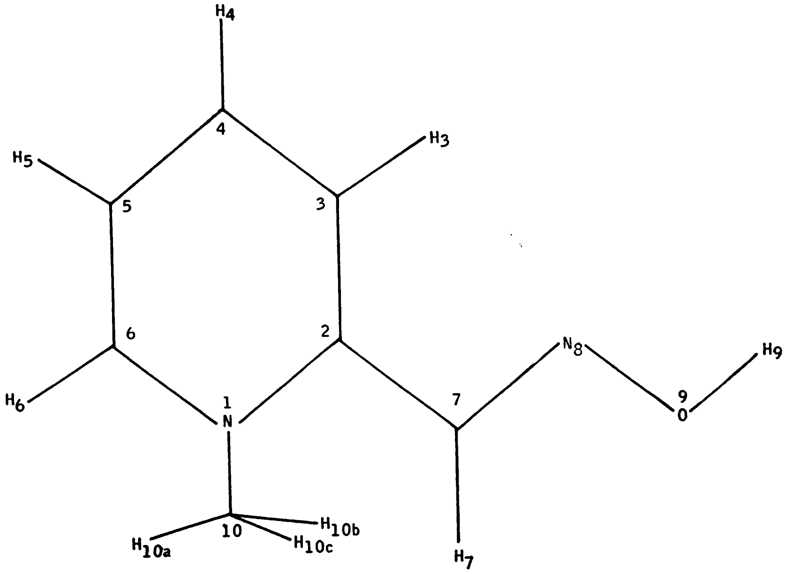

FIG. 1. *Numbering and name convention for 2-formyl N-methyl pyridinium (cation) oxime (2-PAM⁺), $N_3O_sH_s = N_3SS$ conformer*

Purely arbitrary except ring nitrogen and carbon. Atoms in conformer designation refer to those in the aldoxime side chain. N_3 refers to aldoxime nitrogen vicinal to ring 3 position and in the same plane. O_s refers to aldoxime oxygen *syn* (*cis*) to proton of aldoxime carbon (standard American Chemical Society nomenclature). H_s refers to aldoxime hydroxyl proton *syn* (*cis*) to aldoxime nitrogen lone pair electrons (purely arbitrary).

TABLE 2

Bond lengths in angstroms versus bond types

Choice was based on expected values from crystallographic studies (14–16) and footnote 2.

Bond type	Bond length (Å)
Ring C—C or C—N	1.40
C—H (all)	1.08
C_7—N_8	1.26
N_8—O_9	1.39
O_9—H_9	0.97
N_1—C_{10}	1.45
C_2—C_7	1.40 Set I 1.55 Set II 1.70 Set III

with respect to the aldoxime nitrogen lone pair and designated H_s or H_t respectively (see Fig. 1). Three sets were designated according to the bond length between carbon 2 and carbon 7. Table 2 contains these bond lengths as well as the lengths used for all the other bonds throughout this group of calculations. These lengths were chosen by reviewing general tabulations of crystallographic data (14) as well as the extensive list of published and unpublished[2] crystal structures of aldoximes (15, 16). These bond lengths are not to be construed as anything more than a reasonable starting point, and the same point is to be made concerning the bond angles, which were all set equal to 120 degrees. It is further noted that this initial study is concerned solely with the protonated or acidic state of the cation (no anion included).

TABLE 3

Total energies for each conformer at each C_2—C_7 bond length

Total energy (electronic), at zero degrees, of the ground state of a single conformeric molecule in electron volts (the greater the negativity the greater the stability). See text and Fig. 1 for conformeric designations.

	Bond length, C_2—C_7 (Å)		
Conformer	1.40 I	1.55 II	1.70 III
N ↑ TT	−858.84131	−859.79601	−860.38558
N ↑ TS	−858.67233	−859.61012	−860.18550
N ↑ ST	−858.85130	−859.73120	−860.09119
N ↑ SS	−858.68282	−859.56560	−859.91885
N_3TT	−852.58314	−854.43677	−855.77232
N_3TS	−853.71936	−855.59515	−856.77740
N_3ST	−856.79145	−857.85085	−858.47557
N_3SS	−856.94263	−857.99878	−858.63718
N_1TT	−849.67167	−848.58391	−847.90159
N_1TS	−844.02016	−846.59140	−848.16136
N_1ST	−855.93046	−857.28247	−858.01933
N_1SS	−855.33867	−856.69140	−857.42384

