Mechanistic Appraisal of the Charge-Transfer Complexes of Promethazine with Chloranil: A Modelling Approach

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Received August 14, 2000; accepted January 30, 2001

Various mechanisms are often used to explain the interaction between electron donors and acceptors. Commonly proposed mechanisms are those in which the acceptor interacts with the aromatic π-systems in the donor molecule or the acceptor forms a weak interaction of the Lewis acid with Lewis base type. In this study, the above mechanisms were examined as well as other possible mechanisms. Promethazine was chosen as the model drug containing aromatic systems capable of π–π interaction as well as *N*-methyl group capable of forming a complex with the weak Lewis acid, *p*-chloranil. Our modelling studies revealed that the situation where the *p*-chloranil interacts with a protonated *N*-methyl group is the most significant mechanism of interaction, based on the calculated energies for the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), the Tripos force field energy terms and also the stability of the complexes during molecular dynamics simulations.

Key words mechanistic appraisal; charge-transfer; promethazine; chloranil; modelling

π-Acceptors have often been used as important tools in pharmaceutical analysis as they form distinct colours with various drugs.[1,2] Adikwu and co-workers recently reported on the use of π-acceptors for the analysis of promethazine,[3] diethylcarbamazine[4] and moclobemide.[5] Agarwal and others reported on the use of π-acceptors in the analysis of alkaloids,[6] penicillins[7] and sulphonamides.[8] Thus these quinone derivatives have been important tools in the quantitative and qualitative assessment of pharmaceuticals, especially in laboratories where advanced equipment may not be available. However, the mechanism of interaction of the π-acceptors with donors is not clearly understood. A blanket name of "charge-transfer" is often associated with this complexation processes. This name would suggest that electron-rich molecules donate electrons to electron-poor molecules, in this case the π-acceptors. However, various possible mechanisms have been proposed for the complexation phenomenon.

Taha and El-Kader studied the interaction of *N*-ethyl drugs with chloranil on thin layer chromatograms.[9] They proposed a mechanism whereby there could be dehydrogenation of the *N*-ethyl compounds to enamines, which condense with a second molecule of haloquinone to yield blue dienalkylaminoquinones. They also proposed a mechanism of interaction for *N*-methyl secondary amine analogues. Belal *et al*. used chloranil in the assay of naphazoline, clemizole and piperazine.[10] Charge-transfer was the proposed mechanism whereby the drugs acted as n-donors or Lewis base and chloranil as the acceptor or Lewis acid. Similarly, Adikwu *et al.* studied the use of chloranilic acid in the spectrophotometric analysis of promethazine in non-aqueous medium.[3] A charge-transfer process was thought to exist as the mechanism of interaction whereby the promethazine acted as the Lewis base and the chloranilic acid as the Lewis acid. In all these suggested mechanisms of interaction, the exact mode of interaction is not clear. In this study, a molecular modelling approach is applied to the interactions purely from a complexometric view point to further clarify the interaction mechanisms.

