

Molecular polarization maps as a tool for studies of intermolecular interactions and chemical reactivity

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Maps for the interaction energy of acetone, pyrrole, furan, and pyridine with a positive unitary charge were computed using ab initio techniques, together with their molecular electrostatic potentials at the same points. The difference between the interaction and electrostatic potential maps yielded polarization maps for the molecules. Finally, maps for the interaction with a negative charge were obtained as the difference between the polarization and electrostatic potential maps.

The calculations were carried out for three planes, 2 Bohr radii, 4 Bohr radii, and 8 Bohr radii from the plane containing the heavy atoms for all the molecules. At larger distances, the interaction and electrostatic maps resemble each other qualitatively; however, at shorter distances, where the polarization effects are more significant, the differences between the maps are notable.

Interaction and polarization maps can be routinely evaluated for medium-sized molecules, and are likely to become an important tool in drug design and chemical reactivity.

Keywords: *molecular polarization maps, interaction maps*

INTRODUCTION

Molecular electrostatic potentials (MEPs) have emerged as one of the most used theoretical tools in the study of molecular reactivity, as well as in the development of pharmacophores that guide drug discovery efforts. The importance of these maps in the design of novel drugs can be attributed to the fact that electrostatic complementarity is necessary to ensure the interaction between the ligand and the receptor. Since MEPs were first proposed as a tool for analyzing the early stages of the drug–receptor interaction,¹ examples of the application of MEPs to elucidate the mechanism of the biological recognition process have been abun-

dant. At the same time, several techniques have been proposed for the in-depth analysis of this property; some of the most recent are given in Pepe et al.,² Rozas et al.,³ and Arteca et al.⁴

The electrostatic potential, as customarily evaluated, reflects the net electrical effect of the nuclei and electrons of a molecular system, in some fixed conformation. Despite its usefulness, this property does not provide a description of the changes that occur in the molecule as it interacts with an approaching molecule or ion. Most significantly, the changes in the electronic distribution due to the presence of the other system are omitted. The lack of such a description limits the applicability of MEPs to either the early stages of a reaction or to intermolecular interactions, where the polarization effects are relatively minor.⁵

In a limited number of cases, procedures based on sums over states using second-order perturbation theory have been developed to evaluate the molecular polarization, and the result has been applied as a correction to the MEPs, thus generating an interaction potential.^{6–8} Alternatively, the interaction energy of a molecule and a point charge can be computed explicitly.⁹ The interaction contains the electrostatic and polarization terms for this geometry. Indeed, the polarization potential can be obtained as the difference between the interaction energy and the electrostatic potential. The use of the supermolecule approach to determine interaction and polarization maps has never been fully applied. When Bonaccorsi and coworkers first enunciated the explicit approach, the ion–molecule interaction was computed at only a few points, which served to parametrize bond polarizations, from which molecular polarization potential (MPP) maps were derived.⁹

Despite the limited number of studies carried out so far, some interesting qualitative results have been reported. These include, for instance, the reversal of the order of the proton affinities of a series of alkylamines, when the polarization effects are included.⁹ More interestingly, the maps that included the polarization effects were reported to successfully describe regions of nucleophilic attack, a well-documented limitation of the MEPs, for which special procedures that allow the use of MEPs have been attempted.^{5–7,10–11}

The purpose of the present study is to report the computation of the MPP and interaction potentials for a series of

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medium-sized molecules, and to explore similarities and differences among them. Acetone, furan, pyrrole, and pyridine have been selected as test cases. The study should provide additional data to allow the assessment of the polarization contributions to the overall interaction energies for different chemical systems.

METHODS

The interaction energy ΔE between a molecule and a point charge e placed at a point r can be written as the sum of Coulombic and polarization terms evaluated at that point:¹²

$$\Delta E(r) = eV(r) + e^2P(r) \quad (1)$$

The Coulombic term results from the interaction of the charge with the unperturbed charge density of the target molecule, which corresponds to the MEP at r , $V(r)$. The polarization term $P(r)$ represents the interaction of the point charge with the multipoles induced on the molecule because of the electric field generated by the charge.

The interaction energy ΔE was computed as the energy difference between the SCF energy of the molecule in the presence of an unitary positive charge, and the energy of the isolated molecule. The procedure was repeated for a series of grid points defined on three planes parallel to the molecular plane and placed at 2 Bohr radii, 4 Bohr radii, and 8 Bohr radii from it. A distance of 4 Bohr radii corresponds to a typical hydrogen bond distance, while the 2-Bohr radii plane is within the molecular volume. The grid points were placed 1 Bohr radius apart, and the grid extended approximately 6 Bohr radii beyond the position of the atoms in each direction. This resulted in 312 points per plane for acetone and furan, 325 points for pyrrole, and 351 points for pyridine.

All calculations were carried out using 6-31G* basis set,¹³ using the fully optimized geometry computed for each isolated molecule. The HONDO 8.3 program was used.^{14,15} The two-electron integrals were computed only once and stored, as the interaction of the molecule with a point charge modifies only the one-electron integrals. In addition, the molecular orbitals of the i th point on the grid served as the initial guess for the $i + 1$ st point. In the calculation of the two-electron integrals, the product of primitives with preexponential factors lower than 10^{-15} , were not included. The cutoff for keeping the two-electron integrals was 10^{-9} . The SCF calculation was terminated when a convergence of 10^{-5} on the density matrix was achieved. Finally, the tolerance for the individual gradients during the geometry optimization of the isolated molecules was 0.0005, in atomic units, for each individual Cartesian gradient.

The explicit calculation of the interaction energies was prohibitive in the past because of the computational demand. However, we have been able to run all computations on a Silicon Graphics Personal Iris GT30 workstation. Calculations using the stored integrals and molecular orbitals from a previous point took, for pyrrole, an approximate average of 5 minutes per point.

In addition, we computed the MEP for the compounds at the exact same points, using the same basis set and program. From the difference of the interaction maps and MEPs we were able to compute the polarization energy at the same points and therefore obtain polarization maps.

While the MEP and the MPP are intrinsic molecular properties, the interaction energy is not. As it can be seen in Equation (1), $\Delta E(r)$ depends on the nature of the charge with which the molecule is interacting. So far, we have computed the interaction energy with a unitary positive charge; however, from the maps obtained we can easily evaluate the interaction with any other charge using Equation (1). Thus, the interaction energy with a unitary negative charge is:

$$\Delta E^-(r) = P(r) - V(r) \quad (2)$$

These maps were also generated for the four molecules studied, using the values of polarization and MEPs previously evaluated.

RESULTS AND DISCUSSION

Figures 1–16 shows a selection of the MEP, the MPP, and maps for the interaction with a positive and negative unitary point charge for acetone, pyrrole, furan, and pyridine at different planes.

The values for the polarization decrease rapidly as the distance from the molecule increases. At 8 Bohr radii, the polarization map has a simple ellipsoidal shape, and its overall contribution to the interaction is extremely small. The negligible contribution of the polarization at long distances formed the basis for the studies using MEP to understand the initial stages of a chemical reaction.

Nevertheless, at distances smaller than 4 Bohr radii, the MEP and the interaction maps for a positive or negative charge are in all cases significantly different. The difference between these two maps is the MPP, which has significantly larger values and a much more complex topography at shorter distances. The largest values of the MPP are found in the areas close to the nucleus, where the electron density is larger. Moreover, the value of the polarization in the neighborhood of different classes of atoms is significantly different; for example, the polarizability effects are larger around sp^2 and sp -carbon atom than around heteroatoms (N, O).