RESULTS

A. *Total Energy*

The total energy, which is in fact the internal (ground state) energy of a single molecule at zero degrees and under no external perturbations, is here expressed in electron volts (eV), where 1 eV = 23.061 kilocalories (kcal). Table 3 contains the total energies (all have negative sign) for each of the twelve conformers in each of the three sets. The larger the negativity the more stable the molecule. The absolute magnitude of the total energy is not to be considered sufficiently accurate, since the model has not yet been quantitatively parameterized, for comparison with heats of formation as empirically measured, but the relative order should be a fair, but not necessarily an unequivocal indication of

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[2] B. Jerslev, private communication.

stability. Clearly indicated is the marked instability of the N_1TT and N_1TS conformers in all sets. The N_3TT and N_3TS conformers likewise are less stable, but begin to show significant gain in their stability with increasing C_2—C_7 bond length. The planar *syn* (*cis*) conformers are always significantly more stable than the planar *anti* (*trans*) conformers. The N_3S_{-} pair are the most stable planar conformers in all sets, but less significantly so when compared to the N_1S pair at the longer C_2—C_7 bond lengths. In every set, the calculations indicate that the out of plane conformers (OOP) are significantly more stable than any planar isomer, including the N_3S pair. The most stable of the out of plane conformers is N ↑ TT, and the N ↑ ST conformer is more stable than both its proton *syn* isomer or N ↑ TS. The H_t's in the N_1 category are generally more stable than their proton *syn* isomers while the reverse prevails throughout the N_3 category. Looking at Fig. 2 as well as Table 3, it is to be noted that all conformers with the exception of N_1TT get

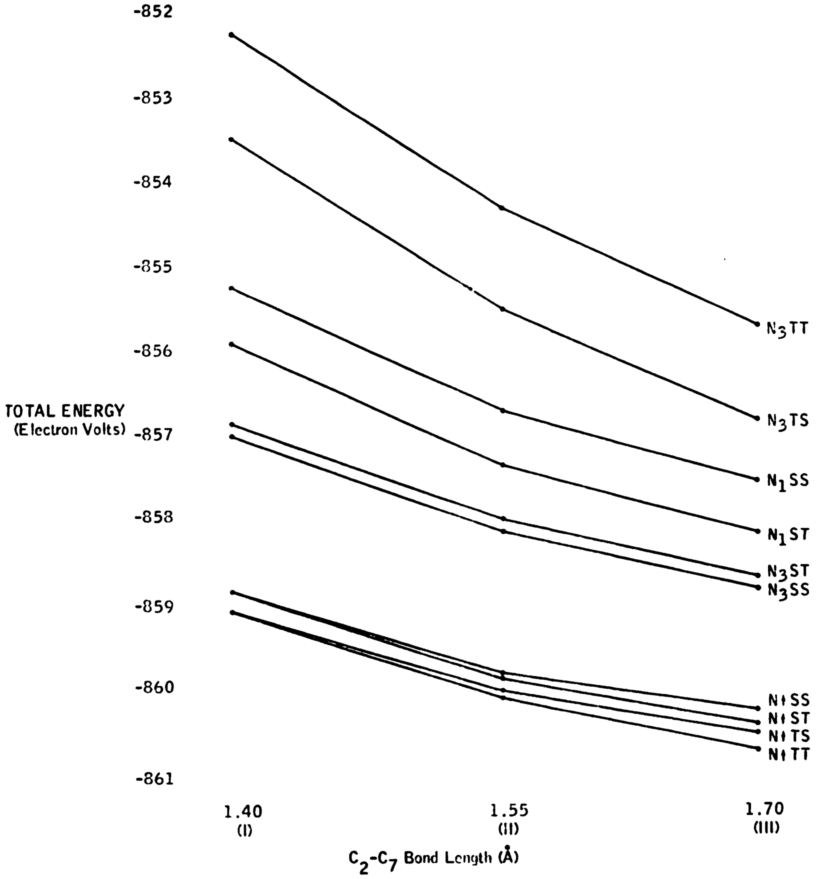

FIG. 2. *Total energy of each conformer versus C_2—C_7 bond length*

The total energy of each conformer is the energy in electron volts for the ground state of the free molecule at zero degrees Kelvin calculated according to the method described in the text. The greater the negativity, the greater the stability. The calculations were made for each conformer at three C_2—C_7 bond lengths (Angstroms) 1.40 (Set I); 1.55 (Set II), 1.70 (Set III). For atom numbering and conformer designation see Fig. 1 and text. The connecting lines are used only for convenience in following each conformer and are not to be considered an energy surface. Conformers N_1TT and N_1TS are so unstable they are off (above) this scale.

appreciably more stable as the C_2—C_7 bond length is increased from 1.40 Å to 1.70 Å.