Experimental

All molecular modelling studies were carried out using Silicon Graphics Impact 10000. The molecular modelling package SYBYL 6.5[11] was used for all the studies. The molecules of promethazine and chloranil were sketched using the SKETCH module within SYBYL and geometry optimised using the force field MAXIMIN of the same program. Conformational search for the molecules was carried out using the SEARCH module of the same program. The chloranil–promethazine complexes were sketched in accordance with dimensions similar to those of similar complexes of chloranil obtained from the Cambridge Crystallographic Database.[12] The chloranil was placed at different geometries and distances from the promethazine and merged into the same molecule area using the MERGE of the program SYBYL.[11] Other possible chloranil–promethazine complexes were sketched. The Powell method was applied during the geometry optimization using Gasteiger–Huckel charges on the molecules. Initial optimization was done using the simplex approach (threshold of 1000) and terminating with the gradient technique at minimum energy change of 0.05 kcal/(mol·Å) and a list terms threshold of −10. During further geometry optimization the molecules carried charges calculated using the PM3 method within the molecular modelling package SPARTAN.[13] The NB cut-off was 8 while a dielectric constant of 4.806 was used indicative of chloroform and to simulate the non-aqueous laboratory solvent in which the complexometric experiments are often carried out. Full geometry optimization was also achieved using MOPAC at the single point state of PM3. Surface properties calculated include molecular orbitals, dipole, electrostatic charges and bond order. The surface energies for the highest occupied molecular orbitals (HOMO) and the lowest unoccupied molecular orbitals (LUMO) were also calculated at medium resolution. The GRID interaction fields for chloranil were computed using Grid Version 16 and NH_2 group (with lone pairs) as the probe.[14] All molecular dynamics simulations were carried out in chloroform using a pre-computed box measuring 48.764×48.764×48.764 Å^3, a cut-off of 15 Å and a duration time of 100000 fs (Fig. 1). The snapshots were taken every 5000 fs while the calculation was done under NTP (normal temperature and pressure) of 300 K and a pressure of 1 atm. The compressibility was fixed at 10^6/atm (the value for chloroform) while the temperature and pressure coupling factors were fixed at 100 and 500, respectively. The Boltzmann velocity of 32759/s was used while the non-bonded update was fixed at 10. The dielectric constant was corrected to 4.806 for chloroform. The conditions were chosen to mimic laboratory conditions in which the complexation is carried out.

Results and Discussion

The structures of promethazine and chloranil are shown in Chart 1. Promethazine is an electron rich compound while chloranil is an electron deficient compound. Chloranil is a derivative of benzoquinone. The reason for its behaviour lies in the distribution of electrons in the excited states. Generally, the electron deficient oxygen is the point of attack.[1]

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The results of the systematic search conducted on the promethazine indicated energy levels ranging from 14.97—27.67 kcal/mol. The conformation with the least energy (the most favourable energy) was therefore selected for complexometric studies.

Chart 2 shows the primary complexes formed between chloranil and promethazine. These were subjected to force field geometry optimizations and the various energy terms are shown in Table 1.

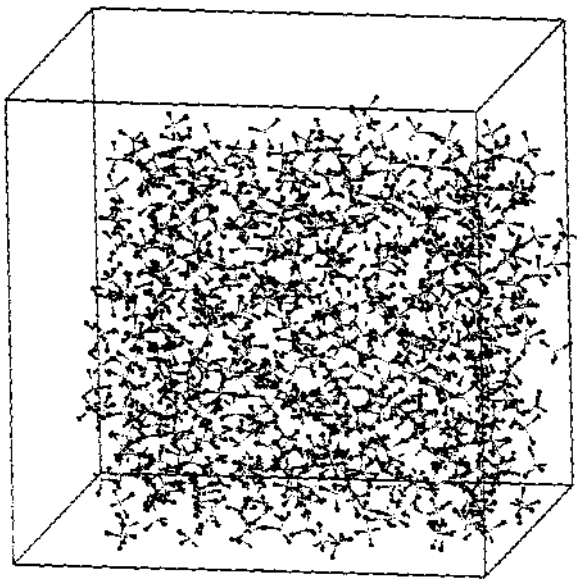


Fig. 1. Pre-computed Box Containing 553 Molecules of Chloroform Used for the Molecular Dynamics Studies

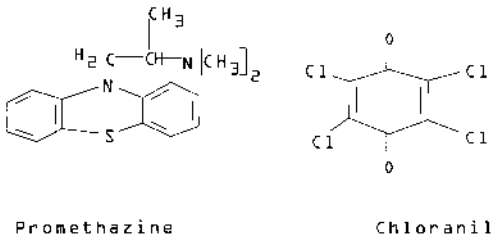


Chart 1. Molecular Structures of Promethazine and Chloranil

The stabilization energies were calculated from the total energies of the complexing species and the apparent total energy of each of the complexes. The total energies obtained from the single compounds were 7.219 kcal/mol for chloranil, −0.5 kcal/mol for promethazine (unprotonated) and 13.554 kcal/mol for promethazine (protonated). The highest van der Waals energy was obtained with complex I while the smallest was obtained with complex IV. There was a reversal with electrostatic energy which was highest for complex IV but smallest for complex I. The high repulsive 1—4 electrostatic energy which exists in complex IV is counterbalanced by the attractive electrostatic energy. This resulted in more van der Waals attractive energy and thus in a strong attraction phenomenon as exemplified by the high negative ΔE. In the other complexes weak attractive forces existed (high positive ΔE) because the repulsive1—4 electrostatic energies were higher than the sum total of the attractive van der Waals and electrostatic energies. There were no significant differences in the cases of the bond stretching, angle bending, torsional, out of plane bending or 1—4 van der Waals energies.