MEPs are well known to reliably predict sites for electrophilic attacks. The prediction of this class of reactions could also be achieved from the maps for the interaction of the molecule with a positive charge. Therefore, both maps contain the same qualitative information, that is, the preferred site for interaction with an electrophile. For instance, both maps indicate that the heteroatom is the preferred protonation site for pyridine and furan. However, at shorter distances the maps show significant differences. The interaction maps for a positive charge are stable at any point over the molecule, and a secondary stable minimum is observed at the center of the ring. While the existence of a secondary minimum has no impact in the protonation process, it can become important for the study of an intermolecular interaction. In this particular case, the maps suggest that it is possible to form a hydrogen bond between a proton donor and an aromatic ring, as the one recently described between water and benzene.¹⁶ In summary, the MPP maps in this case can be important for locating the position of secondary centers for electrophilic attack in the case of molecules with two or more similar minima in the MEP.

One of the most serious limitations of the MEPs has been that they cannot be used to analyze prospective sites for

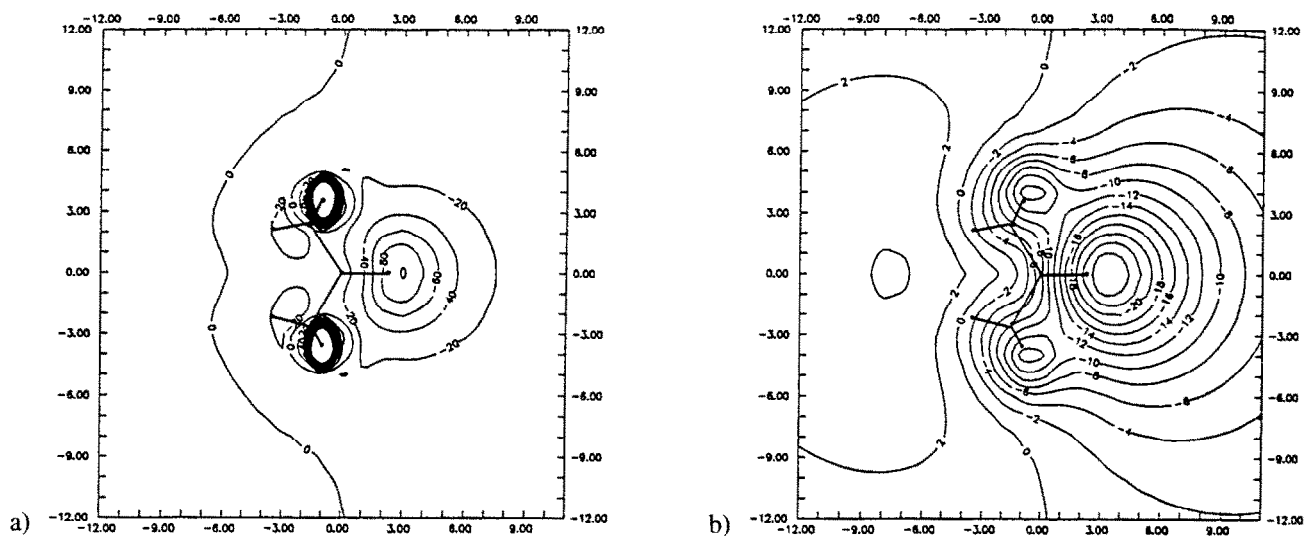


Figure 1. Maps for the interaction of acetone with a positive charge (kcal/mol) at: a) 2 Bohr radii; and b) 4 Bohr radii.

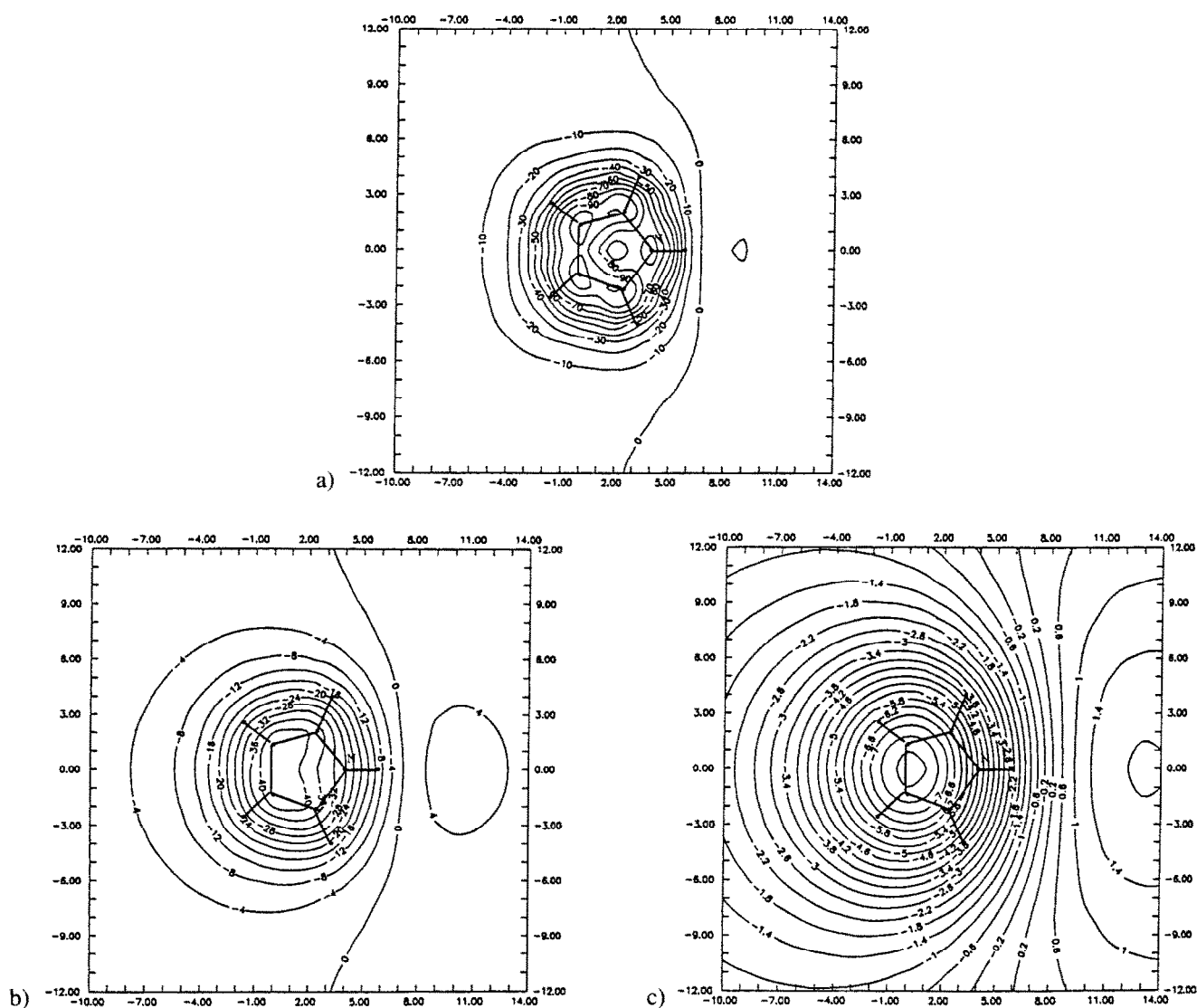


Figure 2. Maps for the interaction of pyrrole with a positive charge (kcal/mol) at: a) 2 Bohr radii; b) 4 Bohr radii; and c) 8 Bohr radii.