B. *Molecular Total Overlap Population (MTOP)*

The electron density between any two atoms i and j, whether bonded or nonbonded, is represented by the total overlap population (TOP) between these centers. This TOP is related to the binding energy between two atoms. If the TOP between any two atoms is summed over all centers, this molecular total overlap population (MTOP) should be somewhat indicative of the total binding energy of the entire molecule and therefore of its stability. Table 4 lists the values calculated for each conformer in each set and it is readily noted that the least stable conformer is N_1TT. It shows marked improvement at longer C_2—C_7 bond lengths as does N_1TS to a lesser extent. The latter, in fact, is more stable than N_1SS and almost as stable as N_1ST at 1.70 Å. The N_3TT conformer improves moderately with increasing bond length and N_3TS does so to a lesser extent. The N_3S_- pair are the most stable planar conformers with the N_1S_- pair close behind. Both demonstrate less stability above 1.55 Å. The out of plane conformers are clearly more stable than the planar conformers with the N ↑ S_- pair the most stable of the entire group. The stability of the out of plane conformers falls off at bond lengths greater than 1.55 Å. The most outstanding example of peaking at or near 1.55 Å was demonstrated by the N ↑ S_- pair as can be seen in Fig. 3 and extrapolation of all others except the unstable N_1T_- and N_3T_- pairs suggest a maximum stability between 1.40 Å and 1.55 Å. Certainly in these "nonsterically hindered" conformers the stability at 1.70 Å is minimal. The proton *anti* (*trans*) is generally more stable throughout the group with the obvious exceptions again of the N_1T_- and N_3T_- pairs. Generally then, the ordering of stabilities mimics that derived from the total energy with the minor exception that the out of plane N ↑ SS and N ↑ TT interchange, as does planar N_3ST with N_3SS, and N_1TS with N_1TT (both being oxime proton configurational changes).

TABLE 4

Molecular total overlap populations for each conformer at each C_2—C_7 bond length

Molecular total overlap population (MTOP) in terms of electron density (probability) (the greater the positivity the greater the stability). See text and Fig. 1 for conformeric designations.

	Bond length, C_2—C_7 (Å)		
Conformer	1.40 I	1.55 II	1.70 III
N ↑ TT	12.87752	12.87124	12.84096
N ↑ TS	12.88003	12.86991	12.83852
N ↑ ST	12.89289	12.97777	12.85640
N ↑ SS	12.88360	13.00684	12.84593
N_3TT	12.02921	12.40763	12.58712
N_3TS	12.76276	12.80891	12.81299
N_3ST	12.85392	12.85346	12.82614
N_3SS	12.85017	12.84785	12.82223
N_1TT	5.32280	9.30883	10.84311
N_1TS	12.18220	12.26605	12.81952
N_1ST	12.82014	12.83448	12.82302
N_1SS	12.81282	12.82660	12.81478

C. *Rotational Barriers and Conformational Analysis*

By taking the differences in total energy or MTOP between any two conformers, the magnitude of the barrier to rotation or conversion from one conformer to any other can be estimated. Tables 5–8 contain compilations of these values. As can be seen from Table 5, the range of the barrier to rotation from the out of plane state to the planar state is smaller for *syn* (*cis*) conformers (1.28–3.30 eV) than for *anti* (*trans*) conformers (3.41–14.65 eV). Generally the conversions are smaller at the longer bond lengths. The conversion to N ↑ SS from N_3SS at 1.70 Å is the smallest energy change in the entire series, and at 1.28 eV is equivalent to 29.44 kcal. Examination of MTOP differences in Table 6 reveal that the largest conversions for hydroxyl *syn* (*cis*) isomers are at 1.55 Å, but in all other respects the trends follow the energy analysis. The energy differences expected from hydroxyl *syn*

