THERE ARE NO ELECTRONS

Kenn Amdahl

Electronics for Earthlings
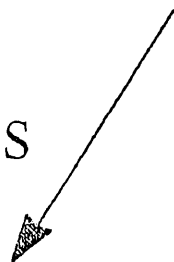
$$\mathbf{H}\Psi = E\Psi$$

$\downarrow \quad \Psi = single\ determinant$

HF equations

Additional
approximations

Addition of
more determinants

Semi-empirical
methods
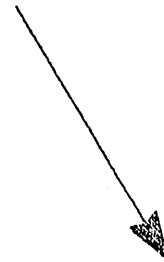
Convergence to
exact solution

Roothaan–Hall equations, which for a closed-shell system are:

FC = SCE

$$F_{\mu\nu} = H_{\mu\nu}^{\text{core}} + \sum_{\lambda=1}^{K} \sum_{\sigma=1}^{K} P_{\lambda\sigma}\left[(\mu\nu|\lambda\sigma) - \tfrac{1}{2}(\mu\lambda|\nu\sigma)\right]$$

$$P_{\lambda\sigma} = 2\sum_{i=1}^{N/2} c_{\lambda i} c_{\sigma i}$$

$$H_{\mu\nu}^{\text{core}} = \int d\nu_1 \phi_\mu(1)\left[-\frac{1}{2}\nabla^2 - \sum_{A=1}^{M} \frac{Z_A}{|r_1 - R_A|}\right]\phi_\nu(1)$$

SCF Techniques

As seen in Section 3.5, the Roothaan–Hall (or Pople–Nesbet for the UHF case) equations must be solved iteratively since the Fock matrix depends on its own solutions. The procedure illustrated in Figure 3.3 involves the following steps.

(1) Calculate all one- and two-electron integrals.
(2) Generate a suitable start guess for the MO coefficients.
(3) Form the initial density matrix
(4) Form the Fock matrix as the core (one-electron) integrals + the density matrix times the two-electron integrals.
(5) Diagonalize the Fock matrix (see Chapter 13 for details). The eigenvectors contain the new MO coefficients.
(6) Form the new density matrix. If it is sufficiently close to the previous density matrix, we are done, otherwise go to step (4).

There are several points hidden in this scheme. Will the procedure actually converge at all? Will the SCF solution correspond to the desired energy minimum (and not a maximum or saddle point)? Can the number of iterations necessary for convergence be reduced? Does the most efficient method depend on the type of computer and/or the size of the problem?
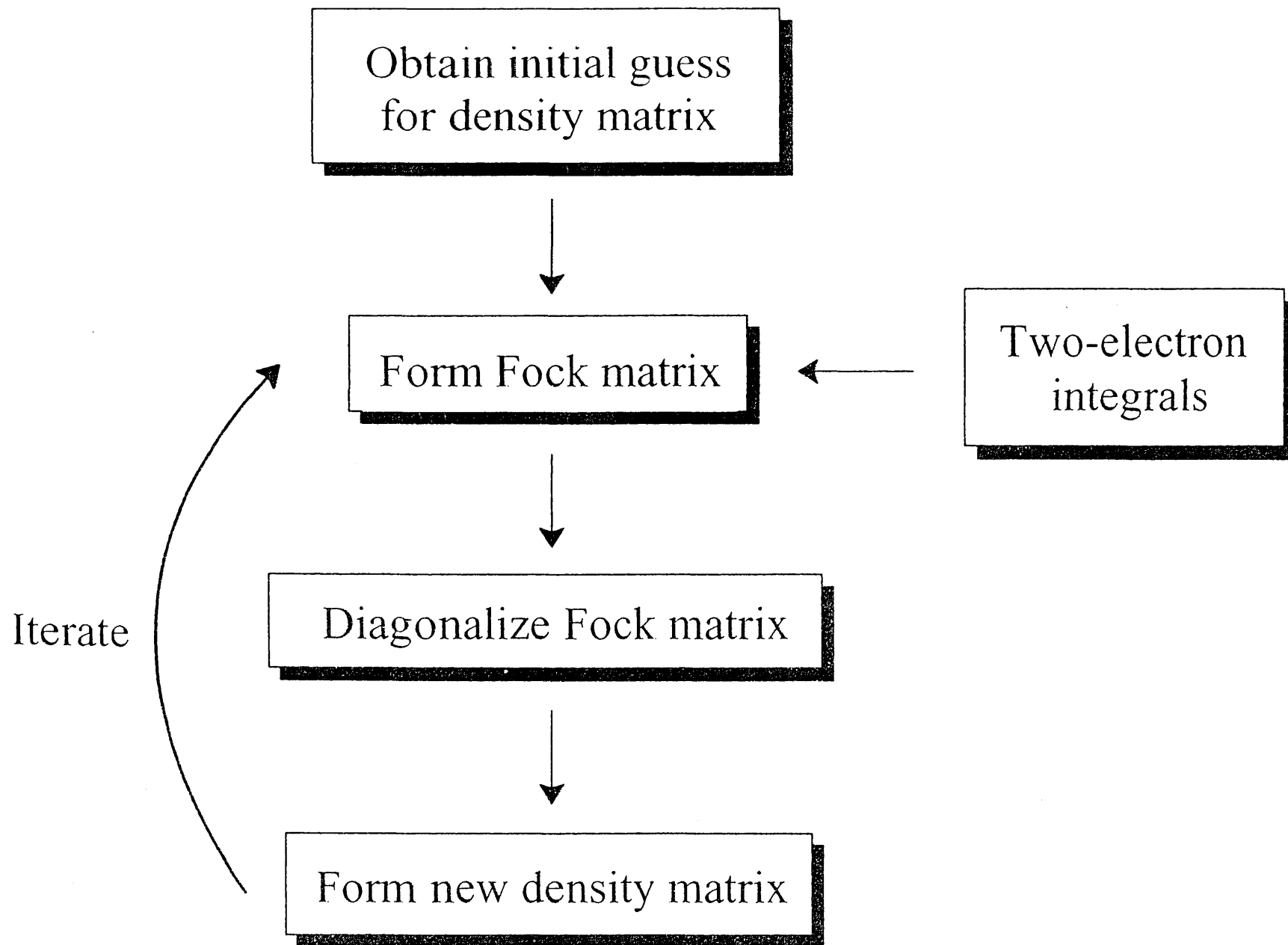
the SCF procedure
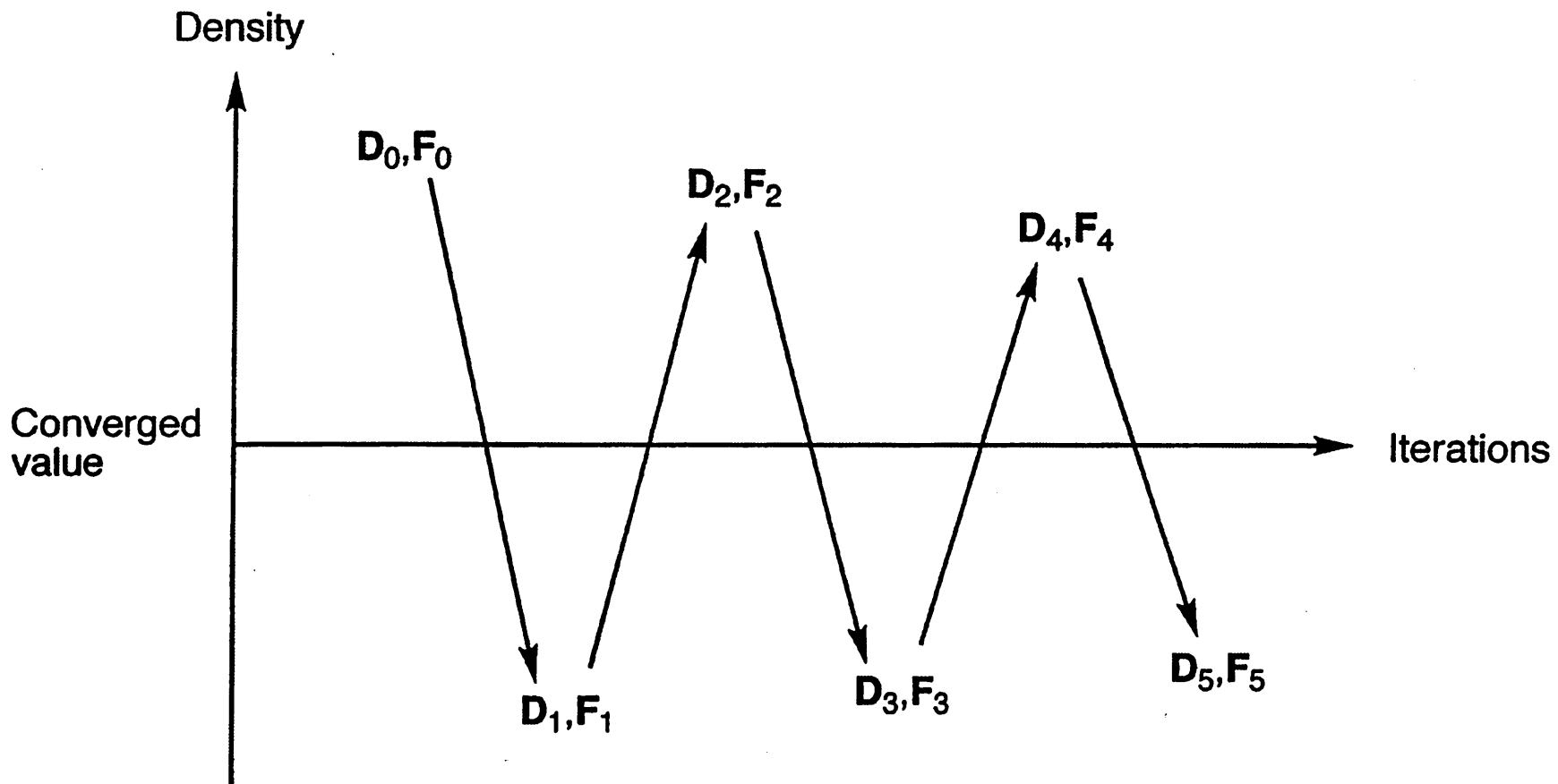
Figure 3.5 An oscillating SCF procedure