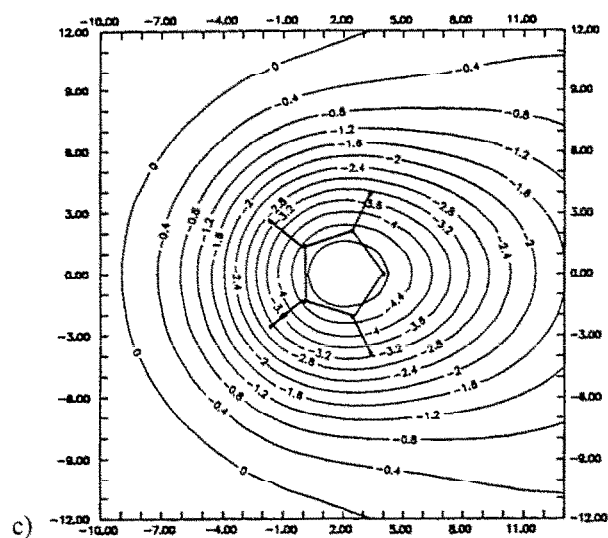
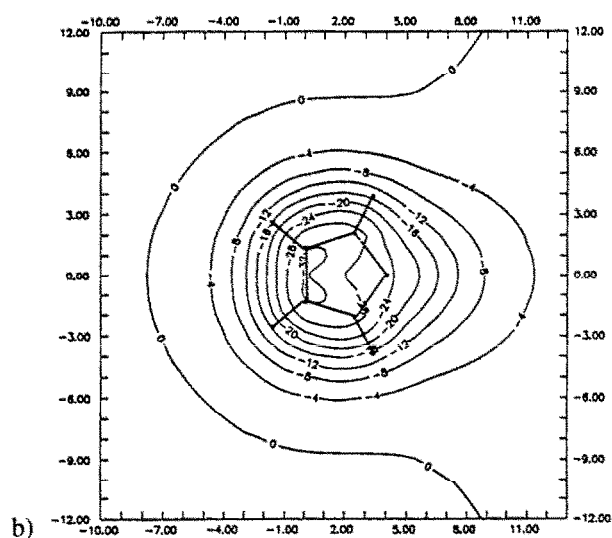
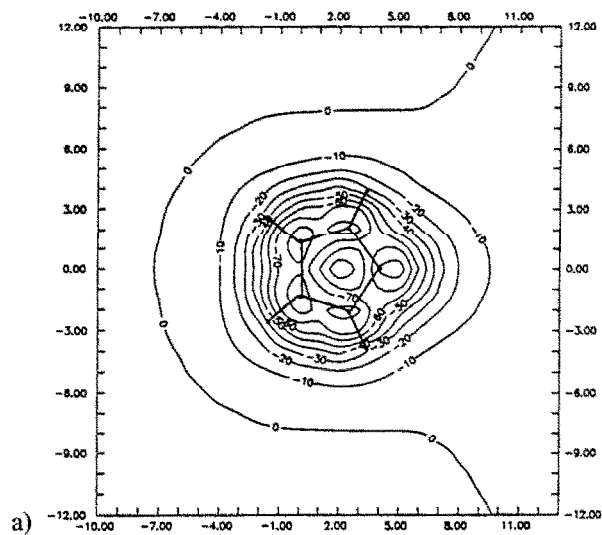


Figure 3. Maps for the interaction of furan with a positive charge (kcal/mol) at: a) 2 Bohr radii; b) 4 Bohr radii; and c) 8 Bohr radii.

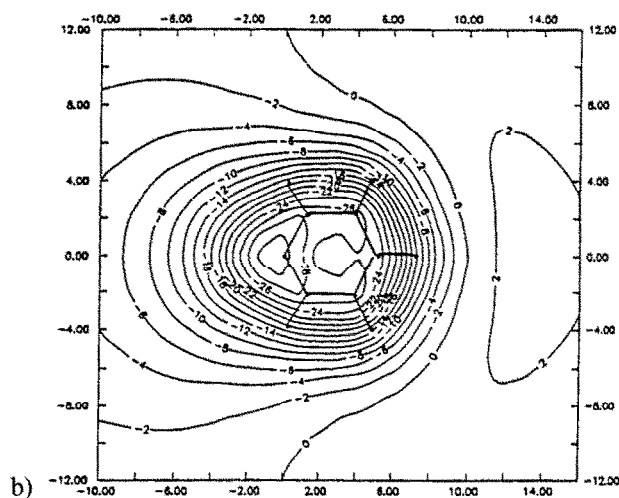
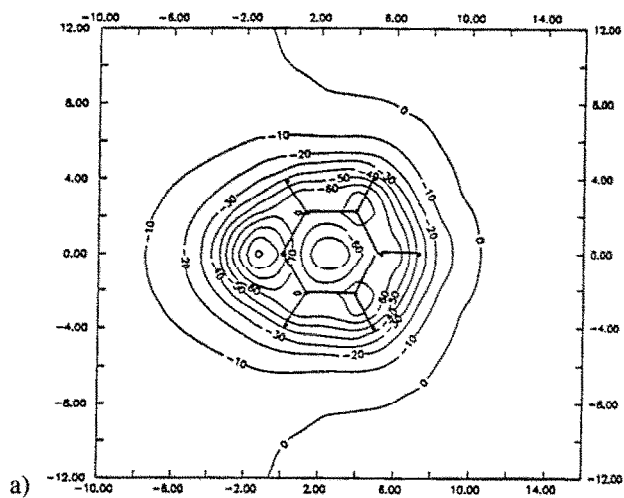


Figure 4. Maps for the interaction of pyridine with a positive charge (kcal/mol) at: a) 2 Bohr radii; and b) 4 Bohr radii.

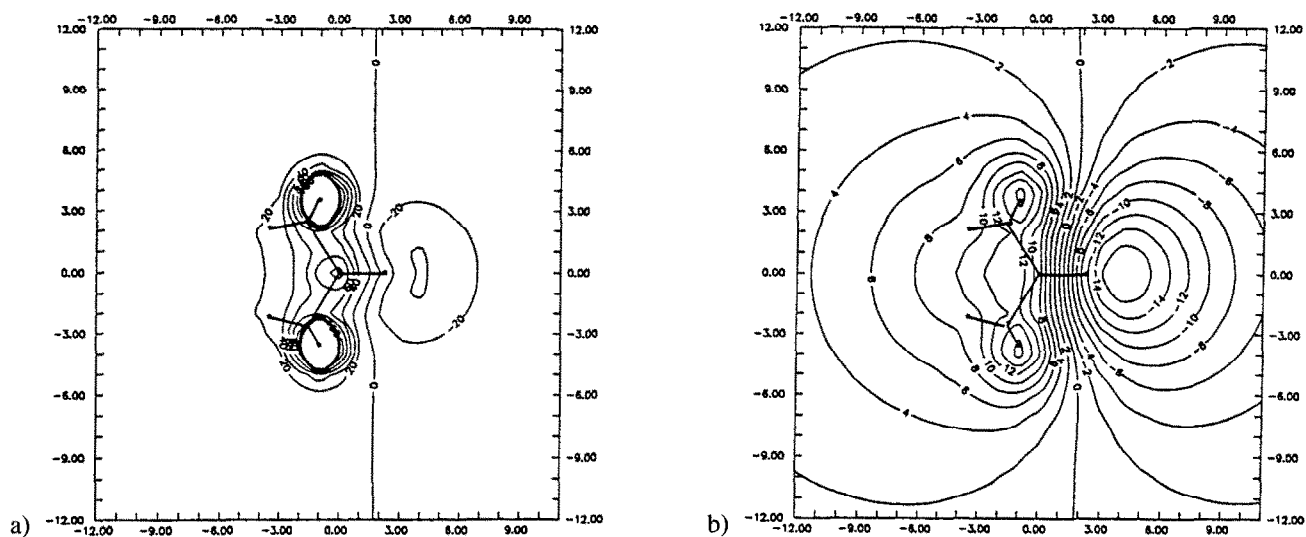


Figure 5. Electrostatic potential maps (kcal/mol) for acetone at a) 2 Bohr radii; and b) 4 Bohr radii.