The force field energy terms do not give any conclusive evidence of complexation but may be indicative of the stability due to the attractive or repulsive forces that exist within a complex. For example, a high positive electrostatic energy is indicative of repulsion while a high negative value is suggestive of attraction as can be seen in complex IV, in which the promethazine is protonated at the *N*-methyl group. However,

Table 1. Force Field Energy Terms for Complexes I—IV

Energy term (kcal/mol)	Complex			
	I	II	III	IV
Bond stretching energy	0.949	1.048	0.942	1.403
Angle bending energy	2.843	2.977	2.804	2.611
Torsional energy	10.391	10.479	10.021	10.093
Out of plane bending energy	0.084	0.067	0.058	0.091
1—4 van der Waals energy	2.461	2.79	1.982	3.754
van der Waals energy	−16.481	−8.773	−13.886	−7.562
1—4 Electrostatic energy	17.201	56.592	57.893	47.207
Electrostatic energy	−11.984	−30.167	−32.549	−47.940
Total energy	5.465	34.522	27.265	−9.652
Energy of stabilization (ΔE)	−1.244	27.803	20.456	−11.120

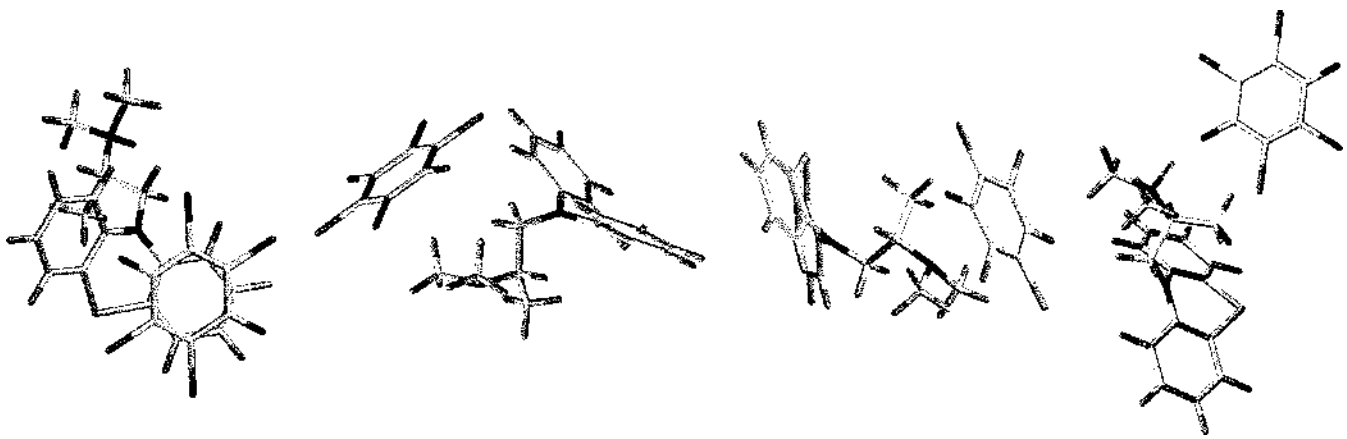


Chart 2. Complexes I—IV

Complex I showing the interaction of chloranil with aromatic ring of promethazine; complex II, the interaction of chloranil with unprotonated *N*-methyl group of promethazine; complex III, the interaction of chloranil with lone pairs of promethazine; complex IV, the interaction of chloranil with protonated *N*-methyl group of promethazine.

the stability of this complex cannot be confirmed by this factor alone since the total and the stabilization energies (ΔE) vary widely, although, the ΔE seems to favour strong interaction in complex IV. Further computations were carried out using the PM3 semi-empirical method. The various heats of formation calculated for the complexes are shown in Table 2.