51. Formamide   Symmetry: C_s

9A' E=−0.601 n

8A' E=−0.672 σ_{NC}, σ_{CH}, σ_{NH_2}

7A' E=−0.767 π'_{NH_2}

6A' E=−0.877 σ_{CH}, σ_{NH_2}

5A' E=−1.239 σ_{NC}, σ_{NH_2}

4A' E=−1.394 σ_{CO}

Formamide (Continued)

12A' σ^*

11A' E= 0.233 σ^*

3A'' E= 0.164 π_3^*

2A'' E=-0.416 π_2

10A' E=-0.436 n

1A'' E=-0.577 π_1
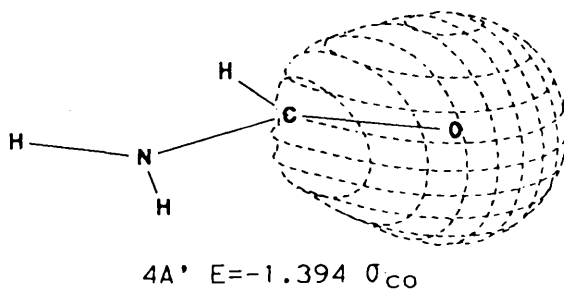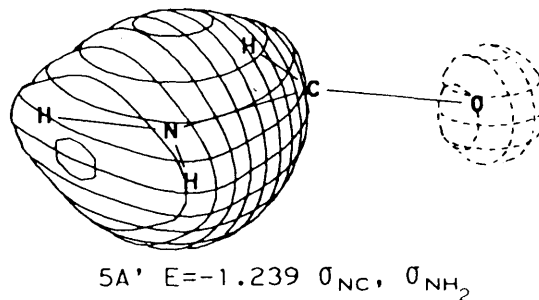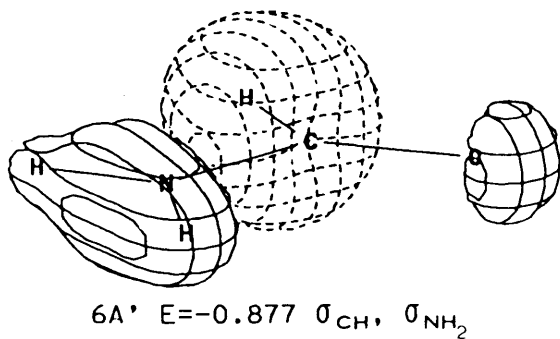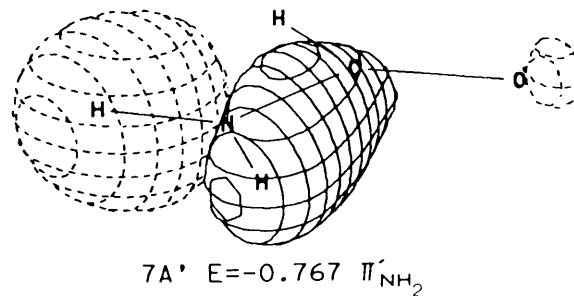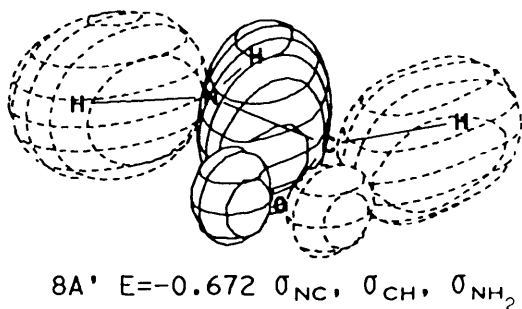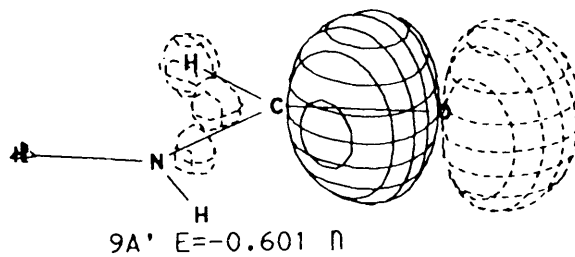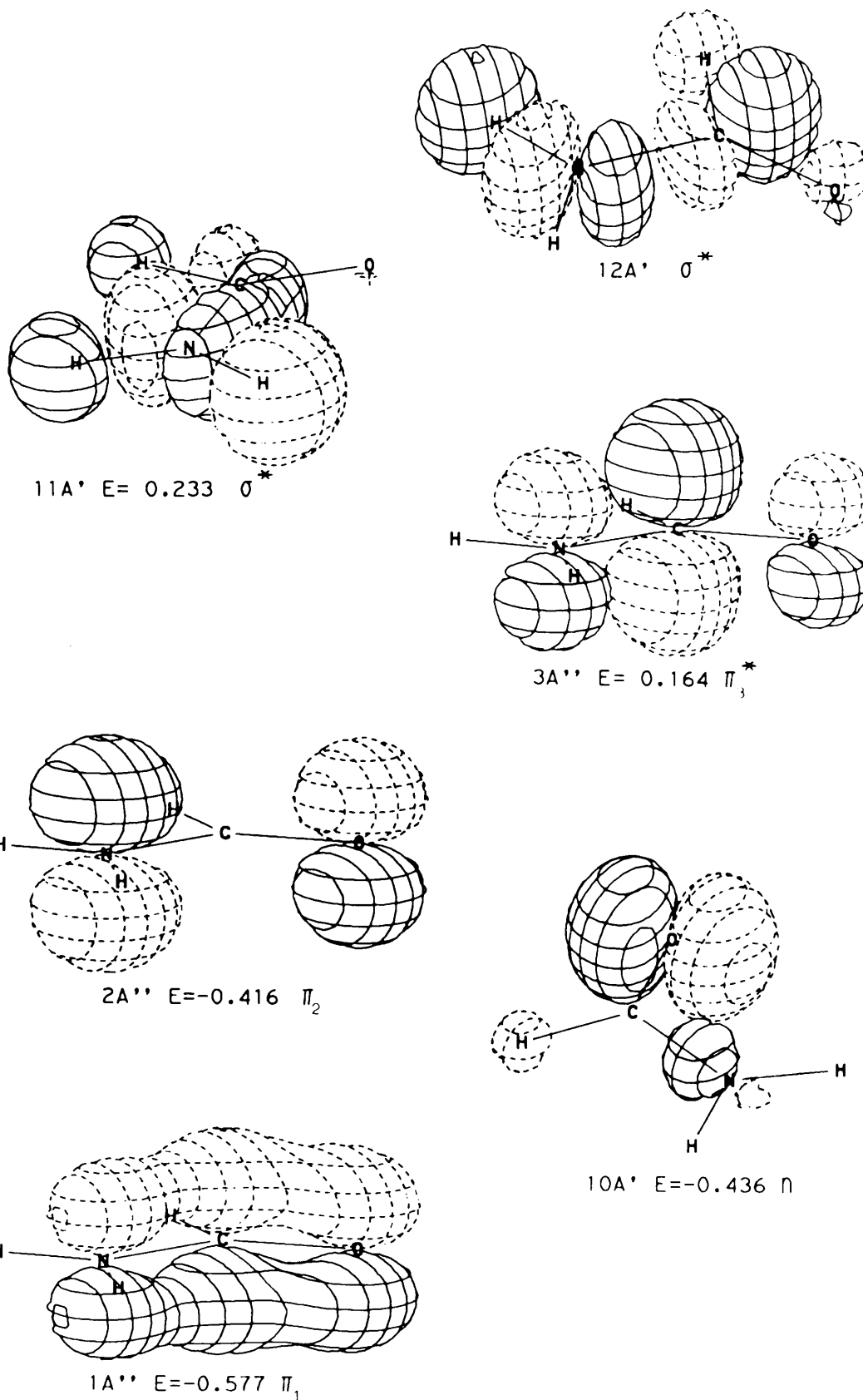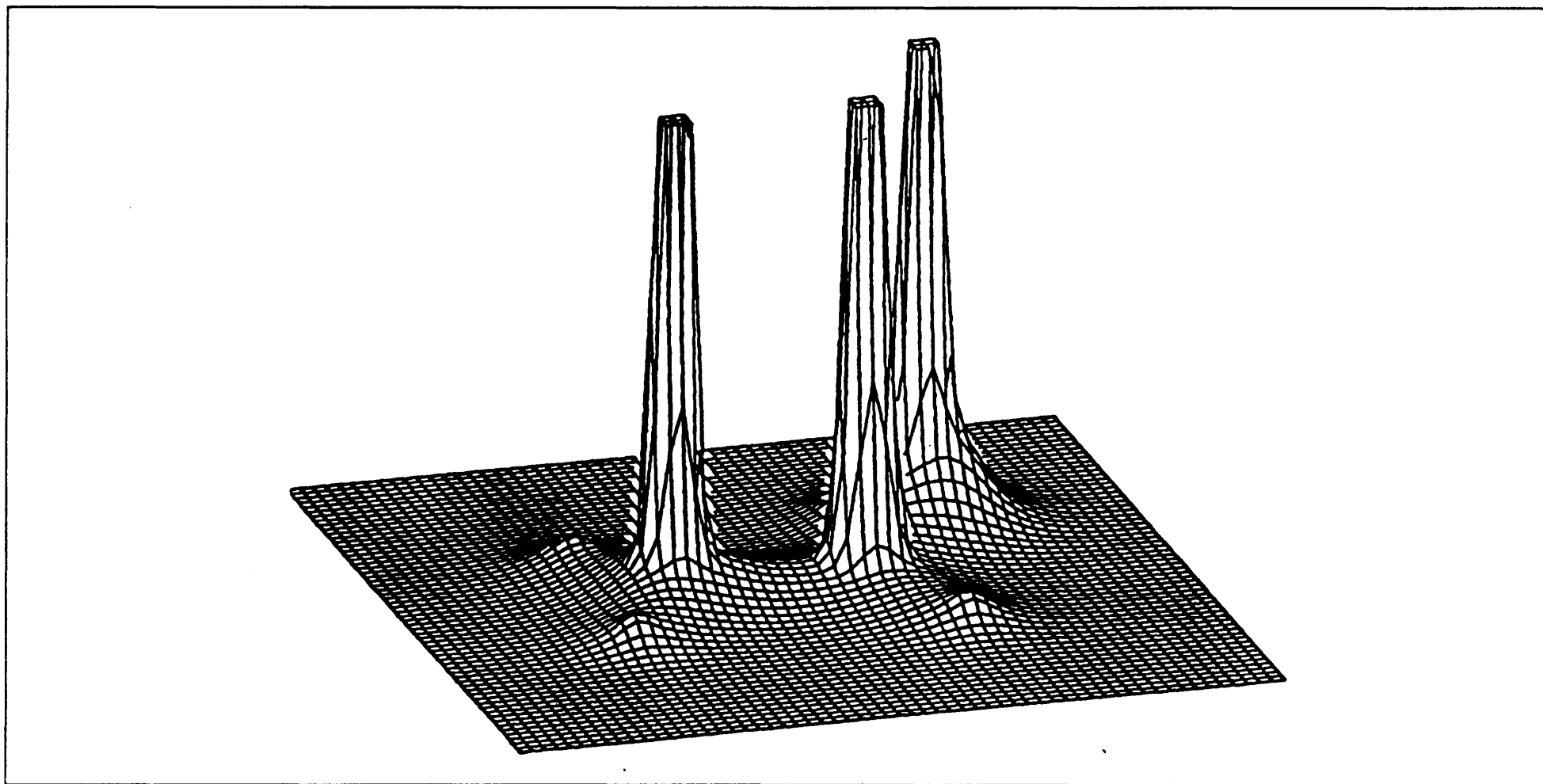