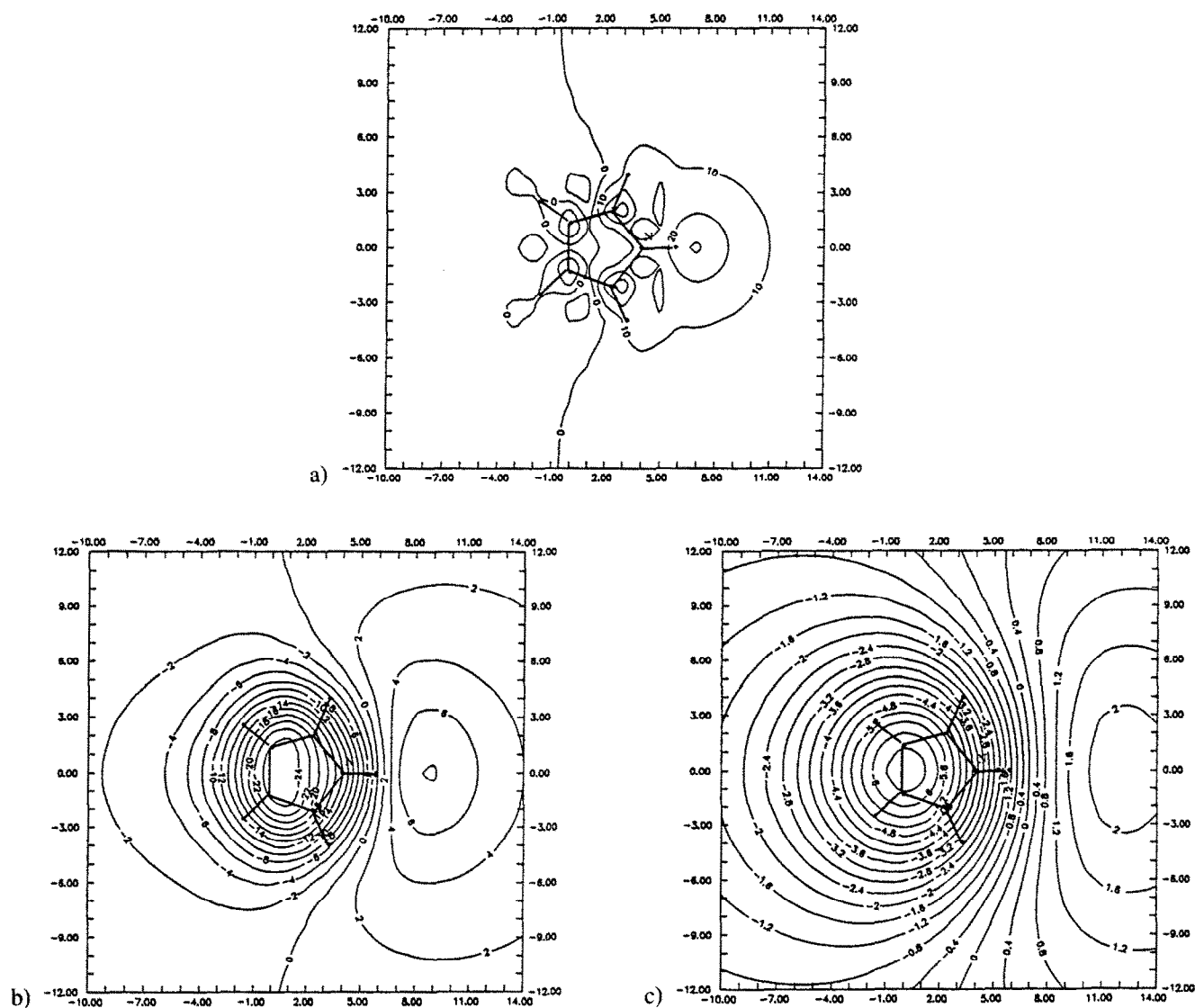


Figure 6. Electrostatic potential maps (kcal/mol) for pyrrole at a) 2 Bohr radii; b) 4 Bohr radii; and c) 8 Bohr radii.

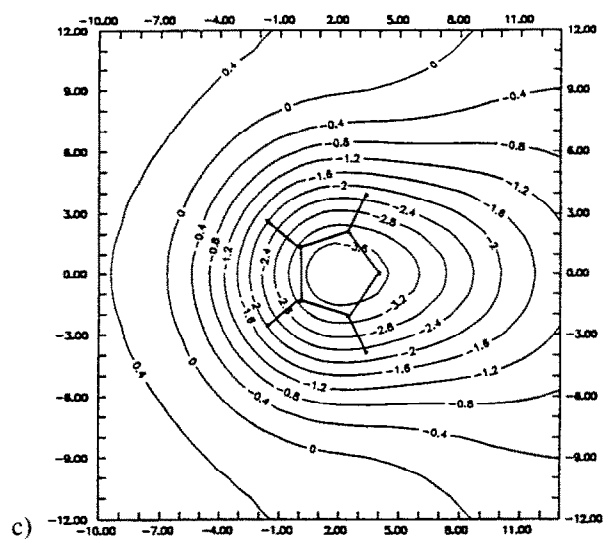
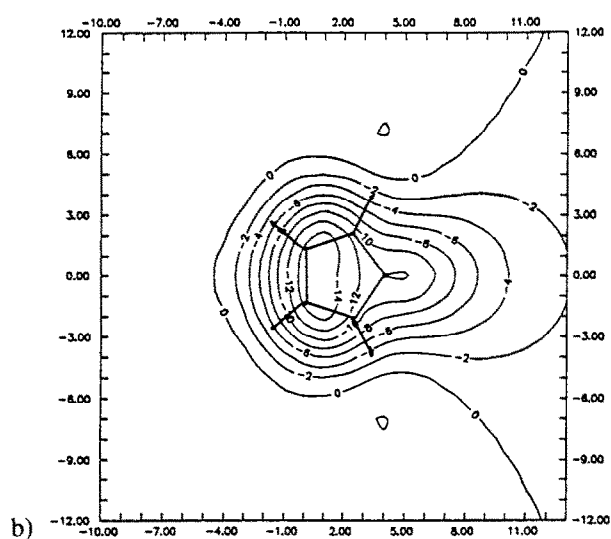
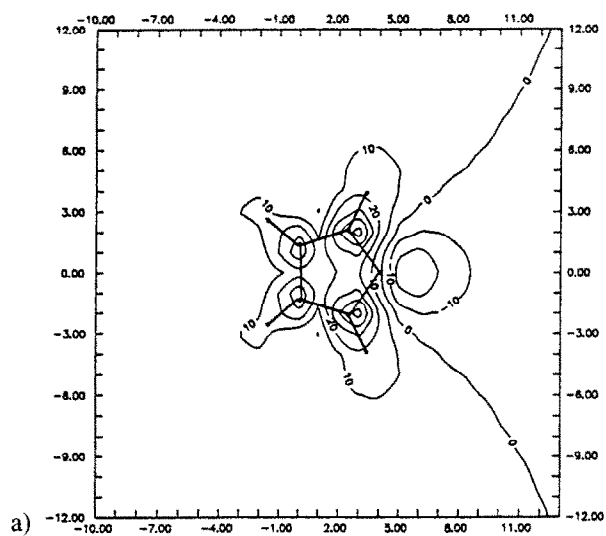


Figure 7. Electrostatic potential maps (kcal/mol) for furan at a) 2 Bohr radii; b) 4 Bohr radii; and c) 8 Bohr radii.

