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IMPLEMENTATION OF THE GAUSSIAN 78 PROGRAMS ON THE NYU VAX/11-780: A PROBE INTO BASIS SET AND CORRELATION EFFECTS ON THE STRUCTURE OF MOLECULAR COMPLEXES

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I. Implementation of the Programs

We report the implementation of the GAUSSIAN 78 system of programs for *ab-initio* quantum mechanical calculations of molecular electronic structure of the New York University VAX/11-780 minicomputer. We illustrate the use of the program package in a theoretical investigation of a model for drug-receptor complexes.

The programs were developed by the Pople group (1) and the present version was designed by them specifically for use of VAX/11-780 minicomputer. Several characteristic features of this version of the program are worth mentioning: Calculations can be performed on systems containing as many as 80 Gaussian basis functions (extension to a larger basis is possible). The Gaussian integrals are efficiently evaluated by use of a) the shell concept (2) and b) the Rys polynomial method (3). Optimization of molecular structure can be performed by the analytic calculation of the nuclear and electronic forces from first derivatives of the Hartree-Fock energy with respect to structural parametrs (4). Effective potential (pseudopotential) integrals and their first derivatives with respect to structural parameters can also be evaluated for simplication of the study of large systems by pseudo-potential calculations (5). The programs can be used to evaluate the contribution of electron correlation effects by use of a) the Moller-Plesset approximation to second and third orders (6) and b) configuration interaction including all single and double excitastions. The efficient control of the flow (overlaying) of these programs is achieved by submitting the main driver program ("LINK 0") as a process which remains resident in the system during the entire calculation and which submits the other programs as subprocesses. The program creates and deletes its own scratch files as necessary and protects against collision of different Gaussian 78 jobs created by the same user. Region requirements are adjusted for each link (subprocess); the maximum region used on a typical run is 300K bytes or about 600 pages. Damages from system crashes are avoided by creation of intermediate input/output files which can be used to restart the calculation at a later time.

A CDC version of Gaussian 76 (an earlier version of this system of programs) is presently available on the CDC-6600 at NYU. By running jobs which do not take advantage of the newer capabilities of Gaussian 78 we were able to make comparisons of jobs run on these 2 machines. Typical jobs were found to run 3 to 4 times longer on the VAX. For example, a self consistent field calculation of parhydroxyaniline reports 525 cpu seconds on the CDC and 2221 cp seconds on the VAX (or 838 SRU on the NYU CDC-6600 and 2980 total on the VAX). Preliminary reports from J.S. Binkley, in Pople's group, claim that a newer version, Gaussian 80 (7), with more sophisticated control of I/O on the VAX reduces I/O time by a factor of ten. This improvement should make execution time of these programs on the VAX similar to that on the CDC-6600.

We report below the use of this system of programs for the theoretical study of molecular complexes that serve as models of drug receptor interactions. The largest calculations in this study contain 67 basis functions and were evaluated to second and third order in Moller-Plesset perturbation theory, requiring approximately 10.5 and 46.5 total hours, respectively.

II. USE OF THE PROGRAMS

Theoretical calculations of the electronic structure of systems of biological and/or pharmacological interest generally require large scale computational efforts to calculate large molecules and models for molecular mechanisms such as enzyme-substrate and drug-receptor interactions. All electron ab-initio methods for the study of such large systems are usually limited to self consistent field (SCF) calculations with minimal basis sets. We have used such approaches to study the interaction of 5-hydroxytryptamine (5-HT) and 6-hydroxytryptamine (6-HT) with imidazolium cation (IMID) to probe the interaction of tryptamines with the LSD/5-HT receptor [9-11]. However, as pointed out specifically for these complexes [9], the use of minimal (e.g., STO-3G) basis sets, the neglect of electron correlation, and the choice of a fixed interplanar separation may affect some of the qualitative conclusions from such calculations. These points are presently investigated in complexes of para-hydroxyaniline (PHA) and meta-hydroxyaniline (MHA) with formamidinium cation (FAM).