Fig. 2.10: Isometric projection of the electron density around formamide.
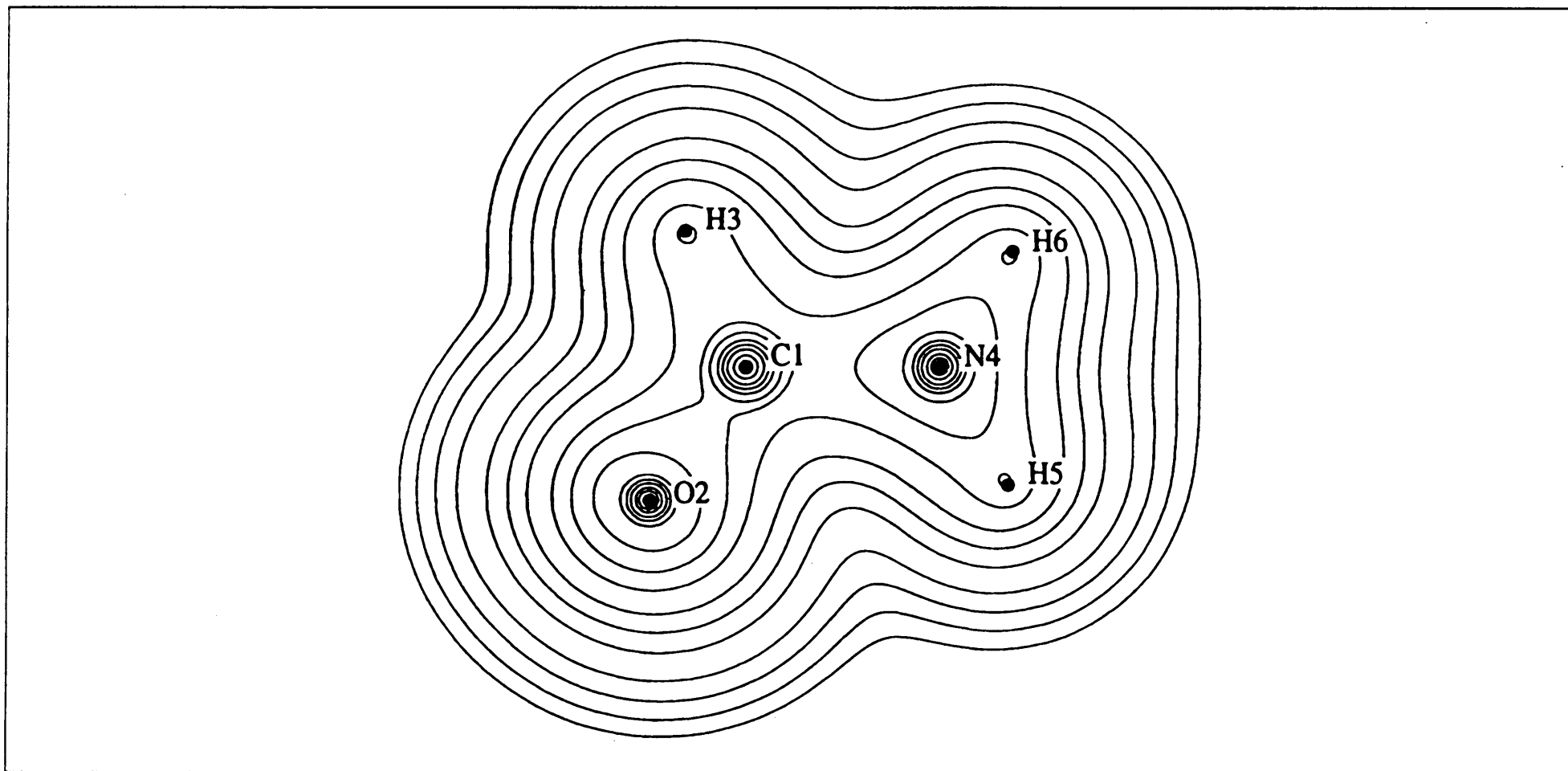
Fig. 2.9: Contour map showing the variation in electron density around formamide.
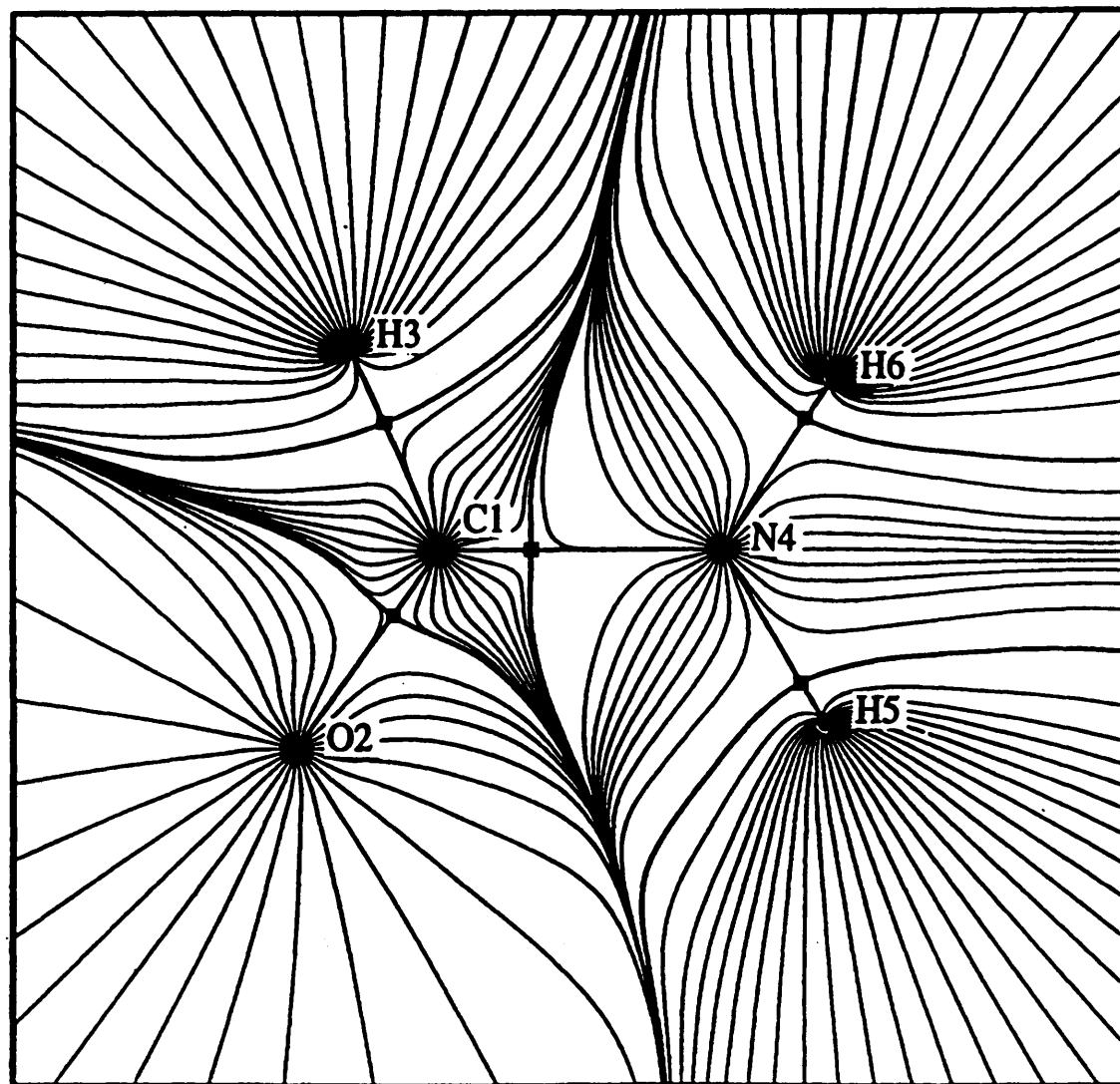
Fig. 2.14: Gradient vector paths around formamide. The paths terminate at