The ΔE is the difference in energy obtained from the total of the energies of the isolated molecules and those of the complexes. The energy of formation for chloranil alone was -51.32 kcal/mol while that for promethazine (unprotonated) was 56.33 kcal/mol, giving a total energy of 5.01 kcal/mol. From Table 2 it is clear that complex IV has the highest ΔE and thus the most stable of all the complexes. The high negative ΔE is indicative of strong complexing affinity. This energy is related to the free energy change and when negative often indicates a spontaneous reaction.[15] Andrews and Keefer[16] earlier demonstrated that as the energy change becomes more negative, the stability constant of molecular complexation increases. The other parameters of ionization potential, HOMO and LUMO energies as well as the dipole moment all point to higher stability in complex IV. However, there was some level of stability in complexes I and II while complex III, in which the chloranil was supposed to interact directly with the lone pairs on promethazine, was totally unstable. Due to the greater stability in complex IV, this interaction was chosen for further studies. Chart 3 shows the chloranil placed at different distances from the promethazine. At a distance of 1.8 Å, there was clear indication of interaction as evidenced by the hydrogen bonding. However, hydrogen bonding may not be the major or only force of attraction in operation here. On protonation, the proton on the *N*-methyl group in promethazine acquired a positive charge of $+0.576$ while the ketone moieties on the chloranil acquired a negative charge of -0.482 when the calculations were done using the SPARTAN *ab initio* method. This favoured the charge-transfer phenomenon. The heats of formation calculated for each of these complexes are shown in Table 3.

Table 2. Heats of Formation Calculated for the Complexes

	Complex			
	I	II	III	IV
Heat of formation (kcal/mol)	4.35	3.83	3.71	149.08
ΔE (kcal/mol)	−0.67	−1.18	−1.20	−10.39
Ionization potential	8.01	8.15	7.95	10.69
Dipole moment (debye)	3.20	1.96	1.99	N/A[a]
HOMO energy (eV)	−8.79	−9.03	−9.05	−10.70
LUMO energy (eV)	−2.21	−2.31	−2.07	−4.90

a) None available.

ΔE was calculated from the difference in energy of formation between the complex and the total of the energies of each of the two isolated molecules. The heat of formation for chloranil alone was -51.32 kcal/mol while that for promethazine (protonated) alone was 210.79 kcal/mol, resulting in a total energy of 159.47 kcal/mol.

Earlier laboratory investigations have shown that protonated promethazine forms a stable complex with chloranilic acid.[3] Similarly, other laboratory studies show that protonated tertiary amines form stable charge-transfer complexes when protonated.[5,10]

From Table 3, it seems that the interaction between the two molecules at a distance of 1.8—4 Å produced the most stable complex based on the energy of stabilization ΔE as well as the HOMO and LUMO energies. After these distances there was a dramatic decrease in the ΔE to -3.46 kcal/mol. When the various complexes were geometry optimised using Tripos force field similar total energy values ranging from 11.50 to 14.19 kcal/mol were obtained. However, at a distance of 6 Å the total energy became high and the distance did not change appreciably from the 6 Å remaining at 5.992 Å. A similar result was obtained for the complex when the molecules were 7 Å apart. The results are shown in Table 4.

Depending on the initial distances, significant changes could be noticed in the various energy terms after geometry optimization, especially in the coulombic energy values. There were significant differences especially at 6 and 7 Å. There were no significant changes in the bond stretching, angle bending, torsional, out of plane bending or 1—4 van der Waals energy; however, there were significant changes in the repulsive and attractive forces as shown by the van der