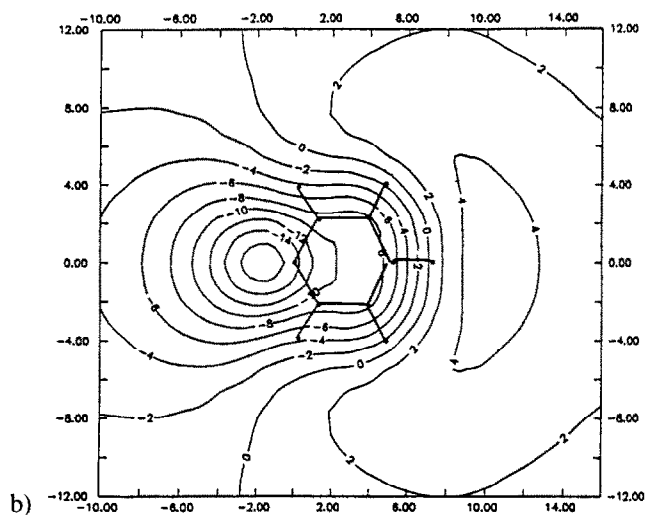
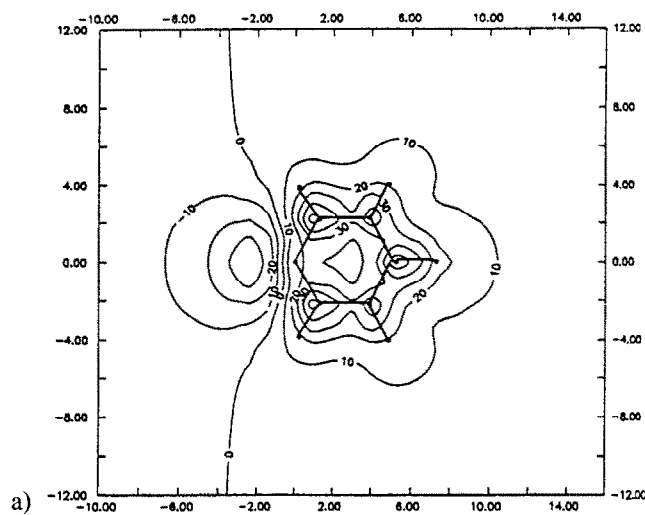


Figure 8. Electrostatic potential maps (kcal/mol) for pyridine at a) 2 Bohr radii; and b) 4 Bohr radii.

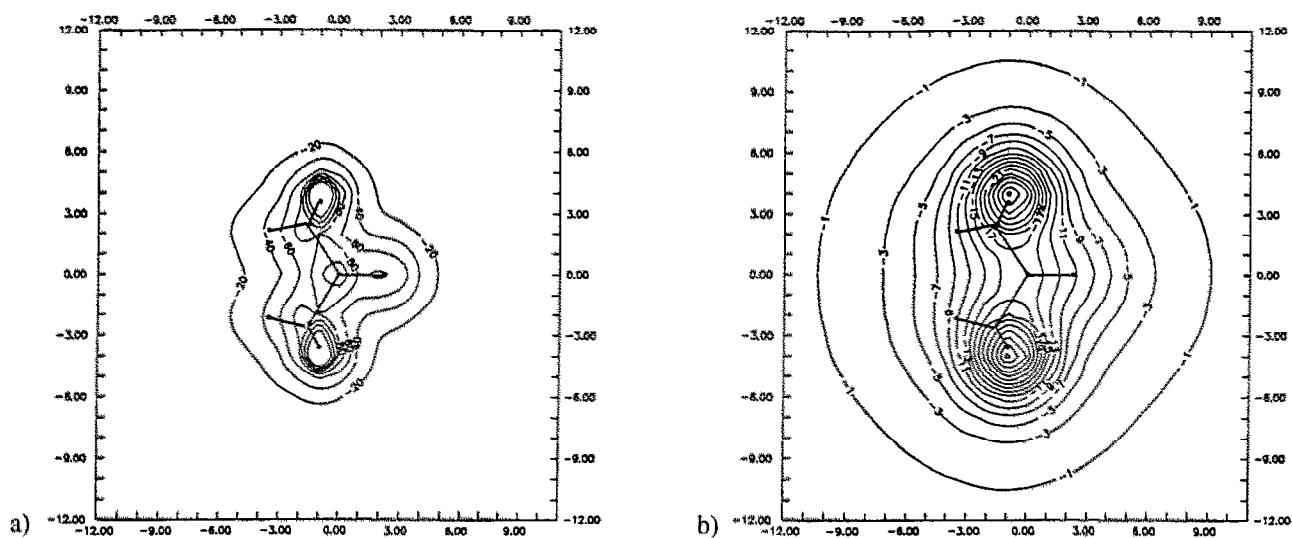


Figure 9. Polarization potential maps (kcal/mol) for acetone at a) 2 Bohr radii; and b) 4 Bohr radii.