atoms or at bond critical points (indicated by squares).
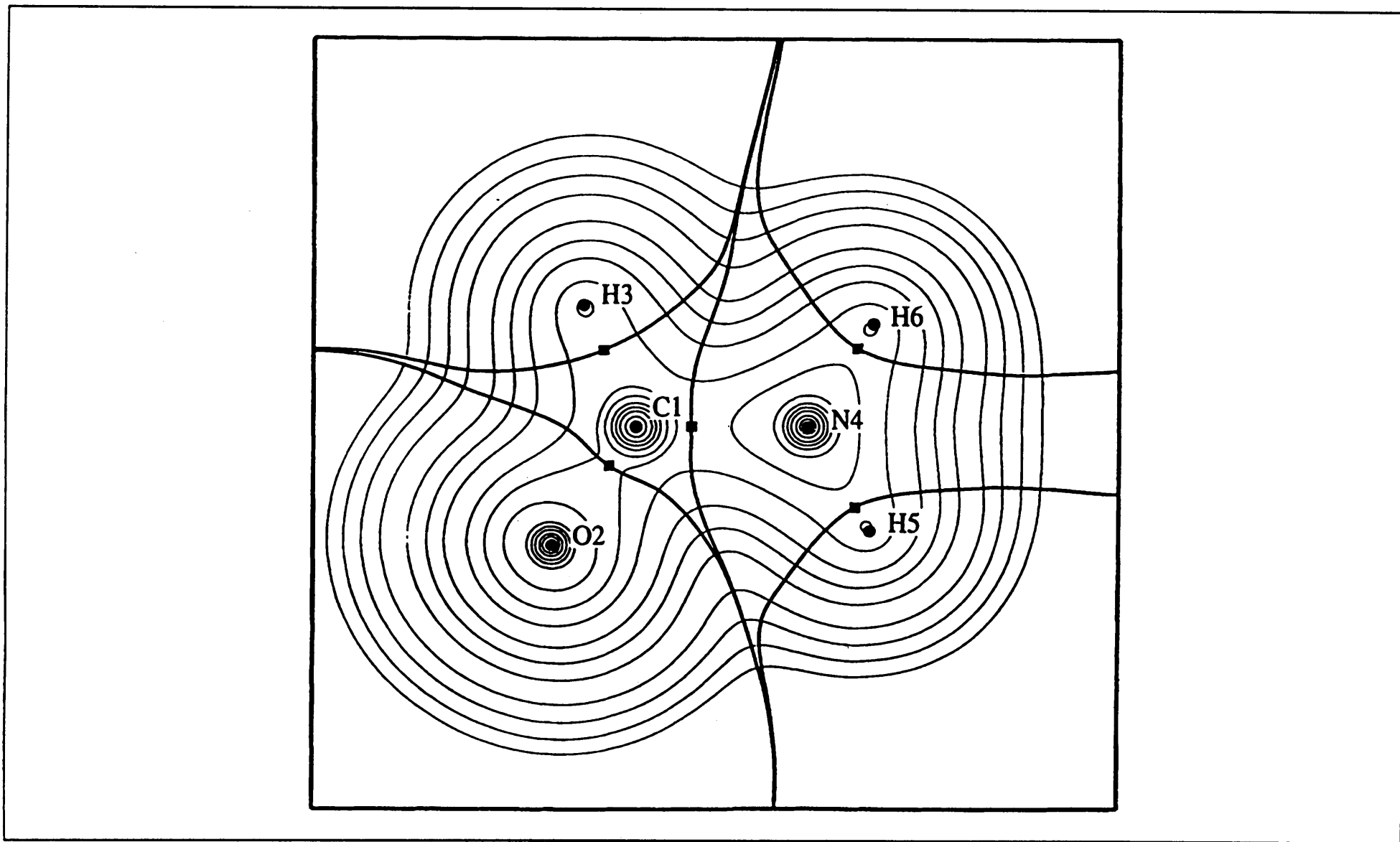
Fig. 2.16: Partitioning the electron density in formamide.
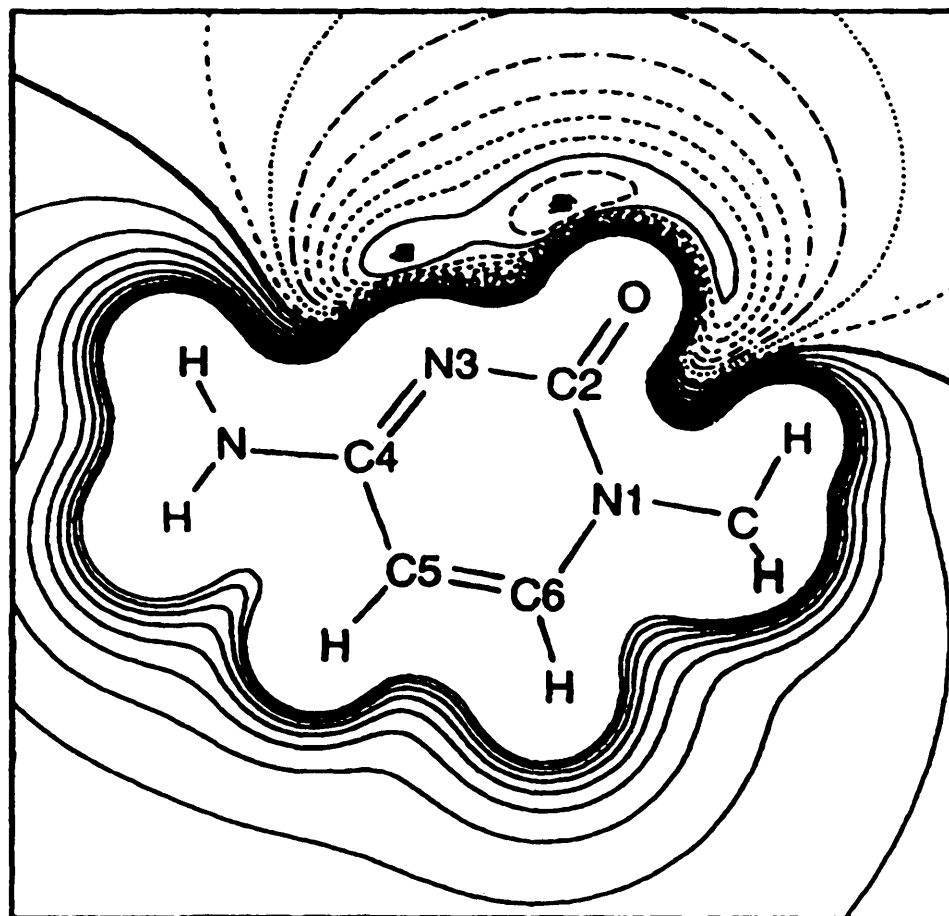
Fig. 2.17: Electrostatic potential contours around cytosine. Negative contours are dashed, the zero contour is bold. The minima near N3 and O are marked.