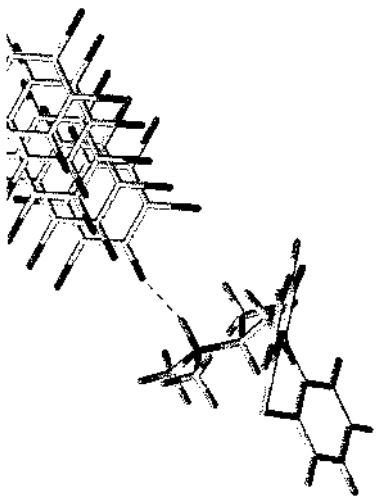


Chart 3. Interaction of Chloranil with Promethazine at Different Distances

Table 3. Various Parameters Calculated for the Interaction of the Ketone Group with Protonated *N*-Methyl Group of Promethazine

	Distance (Å)						
	1.8	2	3	4	5	6	7
Heats of formation (kcal/mol)	149.31	149.60	151.42	151.31	156.01	156.81	158.00
ΔE (kcal/mol)	−10.16	−9.87	−8.05	−8.16	−3.46	−2.66	−1.67
Ionization potential	10.69	10.71	10.77	10.73	10.81	10.86	10.88
HOMO energy (eV)	−10.70	−11.70	−11.74	−11.72	−11.55	−11.38	−11.19
LUMO energy (eV)	−4.930	−4.90	−4.68	−4.58	−4.02	−4.05	−4.12

Table 4. Various Energy Terms Calculated for the Interaction between a Protonated Promethazine and Chloranil Merged at Different Distances from Each Other

Energy term (kcal/mol)	Distances (Å)					
	2	3	4	5	6	7
Bond stretching energy	1.555	1.545	1.548	1.534	1.493	1.492
Angle bending energy	3.196	3.181	3.185	3.400	2.992	2.993
Torsional energy	9.898	9.901	9.921	10.038	10.046	10.041
Out of plane bending energy	0.055	0.055	0.056	0.067	0.055	0.055
1—4 van der Waals energy	3.439	3.452	3.449	3.415	3.507	3.507
van der Waals energy	−8.469	−8.476	−8.544	−11.684	−3.761	−3.708
1—4 Electrostatic energy	14.701	14.313	13.986	14.330	4.140	4.137
Electrostatic energy	−10.187	−10.335	−9.831	−8.361	−1.967	−1.918
Total energy	14.188	13.365	13.752	11.732	16.504	16.599
Final Distances	1.900	1.986	1.919	1.947	5.992	6.976

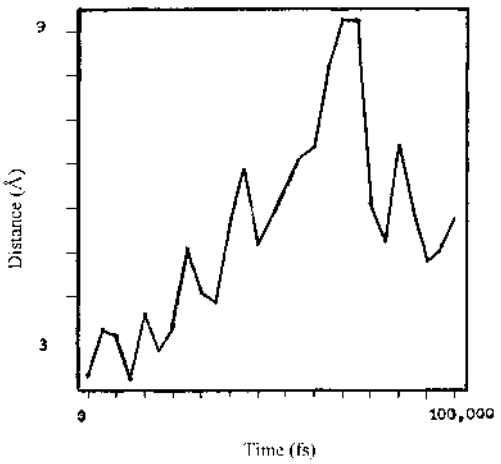


Fig. 2. Graph Generated from the Molecular Dynamics Simulation on Complex I

Waals, 1—4 electrostatic and electrostatic energies. Between 1.8—5 Å the repulsive 1—4 electrostatic energy was almost uniform ranging from 13.986 to 14.701 kcal/mol. Similar uniform values were also obtained for the attractive van der Waals and electrostatic energies. Both the attractive and repulsive forces decreased after 6 Å.

The assessment of all the complexes by molecular dynamics simulations (MDS) is shown in Figs. 2—5. From the graphs there was greater instability in complexes I—III than in complex IV. Figure 2 indicates that complex I was relatively stable and even when there seemed to be a dissociation (as shown by the peak on the graph) the complex stabilized after that. Each of the conformations resulting from the MDS was further assessed by geometry optimization using Tripos force field and PM3 of MOPAC. The results of the MDS studies indicate that some of the conformations were as stable as the parent complex while some were more stable, as shown by the computed ΔE. Some of the favourable results are shown in Table 5.