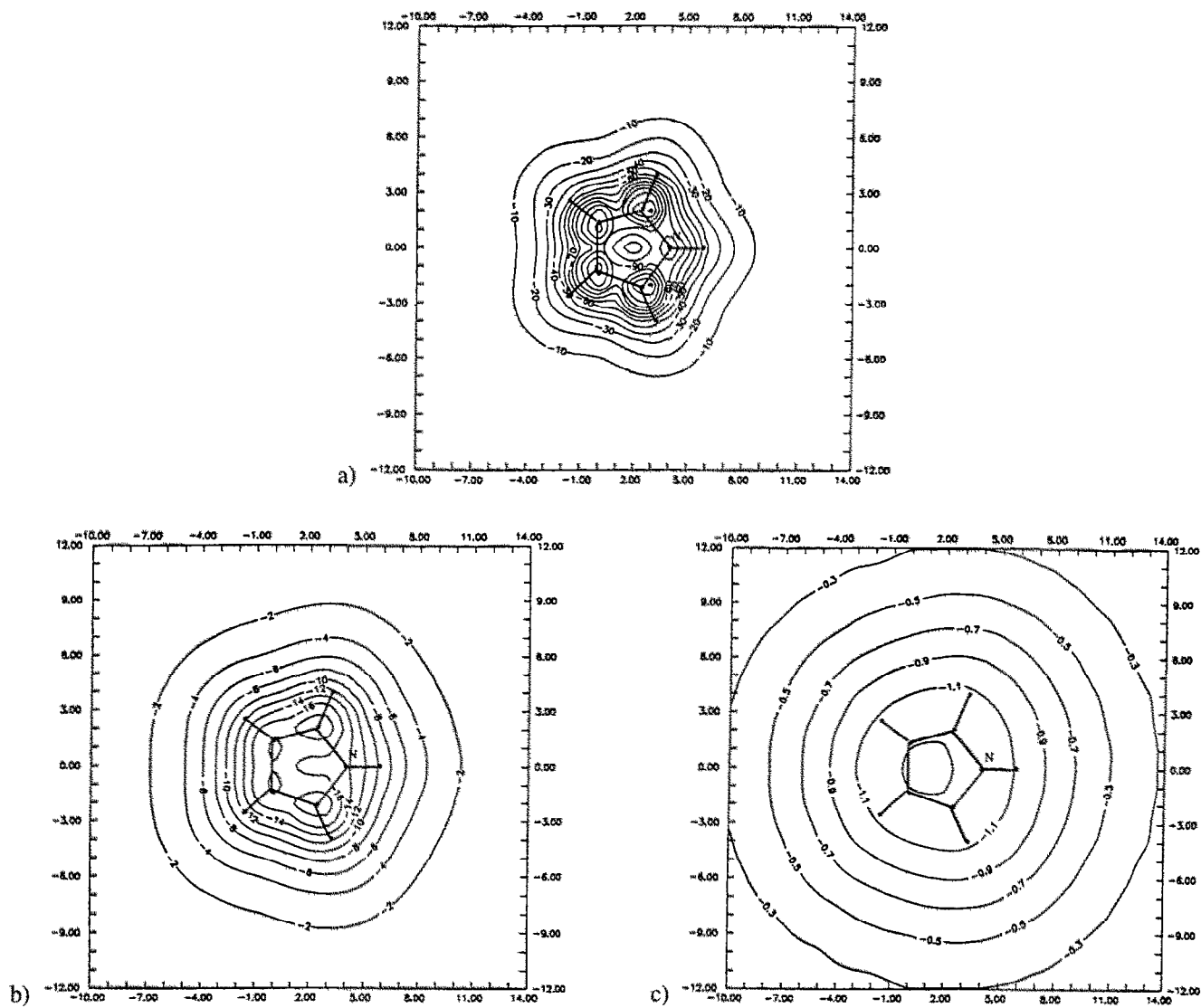


Figure 10. Polarization potential maps (kcal/mol) for pyrrole at a) 2 Bohr radii; b) 4 Bohr radii; and c) 8 Bohr radii.

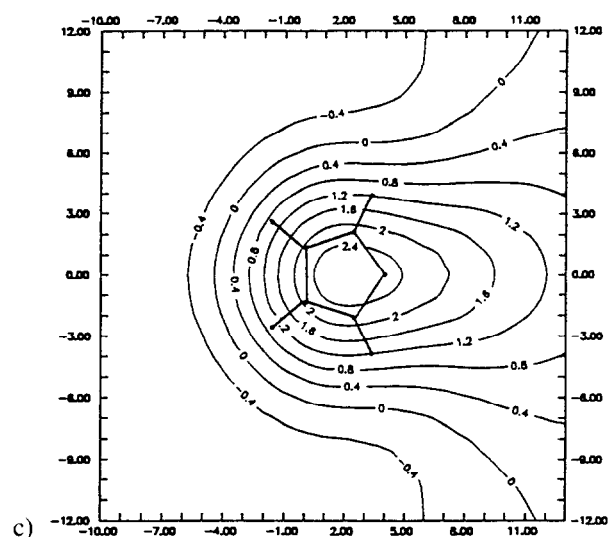
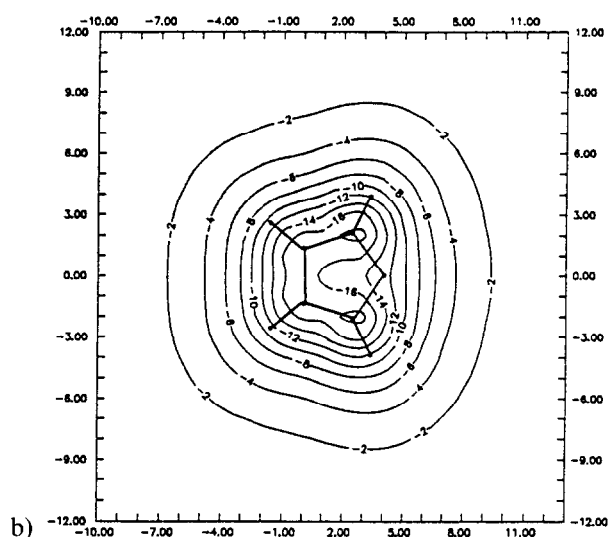
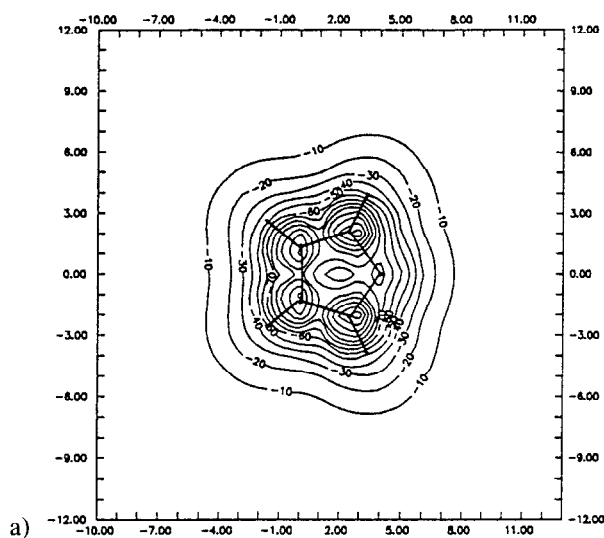


Figure 11. Polarization potential maps (kcal/mol) for furan at a) 2 Bohr radii; b) 4 Bohr radii; and c) 8 Bohr radii.

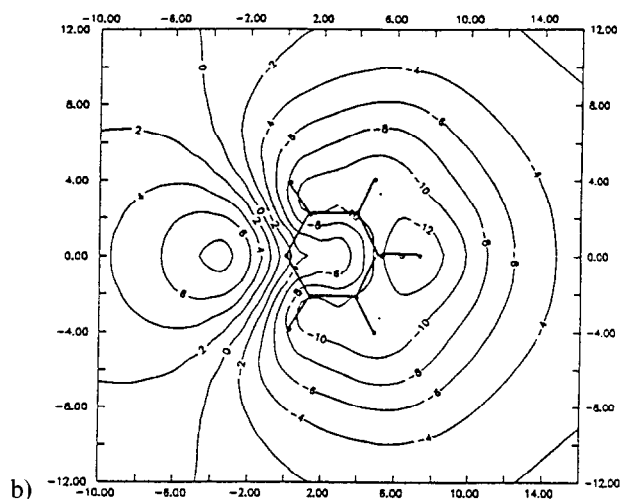
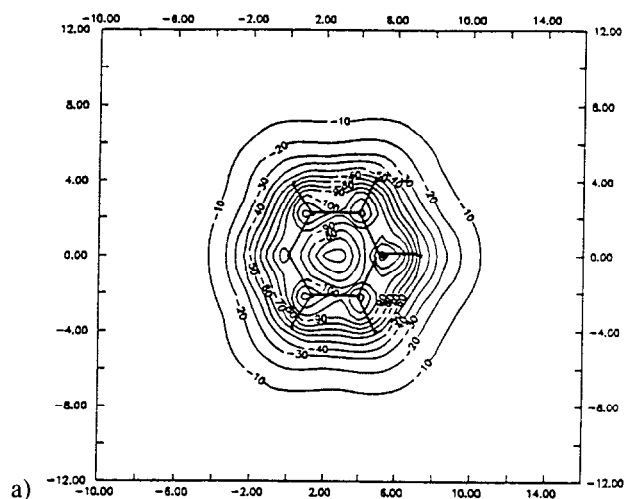


Figure 12. Polarization potential maps (kcal/mol) for pyridine at a) 2 Bohr radii; and b) 4 Bohr radii.