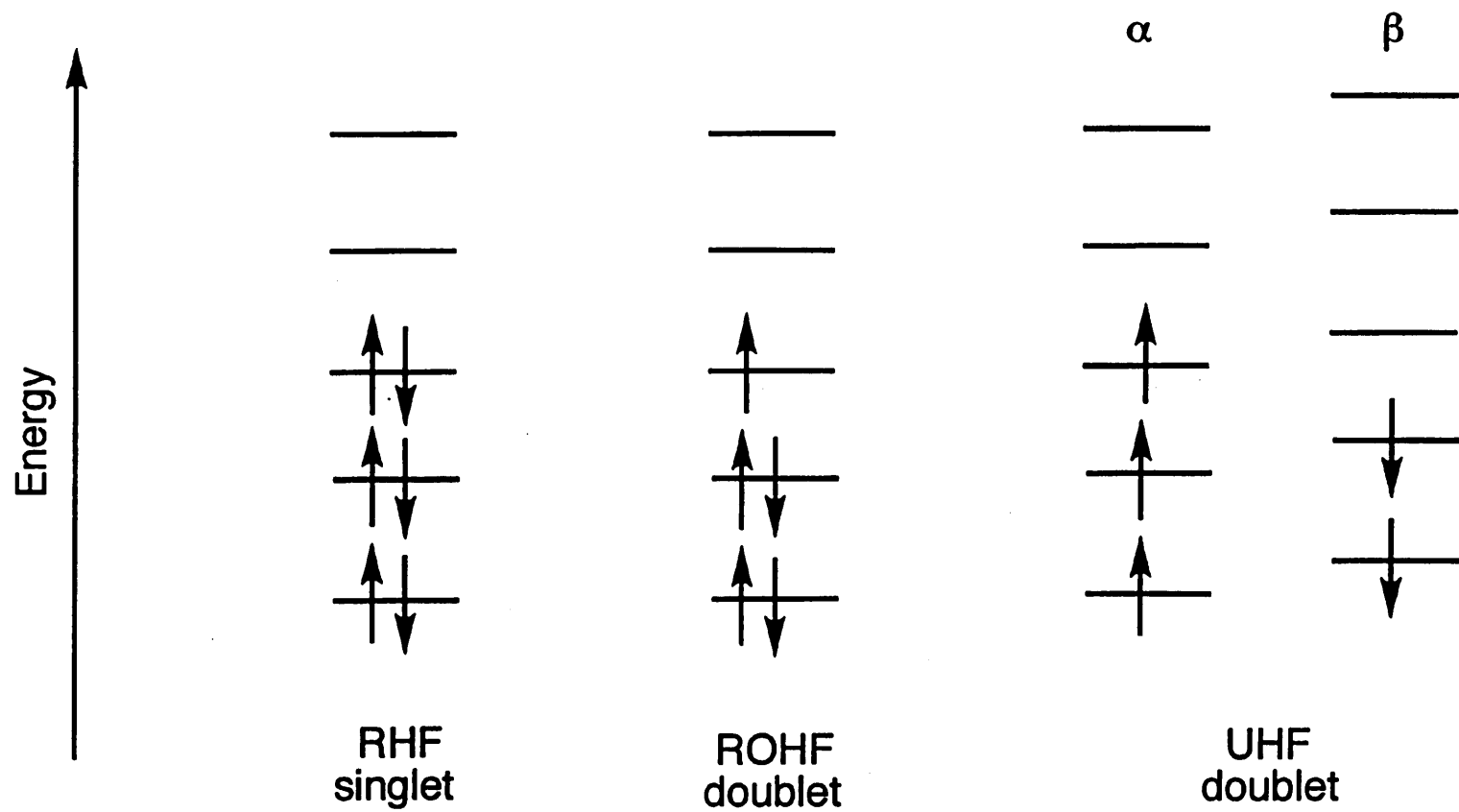
Figure 3.4 Illustrating an RHF singlet, and ROHF and UHF doublet states
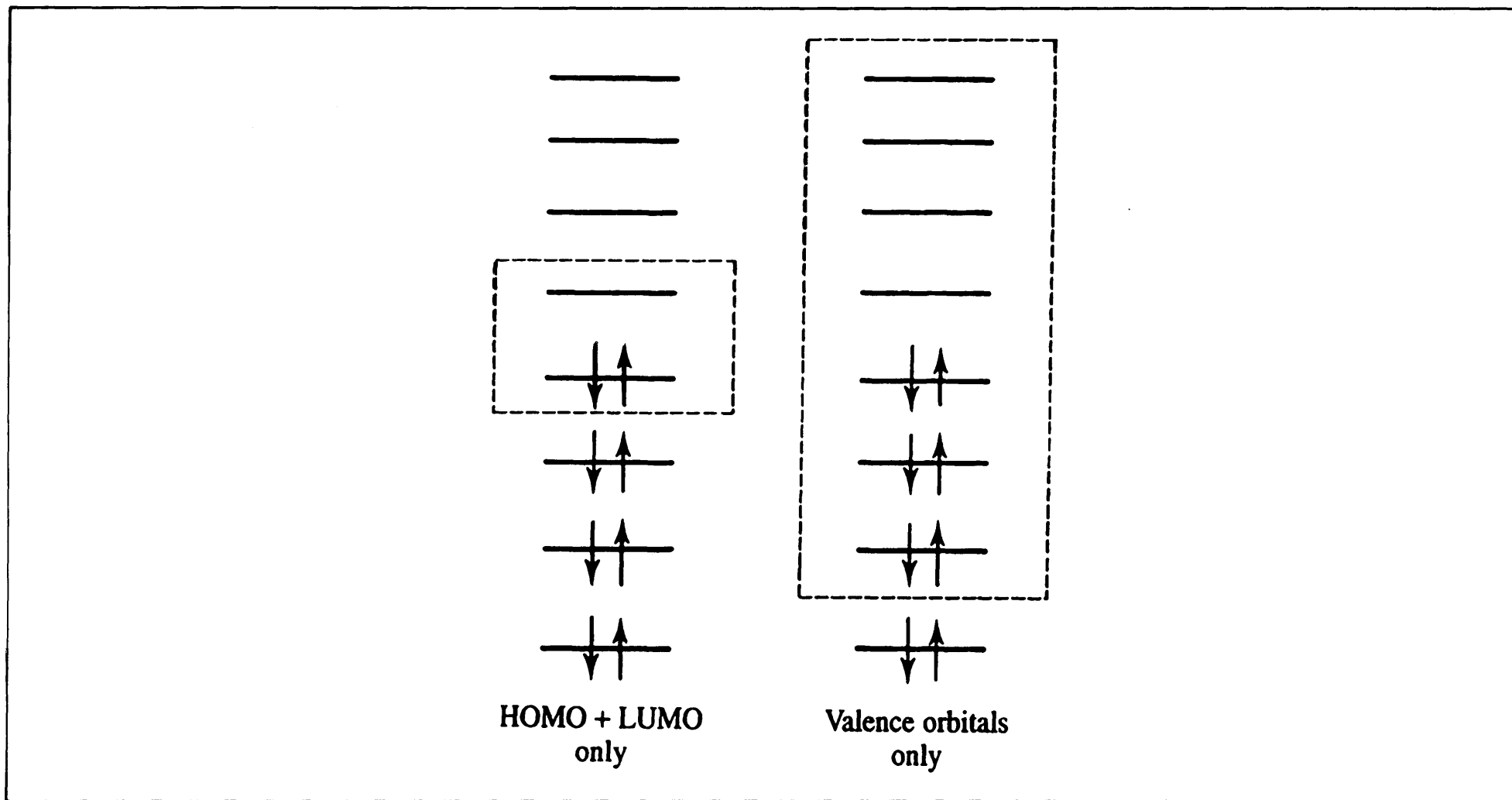
Fig. 3.3: *Some of the ways in which excited-state wavefunctions can be included in a configuration interaction calculation.*