METHODS

A. Theoretical Techniques

Hartree-Fock self consistent field calculations were done with the GAUSSIAN 70 system of programs [13]. The basis sets used were either the minimal STO-3G basis or the split valence 4-31G [14] basis. The interaction energy of the complexes was decomposed as before [11] into electrostatic (ES), polarization (PL), exchange (EX) and charge transfer plus mixing (CT + mix) components using Morokuma's decomposition scheme [15] as implemented in a modified version of GAUSSIAN 70 [16]. Correlation effects were evaluated by calculation of the Möller-Plesset (MP) energy to second (E(MP2)) and third (E(MP3)) order [6,17]. These contributions to the correlation energy were obtained using the GAUSSIAN 78 system of programs [1] (see above).

B. Geometries

Para-hydroxyaniline (PHA) and meta-hydroxyaniline (MHA) were constructed from the corresponding atoms in 5-HT and 6-HT, respectively (see Figure 1). Hydrogen atoms were placed at standard bond lengths wherever needed. Similarly, formamidinium (FAM) was constructed as shown in Fig. 1 from imidazolium. The geometries of the tryptamines used in this construction were based on crystal structures [18]; the coordinates of the parent molecules were given previously [11]. The fixed interplanar separation used for the PHA/FAM and MHA/FAM complexes was 6.238 bohr, based on the average "close contact" separation in the crystal structure of stackings complexes of 5-HT [18].

C. Relative Orientations

Since PHA, MHA and FAM were constructed as analogs of 5-HT 6-HT, and IMID respectively, the alignments chosen for the molecular complexes studied here are analogous to those studied in the complexes of the parent compounds [11]. These alignments were chosen on the basis of molecular reactivity criteria [8] from the electrostatic potential of 5-HT obtained from minimal basis set calculations [8,15, 16]. The potential exhibits two minima - one next to the hydroxyl and the other in the six membered ring of the indole portion - in a paralell plane 2.9 bohr (1.6 A°) above the molecule. Similarly, the electrostatic potential of IMID has two maxima. It was also shown [8,9,11] that the two minima of 5-HT define the direction of a vector which in the 5-HT/IMID complex tends to align with the vector obtained by connecting the two maxima in the electrostatic potential map of IMID. A relative orientation named A-5 was defined accordingly [11] by placing IMID above 5-HT such that the two vectors are parallel and the N1 hydrogen of IMID is above the indole nitrogen of 5-HT. The exact geometry of A-5 was given [11]. The A-5 alignment in the PHA/FAM and MHA/FAM complexes is the same (Figure 2).

Based on prior evidence [11] that the nature of these complexes is predominantly electrostatic a second relative orientation of the interacting molecules is defined as follows: The charge densities of both 5-HT and IMID are used to construct a point charge representation of each of them based on their Mulliken populations [20]. Keeping an interplanar separation of 6.238 bohr, a complete scan of the monopole-monopole representation of the energy of interaction (including rotation in the plane) is performed. The lowest energy position of these point charge models is called MIN-5, and is characterized by the same orientation angle between the vectors as in A-5. Again the alignment MIN-5 in the PHA/FAM complex is taken to be the same as for the 5-HT/IMID complex (Fig 2).

For the MHA/FAM complex the aligments were taken from the corresponding calculations on 6-HT, IMID and the 6-HT/IMID complex. The A-6 and MIN-6 alignments have definitions analogous to A-5 and MIN-5 [11]. Here again the relative angle between the vectors of 6-HT and IMID is the same in A-6 and in MIN-6.

RESULTS

The complexes PHA/FAM and MHA/FAM resulting from the alignments defined as A-5, MIN-5, A-6 and MIN-6 are very similar to the parent complexes [11]. This is exemplified for PHA/FAM in Table I: the stabilization energy for all complexes is derived primarily from the electrostatic component. The next largest component in each of these is the EX term which is approximately in the same proportion for all the complexes. Similarly the PL and CT components are in a similar proportion in these systems. Thus the PHA/FAM and MHA/FAM complexes are in fact strikingly similar in nature to the 5-HT/IMID and 6-HT/IMID complexes, respectively. Each is a predominantly electrostatic complex at the STO-3G SCF level with nearly identical breakdown of the stabilization energy into its components via the Morokuma decomposition scheme.