The values above may be considered significant when compared to the values of ΔE of the parent molecule used for the MDS studies which were −0.670 kcal/mol and −1.244 kcal/mol for PM3 and Tripos force field, respectively. More significant is that the molecule remained stable at the end of the MDS run.

From Fig. 3 it would seem that complex II remained stable

Table 5. Conformations of Complex I with High Interaction Energies

Time (fs)	Conformation	ΔE PM3 (kcal/mol)	ΔE Tripos force field (kcal/mol)
25000	R25000	−0.799	−2.975
40000	R40000	−0.782	−4.444
45000	R45000	−1.771	−4.377
55000	R55000	−0.775	−4.368
60000	R60000	−0.497	−0.431
65000	R65000	−0.540	−4.493
100000	R100000	−1.730	−3.68

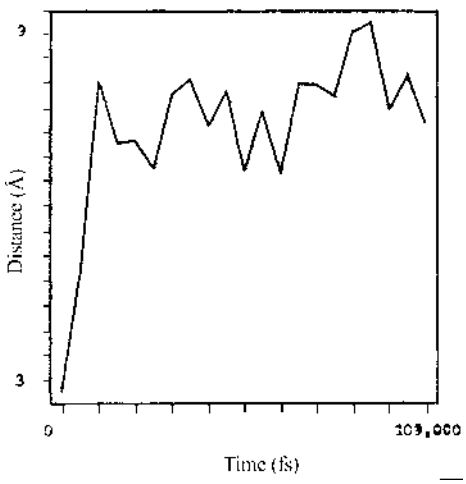


Fig. 3. Graph Generated from the Molecular Dynamics Simulation on Complex II

throughout the MDS run. On analysis of each of the conformations obtained it was discovered that complex II reverted to complex I during the MDS. Thus the situation whereby the chloranil interacts with the methyl group on the nitrogen without protonation is unstable and reverts to complex I in which the chloranil interferes with the aromatic π system.

Figure 4 shows the graph generated from the MDS on complex III in which the chloranil interferes directly with the lone pairs on the *N*-methyl group without protonation. It is clearly evident from the graph that this was also unstable at various time intervals during the molecular dynamics run. All the conformations produced from the MDS studies had positive ΔE for both the PM3 and Tripos force field energies which is indicative of weak interaction.