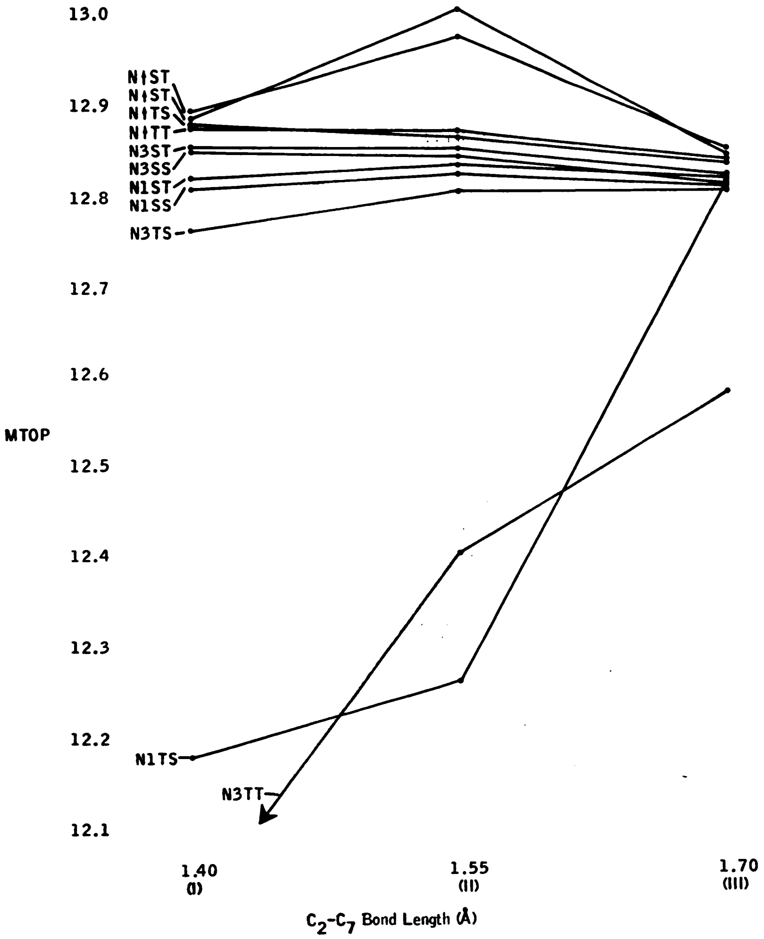

FIG. 3. *Molecular total overlap population (MTOP) for each conformer versus* C_2*—*C_7 *bond length*

The molecular total overlap population of each conformer is the sum of the overlap populations between each atom and every other atom expressed in terms of density (probability) of electrons and calculated according to the method described in the text for the ground state of the free molecule at zero degrees Kelvin. The greater the positivity the greater the stability. The calculations were made for each conformer at three C_2—C_7 bond lengths (Angstroms): 1.40 (Set I); 1.55 (Set II); 1.70 (Set III). For atom numbering and conformer designation see Fig. 1 and text. The connecting lines are used only for convenience in following each conformer and are not to be considered a stability-equivalent surface. Conformer N_1TT and Set I of conformer N_3TT are so unstable they are off (below) this scale.

(*cis*)-*anti* (*trans*) configurational conversion as seen in Table 7 are all positive for planar conformers and mixed for out of plane conformers. Here, where a positive sign implies an energy cost (i.e., less stability), the range in the planar conformers is much larger on the basis of the great instability of the *anti* (*trans*) conformers. Differences within the OOP conformers are small enough to be randomized by thermal effects. In striking contrast, the differences for the same conversions as measured by MTOP in Table 8 are all negative, indicating the greater stability of the *syn* (*cis*) conformers in any rotational and proton configurational state.

DISCUSSION

In the XHMO model the total energy is obtained as the sum over the orbital en-

TABLE 5

Total energy (TE) change in converting (rotating) a planar conformer to its OOP analog at its respective C_2—C_7 bond length

Total energy (electronic), at zero degrees, of the ground state of a single conformeric molecule in electron volts (the greater the negativity the greater the stability). See text and Fig. 1 for conformeric designations. Negative values imply a total energy gain (more stable) due to the conversion.

	Bond length, C_2—C_7 (Å)		
Conversion	1.40 I	1.55 II	1.70 III
To *From*			
N↑TT - N_3TT	−6.25815	−5.35924	−4.61326
N↑TS - N_3TS	−4.95297	−4.01497	−3.40810
N↑ST - N_3ST	−2.05985	−1.88035	−1.61562
N↑SS - N_3SS	−1.74019	−1.56682	−1.28167
N↑TT - N_1TT	−9.16964	−11.21210	−12.48399
N↑TS - N_1TS	−14.65217	−13.01872	−12.02414
N↑ST - N_1ST	−2.92084	−2.44873	−2.07186
N↑SS - N_1SS	−3.34415	−2.87420	−2.49501

ergies of the occupied levels. In that the elements are not yet quantitatively parameterized, the Hamiltonian matrix is not a perfect approximation to the Hartree-Fock Hamiltonian which yields reasonably accurate total energies. Hence the magnitude of the XHMO orbital energies, and consequentially the total energy, is quantitatively undeterminable. Relative differences among the orbital energies as well as

TABLE 6

Differences in molecular total overlap populations (MTOP) in converting (rotating) any planar conformer to its (out of plane) analog at respective C_2—C_7 bond lengths

Molecular total overlap population (MTOP) in terms of electron density (probability) (the greater the positivity the greater the stability). See text and Fig. 1 for conformeric designations. Positive values imply a gain in MTOP (greater stability) due to the conversion.