The effect of basis set extension on the description of electronic structure features of the complex is tested with the PHA/FAM complex (Table 2). Changing the basis set in an SCF calculation from the minimal STO-3G to the split valence 4-31G basis, although nearly doubling the total stabilization energy, has little effect on the relative contributions of the various components to the stabilization energy. Results in Table 2 show that at the 4-31G SCF level the PHA/FAM complex is still predicted to be primarily electrostatic in nature with the next largest component (EX) being half as large and the remainder of the stabilization energy contributed in roughly equal parts by PL and CT.

Further evidence of the similarity of the STO-3G and 4-31G description of these complexes is provided in Table 3. Of the four alignments presented for PHA/FAM at the STO-3G level, that based on a minimized electrostatic energy from point charges (MIN-5) is found to be most stable. At the 4-31G level the MIN-5 position is again found to be the most stable. Similar comparisons for the MHA/FAM complex give analagous results: the MIN-6 position is most stable at both the STO-3G and 4-31G levels. Thus the description of the systems studied here, being predominantly electrostatic in nature, does not change on going from an STO-3G to a 4-31G basis.

The effects of correlation at the MP2 level (with an STO-3G basis) are also presented in Table 3. The most favored alignment of the PHA/FAM at the MP2 level remains MIN-5 i.e., unchanged from the SCF results using either STO-3G or 4-31G bases. Similary the MHA/FAM complex is still favored in the MIN-6 alignment. Thus neither the extension of basis set (to 4-31G) nor the inclusion of correlation energy to second order changes the preferred alignment in these systems. We note also that the additional stabilization energy at MP3 (E3) over that at MP2 (E2) is an order of magnitude lower (e.g., .082 kcal/mole as compared to 1.15 kcal/mole for MHA/FAM at MIN-6) and does not change the conclusions presented here on the effects of electron correlation.

The sensitivity to interplanar separation is shown in Table 4. Both at the SCF and MP2 levels for PHA/FAM in the A-5 and MIN-5 alignments the potential energy dependence on interplanar separation is very shallow. Thus at both the SCF and MP2 levels these complexes are quite insensitive to the interplanar separation. The shorter interplanar separations at MIN-5 than at A-5 are perhaps a reflection of the fact that there is less overlap between the two molecules at MIN-5 than at A-5.

The minima in Table 4 are in remarkable agreement with the average "close-contact" distance of 6.238 bohr observed in complexes of 5-HT with creatinine sulfate [19] and used in our previous calculations [8-11].

CONCLUSIONS

The studies of the small molecular complexes shown here indicate that the description of the nature of interaction obtained at the STO-3G SCF level does not change when the basis set is extended to the 4-31G level or when correlation effects are included to second order in a Møller-Plesset formulation. Furthermore, interplanar separation appears to be a less sensitive parameter than the proper alignment of the fragments. Still to be investigated are the effects of further basis set extension (beyond 4-31G) to include more diffuse basis functions, and the contribution of correlation energy when calculated in more extended basis sets.

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Table 1. Comparison of the decomposition of total stabilization energies in the parent and model complexes. Energies (Kcal/mole) are from calculations with the STO-3G basis set.

Type of Contribution	A-5		MIN-5	
	5-HT + IMID	PHA + FAM	5-HT + IMID	PHA + FAM
ES	-4.52	-3.99	-5.63	-4.87
PL	-1.00	-0.71	-1.21	-0.89
EX	2.39	1.36	1.17	0.93
CT + MIX	-0.59	-0.65	-0.38	-0.37
TOTAL	-3.72	-3.99	-6.05	-5.20

Table 2. The effect of the basis set on the decomposition of total stabilization energies (Kcal/mole) in the model complexes.