Table 3.3 Mulliken charges in formamide with different methods

	MNDO	AM1	PM3	HF/6-31G(d,p)	MP2/6-31G(d,p)
C	0.37	0.26	0.16	0.56	0.40
O	−0.39	−0.40	−0.38	−0.56	−0.43
N	−0.49	−0.62	−0.13	−0.73	−0.63

Table 3.4 Average heat of formation error in kcal/mol (number of compounds)

Compounds	MNDO	AM1	PM3	MNDO/d	SAM1	SAM1d
Al (29)	22.1	10.5	16.4	4.9		
Si (84)	12.0	8.5	6.0	6.3	8.0	11.2
P (43)	38.7	14.5	17.1	7.6	14.4	15.0
S (99)	48.4	10.3	7.5	5.6	8.3	7.9
Cl (85)	39.4	29.1	10.4	3.9	11.1	4.7
Br (51)	16.2	15.2	8.1	3.4	8.7	5.2
I (42)	25.4	21.7	13.4	4.0	6.6	6.6
Zn (18)	21.0	16.9	14.7	4.9		
Hg (37)	13.7	9.0	7.7	2.2		
Al, Si, P, S, Cl, Br, I, Zn, Hg (488)	29.2	15.3	10.0	4.9		
Si, P, S, Cl, Br, I (404)	31.4	16.1	9.5	5.1	9.3	8.2

Density functional theory (DFT) is an approach to the electronic structure of atoms and molecules which has enjoyed a dramatic surge of interest since the late 1980s and 1990s [Parr 1983; Wimmer 1997]. Our approach here will be to introduce the key elements of the theory and to identify the similarities and differences between DFT and the Hartree–Fock approach. In Hartree–Fock theory the multi-electron wavefunction is expressed as a Slater determinant which is constructed from a set of N single-electron wavefunctions (N being the number of electrons in the molecule). DFT also considers single-electron functions. However, whereas Hartree–Fock theory does indeed calculate the full N-electron wavefunction, density functional theory only attempts to calculate the total electronic energy and the overall electronic density distribution. The central idea underpinning DFT is that there is a relationship between the total electronic energy and the overall electronic density. This is not a particularly new idea; indeed an approximate model developed in the late 1920s (the Thomas–Fermi model) contains some of the basic elements. However, the real breakthrough came with a paper by Hohenberg and Kohn in 1964 [Hohenberg and Kohn 1964], who showed that the ground-state energy and other properties of a system were uniquely defined by the electron density. This is sometimes expressed by stating that the energy, E, is a unique *functional* of $\rho(\mathbf{r})$.

The second landmark paper in the development of density functional theory was by Kohn* and Sham who suggested a practical way to solve the Hohnberg–Kohn theorem for a set of interacting electrons [Kohn and Sham 1965]. The difficulty with Equation (3.37) is that we do not know what the function $F[\rho(\mathbf{r})]$ is. Kohn and Sham suggested that $F[\rho(\mathbf{r})]$ should be approximated as the sum of three terms:

$$F[\rho(\mathbf{r})] = E_{KE}[\rho(\mathbf{r})] + E_{H}[\rho(\mathbf{r})] + E_{XC}[\rho(\mathbf{r})] \qquad (3.42)$$

where $E_{KE}[\rho(\mathbf{r})]$ is the kinetic energy, $E_{H}[\rho(\mathbf{r})]$ is the electron–electron Coulombic energy, and $E_{XC}[\rho(\mathbf{r})]$ contains contributions from exchange and correlation. It is important to note that the first term in Equation (3.42), $E_{KE}[\rho(\mathbf{r})]$, is defined as the kinetic energy of a system of *non-interacting* electrons with the same density $\rho(\mathbf{r})$ as the real system:

$$E_{KE}[\rho(\mathbf{r})] = \sum_{i=1}^{N} \int \psi_i(\mathbf{r}) \left(-\frac{\nabla^2}{2} \right) \psi_i(\mathbf{r}) \, d\mathbf{r} \qquad (3.43)$$

The second term, $E_{H}(\rho)$, is also known as the Hartree electrostatic energy. The Hartree approach to solving the Schrödinger equation was introduced briefly in Section 2.3.3 and almost immediately dismissed because it fails to recognise that electronic motions are correlated. In the Hartree approach this electrostatic energy arises from the classical interaction between two charge densities, which, when summed over all possible pairwise interactions, gives:

$$E_{H}[\rho(\mathbf{r})] = \frac{1}{2} \int\int \frac{\rho(\mathbf{r}_1)\rho(\mathbf{r}_2)}{|r_1 - r_2|} \, d\mathbf{r}_1 \, d\mathbf{r}_2 \qquad (3.44)$$