	Bond length, C_2—C_7 (Å)		
Conversion	1.40 I	1.55 II	1.70 III
To *From*			
N↑TT - N_3TT	.84831	.46361	.25384
N↑TS - N_3TS	.11727	.06100	.02553
N↑ST - N_3ST	.03897	.12431	.03026
N↑SS - N_3SS	.03343	.15899	.02370
N↑TT - N_1TT	7.55472	3.56241	1.99785
N↑TS - N_1TS	.69783	.60386	.01900
N↑ST - N_1ST	.07275	.14329	.03338
N↑SS - N_1SS	.07078	.18024	.03115

TABLE 7

Total energy (TE) differences for all conversions of OH from syn (cis) to anti (trans) for each C_2—C_7 bond length

Total energy (electronic), at zero degrees, of the ground state of a single conformeric molecule in electron volts (the greater the negativity the greater the stability). Positive values imply loss in energy (less stability) due to the conversion.

	Bond length, C_2—C_7 (Å)		
Conversion	1.40 I	1.55 II	1.70 III
To *From*			
N↑TT - N↑ST	.00999	−.06481	−.29439
N↑TT - N↑SS	−.15849	−.23041	−.46653
N↑TS - N↑ST	.17897	.12108	−.09431
N↑TS - N↑SS	.01049	−.04452	−.17234
N_3TT - N_3ST	4.20831	3.41408	2.70325
N_3TT - N_3SS	4.35949	3.56201	2.86486
N_3TS - N_3ST	3.07209	2.25570	1.69811
N_3TS - N_3SS	3.22327	2.40363	1.85978
N_1TT - N_1ST	6.25879	8.69856	10.11774
N_1TT - N_1SS	5.66700	8.10749	9.52225
N_1TS - N_1ST	11.91030	10.69107	9.85797
N_1TS - N_1SS	11.31851	10.10000	9.26248

TABLE 8

Molecular total overlap population (MTOP) differences for all conversions of OH from syn (cis) to anti (trans) for each C_2—C_7 bond length

Molecular total overlap population (MTOP) in terms of electron density (probability) (the greater the positivity the greater the stability). Negative values imply loss in MTOP (less stability) due to the conversion.

	Bond length, C_2—C_7 (Å)		
Conversion	1.40 I	1.55 II	1.70 III
To *From*			
N ↑ TT - N ↑ ST	−.01537	−.10653	−.01544
N ↑ TT - N ↑ SS	−.00617	−.13560	−.00497
N ↑ TS - N ↑ ST	−.01286	−.10786	−.01788
N ↑ TS - N ↑ SS	−.00357	−.13693	−.00741
N_3TT - N_3ST	−.82471	−.44583	−.23902
N_3TT - N_3SS	−.82096	−.44022	−.23511
N_3TS - N_3ST	−.09116	−.04455	−.01315
N_3TS - N_3SS	−.08741	−.03894	−.00924
N_1TT - N_1ST	−7.49734	−3.52565	−1.97991
N_1TT - N_1SS	−7.49002	−3.51777	−1.97167
N_1TS - N_1ST	−.63794	−.56843	−.00350
N_1TS - N_1SS	−.63062	−.56055	−.00474

among the total energies for comparable systems, however, have been observed to be satisfactory for predictions of electronic transition energies and relative molecular stabilities.

The choice of MTOP as a measure of the stability of a molecular system depends formally upon the validity of the interpretation of the maximum overlap principle, i.e., that physical systems tend to exist in a state characterized by a conditional maximum of the overlap. It has been shown that in the simple Hückel model of homonuclear π-electron systems the solution of the minimum-energy problem is equivalent to the solution of the maximum-overlap problem when $H_{ij} = \mathrm{K}\, S_{ij}$. For a heteroatomic system, or when H_{ij} is not directly proportional to S_{ij}, as in our XHMO model, the two solutions deviate and the deviation is some measure of the noncommutability of H and S, i.e., $HS \neq SH$ (17). It is to be noted that when the two variational principles do not lead to equivalent results it would be expected that the minimum-energy principle is the more valid of the two; however, it is well known that in Hückel models different parameters are necessary for calculating different properties (18). Hence it is possible to have a Hamiltonian matrix which yields better electron distributions (as obtained from a Mulliken wave function analysis) than energies.