Type of Contribution	PHA + FAM @ A-5		MHA + FAM @ A-6	
	STO-3G	4-31G	STO-3G	4-31G
ES	-3.99	-7.01	-4.56	-7.67
PL	-0.71	-1.62	-0.68	-1.60
EX	1.36	3.54	1.49	4.08
CT + MIX	-0.65	-2.47	-0.35	-2.22
TOTAL	-3.99	-7.56	-4.10	-7.41

Table 3. The effect of electron correlation on the stabilization energies (Kcal/mole) in model complexes.

	SCF: STO-3G		SCF: 4-31G		UMP2:STO-3G		E2	
ALIGNMENT	PHA	MHA	PHA	MHA	PHA	MHA	PHA	MHA
A-5	-3.99	-3.68	-7.56	-7.25	-4.96	-4.74	-0.97	-1.06
MIN-5	-5.20	-2.95	-8.60	-5.66	-5.87	-3.94	-0.67	-0.99
A-6	-3.37	-4.10	-6.30	-7.41	-4.60	-5.36	-1.23	-1.25
MIN-6	-3.35	-4.65	-6.67	-8.72	-4.54	-5.80	-1.20	-1.15

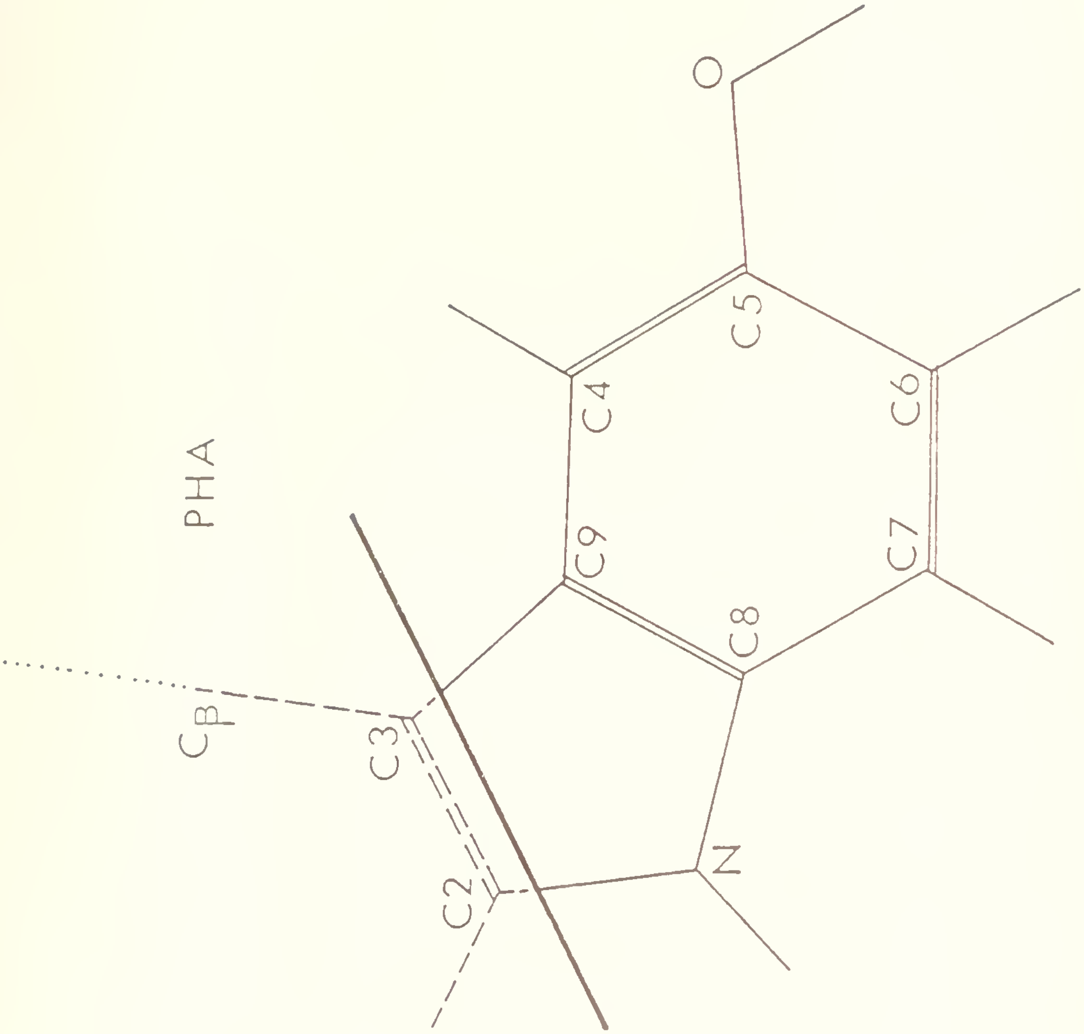
Table 4. Variation of complex stabilization energies with interplanar distance[1)]