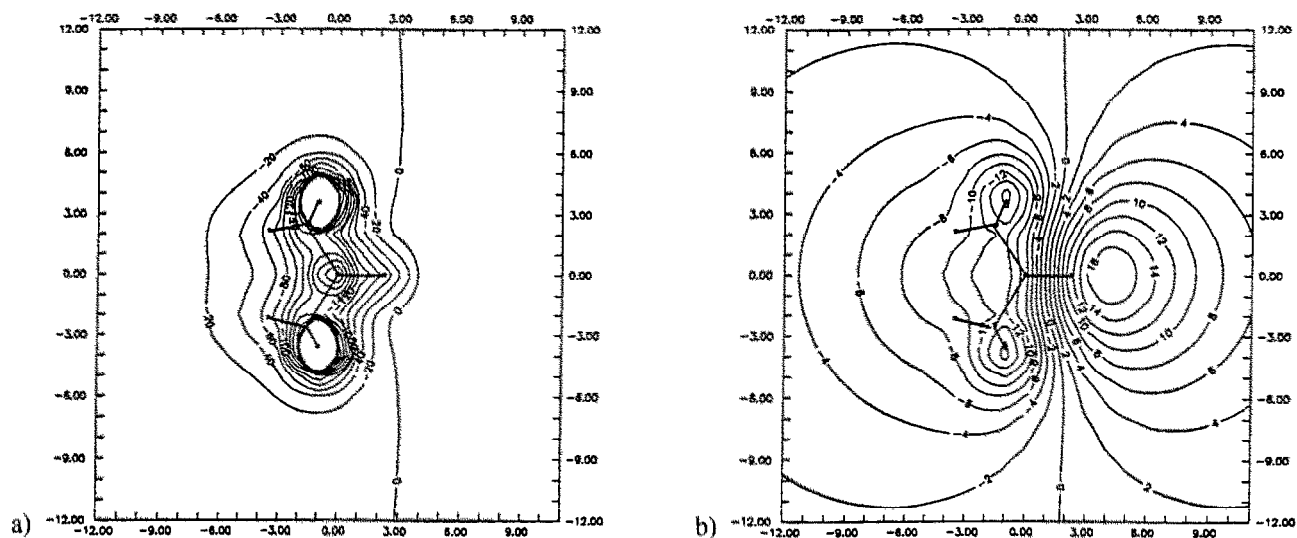


Figure 13. Maps for the interaction of acetone with a negative charge (kcal/mol) at a) 2 Bohr radii; and b) 4 Bohr radii.

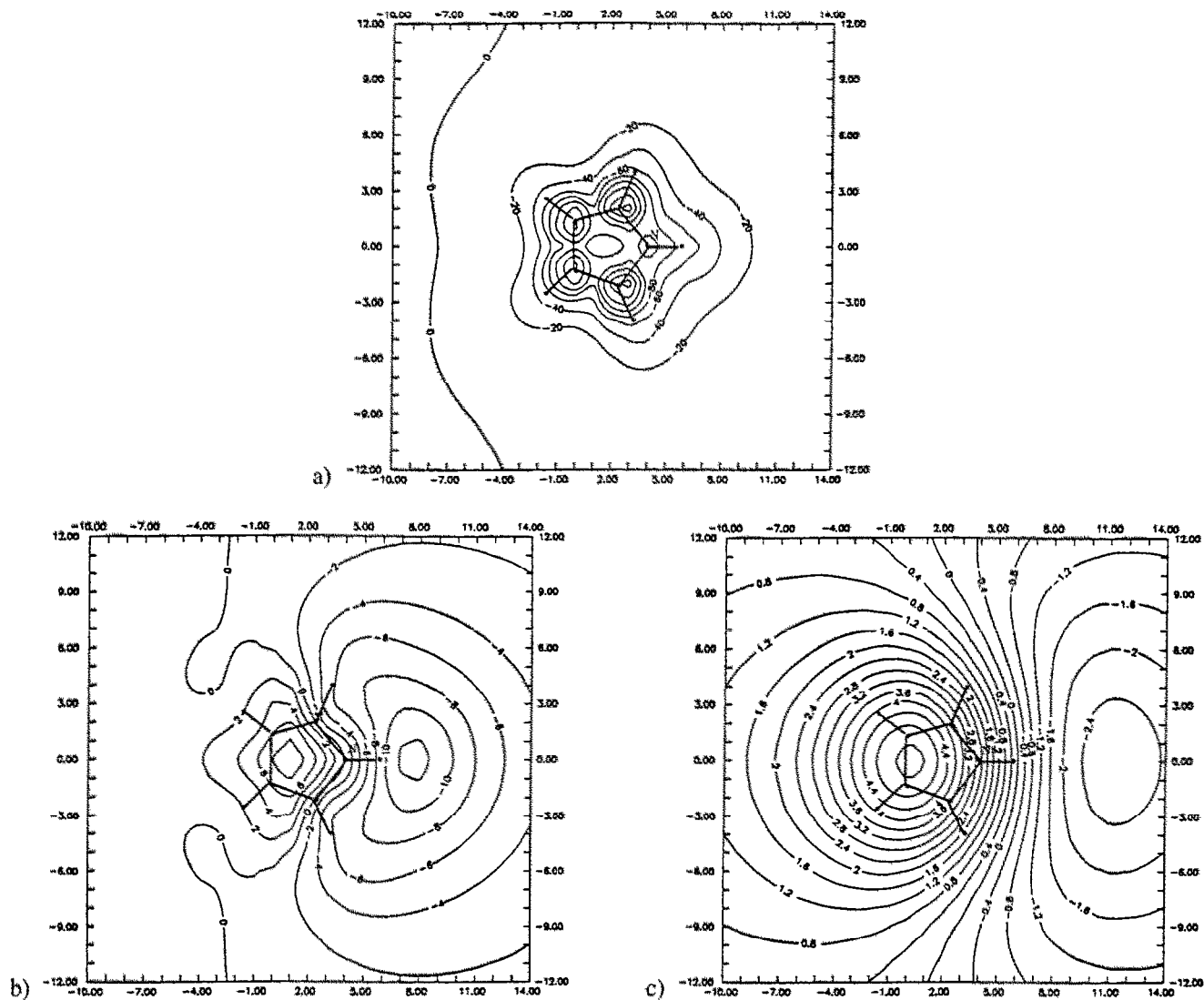


Figure 14. Maps for the interaction of pyrrole with a negative charge (kcal/mol) at a) 2 Bohr radii; b) 4 Bohr radii; and c) 8 Bohr radii.