Finally, it should be pointed out that the more general validity of the minimum-energy principle is inferred from its relation to the maximum-entropy principle,[3] and from a generalization of a previous perturbation treatment of molecular stability (19). In this latter, the total energy E is written as

$$E = \sum_{i} [(\mathrm{NAP})_i H_{ii}] + 2 \sum_{i \neq j} \left[\frac{(\mathrm{TOP})_{ij}}{S_{ij}} H_{ij} \right]$$

Hence it is seen that the overlap population between orbitals i and j ($[\mathrm{TOP}]_{ij}$) enters as one factor among several in the expression for E and MTOP $= \Sigma_{i \neq j} (\mathrm{TOP})_{ij}$ is not involved explicitly as such.

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[3] J. R. Hamann and W. Giordano, submitted to *Theoret. Chim. Acta.*

In accord with this view, it can be observed that MTOP has an extremum as a function of the $C_2—C_7$ bond distance which appears within the expected bounds for a $C_2—C_7$ bond length in aromatic ring linked aldoximes; however, the total energy exhibits no such extremum. It should be emphasized that this lack of correlation of the energy with optimum bond length applies to the magnitude of the energy and not necessarily to energy differences. In fact, the relative ordering of the total energies generally mimics the ordering of the MTOP's; hence the two methods of estimating relative stabilities are largely mutually consistent.

Assuming then that on theoretical grounds the MTOP analysis can be expected to be a reasonable indication of molecular stability and since the total energy correlation is good, certain observations may be made. To begin with, proton configuration may be a significant perturbation as suggested by these calculations. Certainly this would not be expected for the nonsterically hindered conformers on classical grounds. Secondly, planar *anti* (*trans*) conformers should have a very low probability of existence. In fact, some TOP's of certain bonds in N_1TT were negative, indicative of an antibonding state (7); that is, there would be two fragments and, therefore, no longer a single molecule. Furthermore, although there was indication of $C_3—H_3———0_5$ hydrogen bonding in N_3TS (7) there is no improvement of the molecular wave function over N_3SS as demonstrated by MTOP analysis. Third, the markedly greater stability of N_3S and N_1S planar conformers in this study has been suggested experimentally by previous work (5, 6). Furthermore, since the *syn* (*cis*) out of plane conformers are generally as stable as *anti* (*trans*) out of plane conformers the *syn* (*cis*) configuration that was reported may in fact be the out of plane *syn* (*cis*). Fourth, recent crystallographic analysis of 2-PAM-I (16),[2] has demonstrated that the N_3S conformation prevails in the solid state. The markedly greater stability of the out of plane conformers in the present study, which is a study of the free molecular state and, therefore, slightly more analogous to the state in dilute solution, may be either an indication of a conformeric conversion in changing state from solid to solution or may be attributable to an inadequacy of the theoretical model used in this study.

In favor of the former is the reasonable theoretical foundation of the MTOP analysis and the fact that this study has indicated N_3S_- is the most stable planar conformeric pair. Classically, on qualitative and prior empirical grounds, the resonance energy gain in the planar state would be thought sufficient to outweigh the loss, if any, in "nonbonded interactions." In fact, the reverse is what these calculations have implied. It might be added that although "planar" 2-PAM-I solid is yellow, the chloride salt is white, and since both are yellow in basic solution (deprotonated), but colorless in acid (protonated), these observations (20) might be interpreted as a correlation of color with planarity and lack of it with nonplanarity! A crystallographic study of 2-PAM-Cl should help resolve this issue. Recent electron spin resonance spectroscopy[4] of the chemical oxidation intermediates of 2-PAM in aqueous solution has demonstrated two, and at times three, distinct free radical species, one of which suggests an out of plane state.

The adequacy of the XHMO model chosen in this study cannot be established unequivocally by this preliminary work and since it must await additional evaluation now in process the interpretation of results must be spoken of reservedly. If nothing else, a serious question is raised with respect to the relation in general of crystallographic analysis of the solid state of molecules and their structures in solution. The implications that these observations suggest and the considerations that they should provoke must be evaluated for incorporation in future experimental studies and design.

[4] W. Giordano and P. G. Mennitt, unpublished results.

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