INTERPLANAR DISTANCE (BOHR)	E (SCF; STO-3G) (KCAL/MOLE)	E (UMP2; STO-3G) (KCAL/MOLE)
	PHA + FAM at A-5	
5.938	-3.40	-4.76
6.238	-3.84	-4.91
6.538	-3.86	-4.73
6.838	-3.71	-4.43
	PHA + FAM at MIN-5	
5.638	-4.38	-5.39
5.938	-5.05	-5.85
6.238	-5.17	-5.82
6.538	-5.04	-5.58

1) The optimal distance for PHA/FAM at A-5 is 6.485 bohr at SCF and 6.235 bohr at UMP2 levels; for PHA/FAM at MIN-5 the optimal distances are 6.248 bohr and 6.132 bohr respectively.

Figure 1. Construction of a) p-hydroxyaniline (PHA); b) m-hydroxyaniline (MHA); and c) formamidimium (FAM), from the parent compounds.

Figure 2. Relative orientations in PHA/FAM complexes:
a) the Λ-5 alignment; b) the MIN-5 alignment.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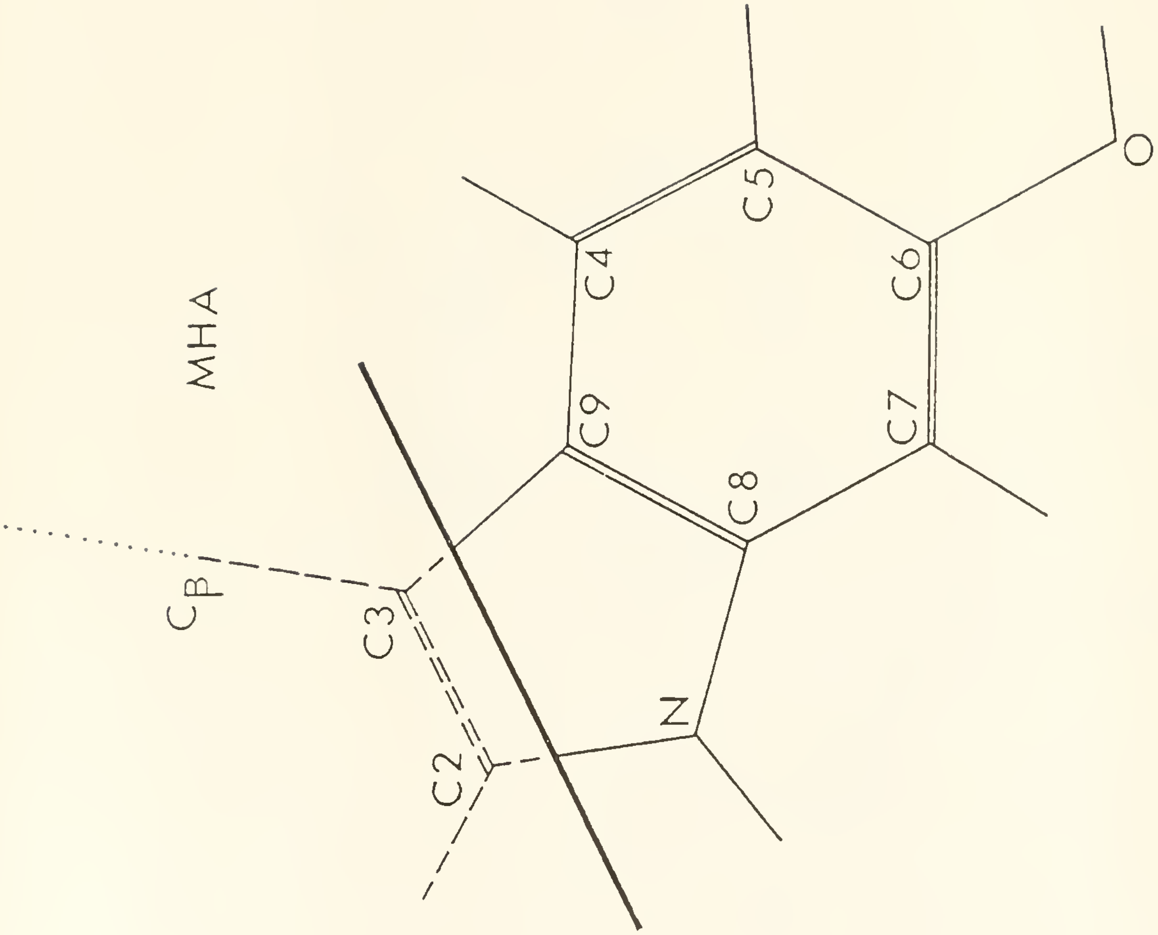
O
C5
C4
C6
C9
C7
C8
C3
C2
N
C_β