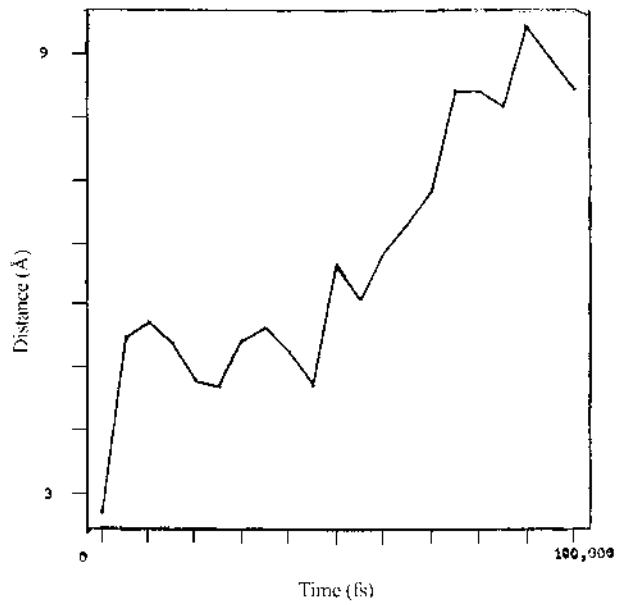


Fig. 4. Graph Generated from the Molecular Dynamics Simulation on Complex III

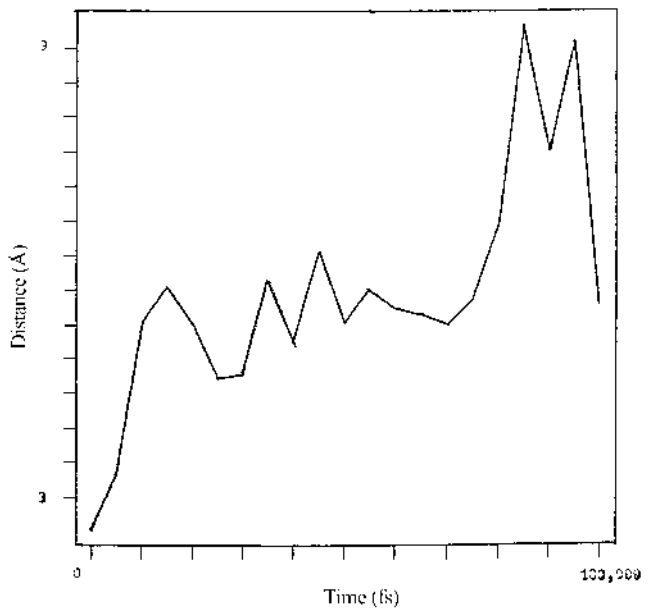


Fig. 5. Graph Generated from the Molecular Dynamics Simulation on Complex IV

The graph generated from molecular dynamics run on complex IV is shown in Fig. 5. The figure indicates a stability in the complex until about the 80000—90000 fs run of the MDS. After this period the complex regained stability. Various conformers were isolated which had ΔE values similar to the original values for complex IV. Generally, the ΔE values for the various conformations were quite high. Some values are indicated in Table 6.

The lowest ΔE values of -3.51 kcal/mol and -3.37 for PM3 and Tripos force field energies, respectively, were obtained at 90000 fs when the complex was most unstable. Apart from the closeness of the ΔE values to the values of -10.39 kcal/mol and -11.20 for PM3 and Tripos force field energies, respectively, many of the isolated conformers maintained the hydrogen bonding observed with the parent molecule as shown in Chart 4 by schemes 1, 2, 3 and 4 which represent conformations R15000, R50000, R65000 and R100000 respectively. Hydrogen bonding is often evidence that interaction exists.

Table 6. Conformations from MDS on Complex IV with High Interaction Energies

Time (fs)	Conformation	ΔE PM3 (kcal/mol)	ΔE Tripos force field (kcal/mol)
15000	R15000	−9.20	−7.41
35000	R35000	−6.20	−14.17
40000	R40000	−9.35	−14.18
50000	R50000	−8.89	−7.36
65000	R65000	−10.23	−7.48
75000	R75000	−7.17	−8.34
100000	R100000	−8.24	−11.78

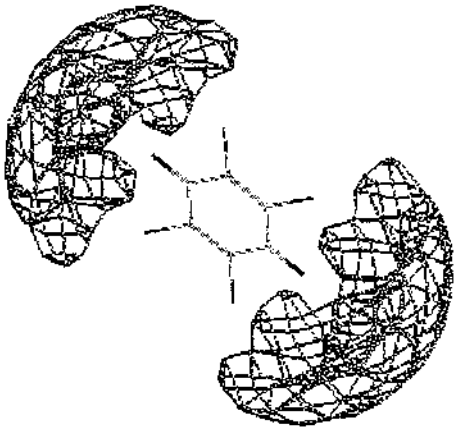


Fig. 6. Grid Interaction Fields of Chloranil Generated Using an NH_2 (with Lone Pairs) Probe at a Contour Level of -2

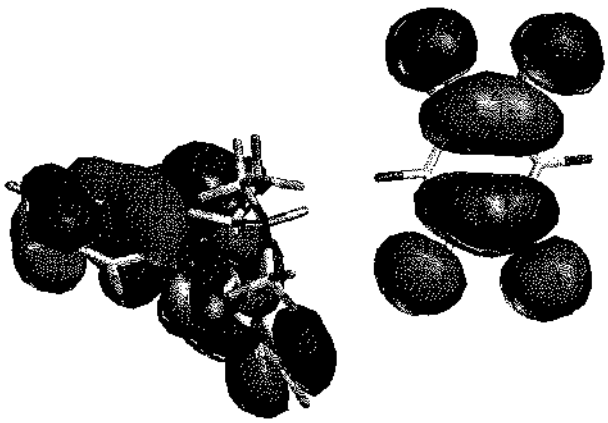
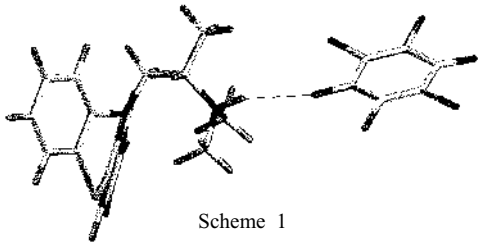