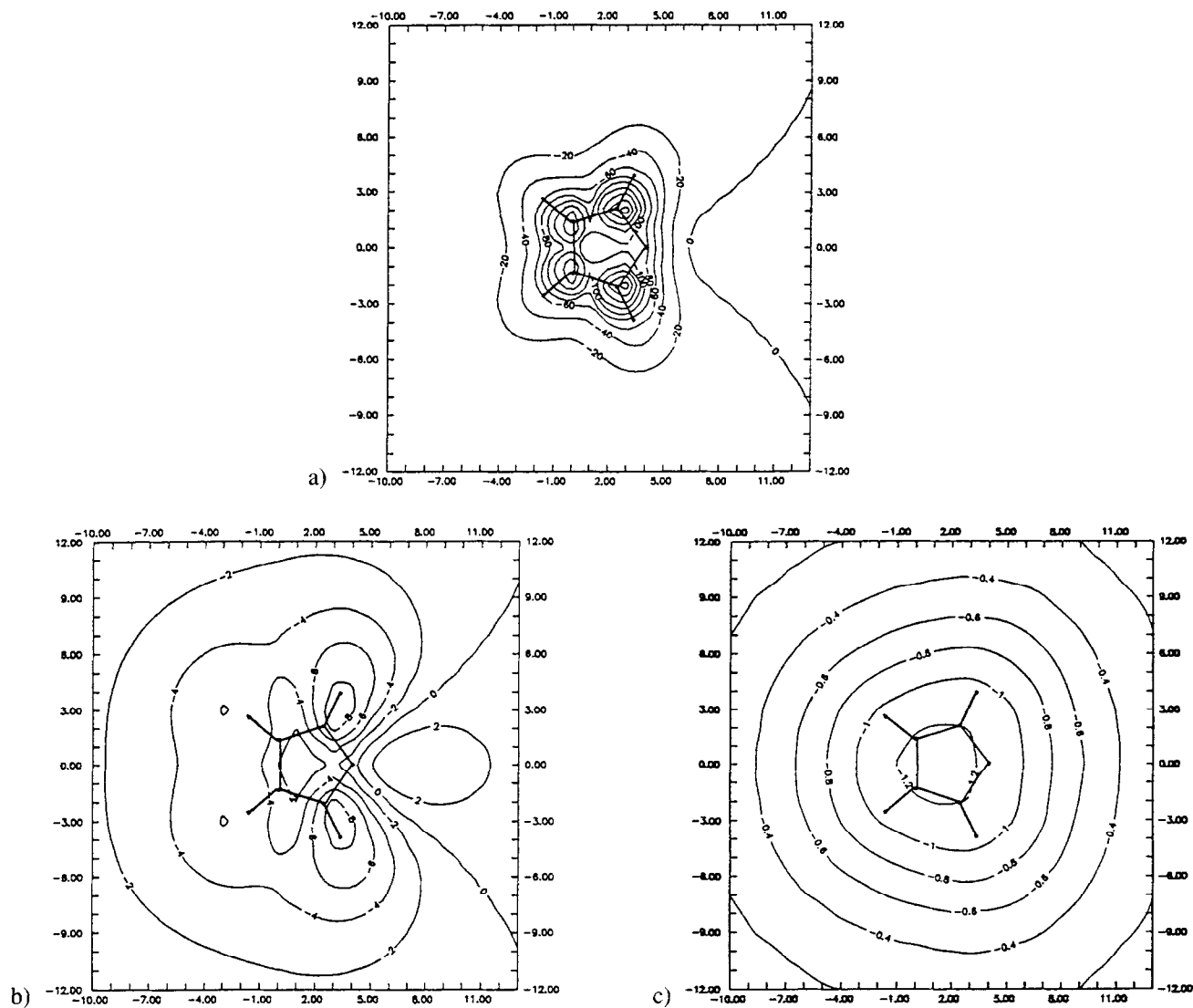


Figure 15. Maps for the interaction of furan with a negative charge (kcal/mol) at a) 2 Bohr radii; b) 4 Bohr radii; and c) 8 Bohr radii.

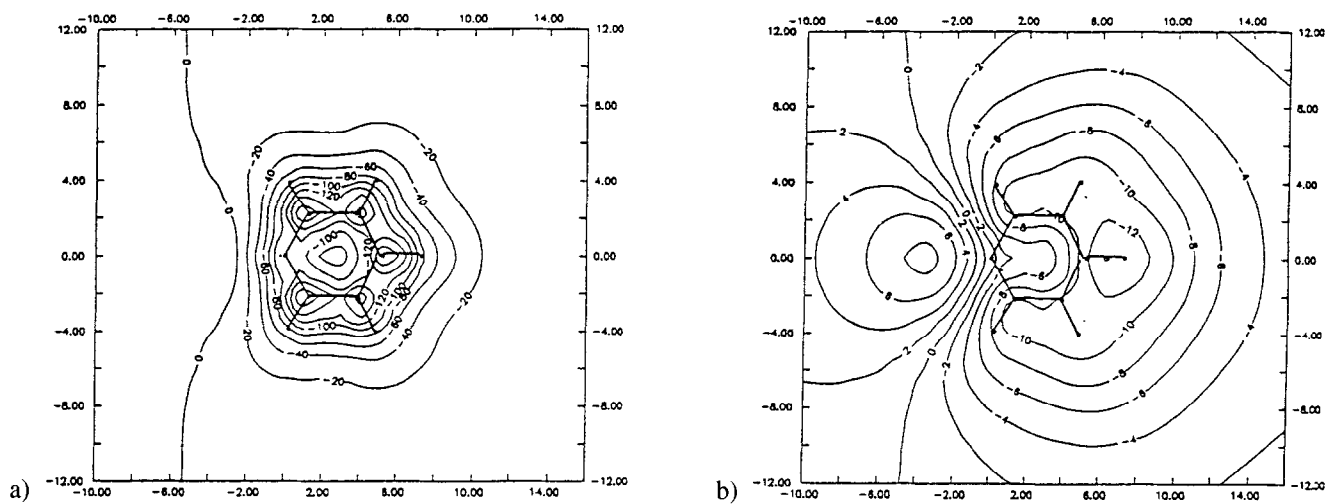


Figure 16. Maps for the interaction of pyridine with a negative charge (kcal/mol) at a) 2 Bohr radii; and b) 4 Bohr radii.

nucleophilic attack. The electrostatic contribution of the nuclei dominates the positive regions of the maps, making them useless for this purpose. This is an area where interaction maps for a negative charge could be most useful, as has already been indicated. For example, the MEP of furan at 4 Bohr radii does not show any positive region close to the molecule. Instead, the negative interaction map shows two well-defined minima close to the α -carbons, where it is experimentally known that the nucleophilic attack occurs.¹⁷ For acetone, the map clearly shows a minimum in the proximity of the carbonyl, which is the center for nucleophilic attack. Moreover, both the MEP and the negative charge interaction map show that the maximum is far from the carbonyl group, but the shape of the latter provides insight on the direction of the attack for the nucleophilic agent.

CONCLUSION

The purpose of this study was to present results on the evaluation of explicit interaction maps as powerful tools for the study of intermolecular interactions and chemical reactivity. Over the years, MEPs have been one of the most widely used tools for the analysis of plausible reaction mechanisms in intermolecular interactions. However, MEPs have some limitations that interaction maps can easily overcome—most remarkably, the prediction of the preferred site for nucleophilic attacks, and the presence of charge-induced secondary minima for intermolecular interactions.

This is the first time that the maps have been evaluated explicitly. While the evaluation of these maps still has a significant computational cost, both maps, for interactions with positive or negative charges, can routinely be computed from a single interaction map and the MEP.

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