Figure 1a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C6
C4
C9
C7
C8
C_β
C3
N
C2

Figure 1b

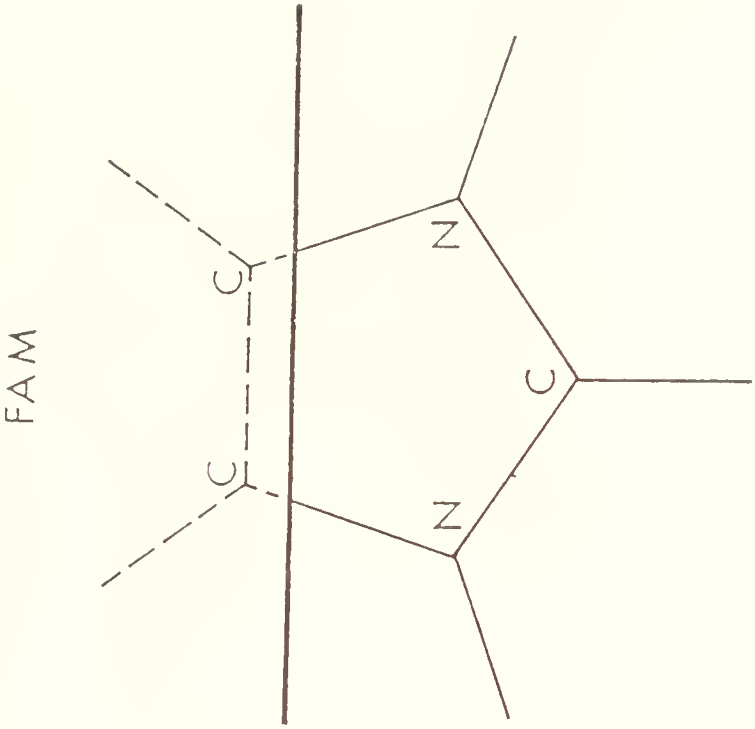
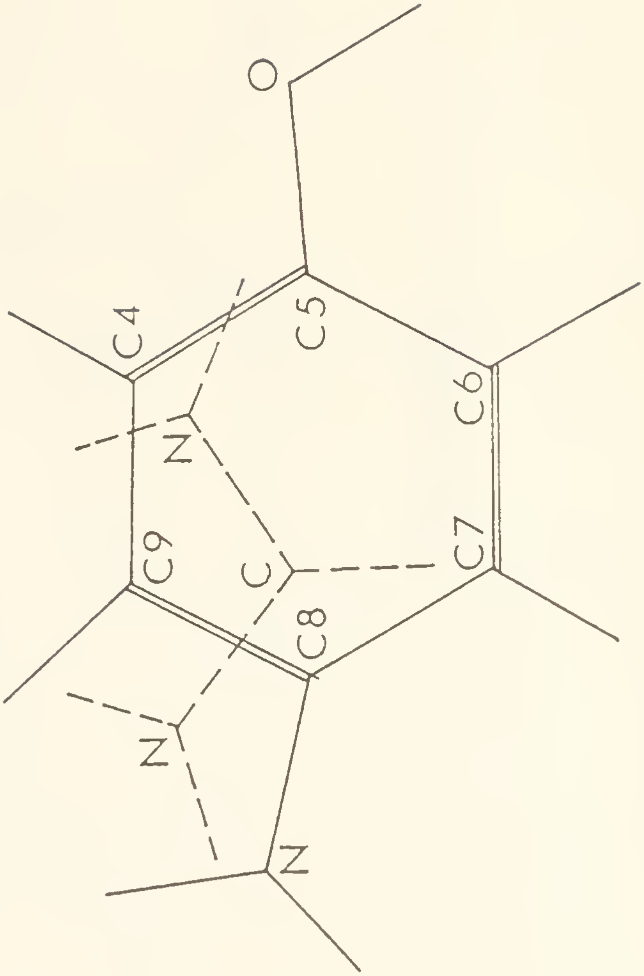