Fig. 7. Computed HOMO and LUMO for Chloranil–Promethazine Complex

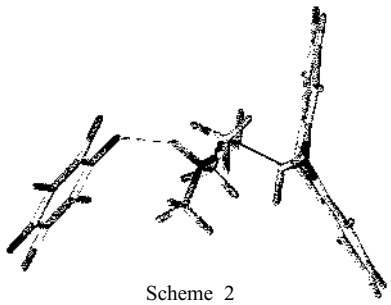
Apart from the above facts, the GRID field generated using the NH_2 probe (with lone pairs) indicates that the favoured mode of interaction (as shown by the GRIDS in Fig. 6) would be that in which the ketone moieties interacts with an electropositive moiety on the NH_2 group.

Figure 7 shows the computed HOMO and LUMO contours for the complex. From the figure it could be observed that the contours are separate making charge-transfer feasi-

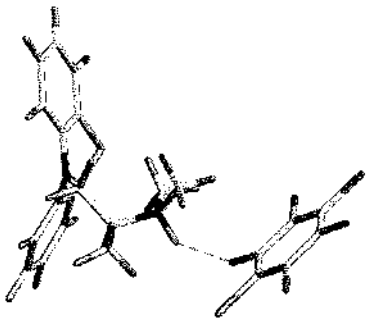
ble. Joined contours would mean a salt rather than a complex. Similarly, the HOMO and LUMO energies indicate an energy difference as shown in Tables 2 and 3. This difference makes it possible to transfer electrons from the HOMO of the donor to the LUMO of the acceptor .Thus, the end product



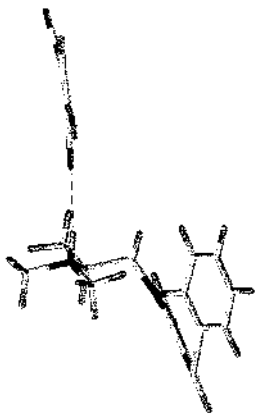
Scheme 1



Scheme 2



Scheme 3



Scheme 4

Chart 4. Hydrogen Bonding of Complex IV for Various Conformations Produced after Molecular Dynamics Simulations

indicates that the oxygen on the chloranil had a negative charge of −0.482 indicating that this electron poor compound must have acquired additional electrons from the promethazine. This is in agreement with the earlier observations made by Adikwu and co-workers[17] that charge-transfer complexes of moclobemide and promethazine follow the pattern:

$$D + A \longrightarrow \underbrace{(D \longrightarrow A)}_{\text{outer complex}} \longrightarrow \underbrace{D^{+}A^{-}}_{\text{inner complex}}$$

The formation of an anion radical by chloranil is only possible by acceptance of electrons from n-donors, of which promethazine is one.

Conclusion

From this work, the following conclusions can be drawn. Complex IV in which the chloranil interacts with nitrogen of the *N*-methyl group is the favoured mode of complexation. The orientation in which the interacting atoms, oxygen and proton are about 2 Å apart from each other is the correct model and is the parent complex used for his study. It should be noted that this model of interaction is only possible in protic systems where the weak base, promethazine can acquire a proton. Under most laboratory conditions complexation between chloranil and promethazine is carried out in non-aqueous systems and complex I in which the chloranil interferes with the aromatic π system is favoured. In this condition the chloranil lies parallel to the aromatic ring of the promethazine about 3.224 Å apart as exemplified by conformation R45000 in this study.

Acknowledgements One of the authors, Dr. M. U. Adikwu, is grateful to the Alexander von Humboldt Foundation, Bonn, Germany, for granting him a fellowship (fellow number 1064098) to carry out this work. Assistance of all the working group members of Prof. Dr H.-D. Höltje is highly acknowledged.

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