Figure 1c

A - 5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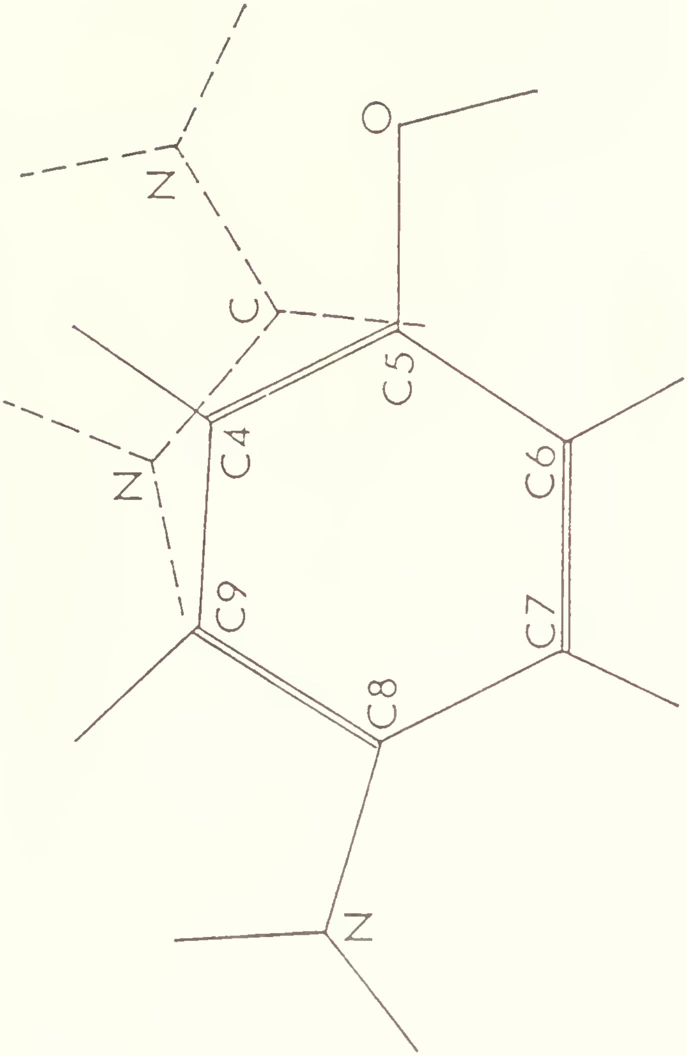
C5
C6
C7
C8
C9
C
N
N
N

Fig. 2a


O
N
C
C5
C4
N
C6
C9
C7
C8
N

MIN-5

Fig. 2b

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