Combining these two and adding the electron–nuclear interaction leads to the full expression for the energy of an N-electron system within the Kohn–Sham scheme:

$$E[\rho(\mathbf{r})] = \sum_{i=1}^{N} \int \psi_i(\mathbf{r}) \left(-\frac{\nabla^2}{2} \right) \psi_i(\mathbf{r}) \, d\mathbf{r} + \frac{1}{2} \int\int \frac{\rho(\mathbf{r}_1)\rho(\mathbf{r}_2)}{|\mathbf{r}_1 - \mathbf{r}_2|} \, d\mathbf{r}_1 \, d\mathbf{r}_2 + E_{XC}[\rho(\mathbf{r})]$$

$$- \sum_{A=1}^{M} \int \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} \rho(\mathbf{r}) \, d\mathbf{r} \tag{3.45}$$

This equation acts to *define* the exchange-correlation energy functional $E_{XC}[\rho(\mathbf{r})]$, which thus contains not only contributions due to exchange and correlation but also a contribution due to the difference between the true kinetic energy of the system and $E_{KE}[\rho(\mathbf{r})]$.

Kohn and Sham wrote the density $\rho(\mathbf{r})$ of the system as the sum of the square moduli of a set of one-electron orthonormal orbitals:

$$\rho(\mathbf{r}) = \sum_{i=1}^{N} |\psi_i(\mathbf{r})|^2 \tag{3.46}$$

By introducing this expression for the electron density and applying the appropriate variational condition the following one-electron Kohn–Sham equations result:

$$\left\{ -\frac{\nabla_1^2}{2} - \left(\sum_{A=1}^{M} \frac{Z_A}{r_{1A}} \right) + \int \frac{\rho(\mathbf{r}_2)}{r_{12}} d\mathbf{r}_2 + V_{XC}[\mathbf{r}_1] \right\} \psi_i(\mathbf{r}_1) = \varepsilon_i \psi_i(\mathbf{r}_1) \qquad (3.47)$$

In Equation (3.47) we have written the external potential in the form appropriate to the interaction with M nuclei. ε_i are the orbital energies and V_{XC} is known as the exchange-correlation functional, related to the exchange-correlation energy by:

$$V_{XC}[\mathbf{r}] = \left(\frac{\delta E_{XC}[\rho(\mathbf{r})]}{\delta \rho(\mathbf{r})} \right) \qquad (3.48)$$

The total electronic energy is then calculated from Equation (3.45).

To solve the Kohn–Sham equations a self-consistent approach is taken. An initial guess of the density is fed into Equation (3.47) from which a set of orbitals can be derived, leading to an improved value for the density, which is then used in the second iteration, and so on until convergence is achieved.

Table 11.1. H_2O geometry as a function of basis set at the HF level of theory

Basis	R_{OH} (Å)	α_{HOH}
cc-pVDZ	0.9463	104.61
cc-pVTZ	0.9406	106.00
cc-pVQZ	0.9396	106.22
cc-pV5Z	0.9396	106.33
cc-pV6Z	0.9396	106.33

Table 11.2 H_2O geometry as a function of basis set at the MP2 level of theory

Basis	R_{OH} (Å)	α_{HOH}	ΔR_{OH} (Å)	$\Delta\alpha_{HOH}$
cc-pVDZ	0.9649	101.90	0.0186	− 2.71
cc-pVTZ	0.9591	103.59	0.0185	− 2.48
cc-pVQZ	0.9577	104.02	0.0181	− 2.20
cc-pV5Z	0.9579	104.29	0.0184	− 2.04
cc-pV6Z	0.9581	104.36	0.0185	− 1.97

Table 11.10 H_2O dipole moment (Debye) as a function of theory (valence correlation only), experimental value is 1.847 D

Basis	HF	MP2	CCSD(T)
cc-pVDZ	2.057	1.964	1.936
cc-pVTZ	2.026	1.922	1.903
cc-pVQZ	2.008	1.904	1.890
cc-pV5Z	2.003	1.895	
cc-pV6Z	1.990		
aug-cc-pVDZ	2.000	1.867	1.848
aug-cc-pVTZ	1.984	1.852	1.839
aug-cc-pVQZ	1.982	1.858	1.848
aug-cc-pV5Z	1.982	1.861	

Table 11.11 H_2O dipole moment (Debye) as a function of theory (all electrons)

Basis	HF	MP2	CCSD(T)
aug-cc-pCVDZ	2.001	1.868	1.849
aug-cc-pCVTZ	1.983	1.857	1.843

Table 11.12 H_2O dipole moment (Debye) as a function of DFT functional and basis set; the experimental value is 1.847 D

Basis	SVWN	BLYP	BPW91	B3LYP	B3PW91
aug-cc-pVDZ	1.853	1.796	1.803	1.855	1.859
aug-cc-pVTZ	1.857	1.799	1.800	1.854	1.854
aug-cc-pVQZ	1.855	1.798	1.797	1.854	1.852
aug-cc-pV5Z	1.856	1.799	1.798	1.855	1.852

Table 11.7 % electron correlation recovered by different methods in the cc-pVDZ basis

Method	% EC
MP2	94.0
MP3	97.0
MP4	99.5
MP5	99.8
CCSD	98.3
CCSD(T)	99.7
CISD	94.5
CISDT	95.8
CISDTQ	99.9

Table 11.8 Total energy (+76 a.u.) as a function of basis set and electron correlation (valence only)

Method	cc-pVDZ	cc-pVTZ	cc-pVQZ	cc-pV5Z	cc-pV6Z	cc-pV∞Z
HF	− 0.02677	− 0.05713	− 0.06479	− 0.06704	− 0.06735	− 0.0676
MP2	− 0.22844	− 0.31863	− 0.34763	− 0.35860	− 0.36264	− 0.368
MP3	− 0.23544	− 0.32275	− 0.34939	− 0.35815	− 0.36094	− 0.364
MP4	− 0.24067	− 0.33302	− 0.36104	− 0.37051	− 0.37357	− 0.377
MP5	− 0.24120	− 0.33159				
CCSD	− 0.23801	− 0.32455	− 0.35080	− 0.35952		− 0.366
CCSD(T)	− 0.24104	− 0.33219	− 0.35979	− 0.36904		− 0.376
CISD	− 0.22997	− 0.31384	− 0.33922	− 0.34765		− 0.354

Table 11.9 Total energy (+76 a.u.) as a function of basis set and electron correlation (all electrons)

Method	cc-pCVDZ	cc-pCVTZ	cc-pCVQZ	cc-pCV5Z	cc-pCV∞Z (%EC)
HF	− 0.02718	− 0.05731	− 0.06490	− 0.06706	− 0.0677 (0.0)
MP2	− 0.26855	− 0.37486	− 0.40758	− 0.41939	− 0.430 (97.4)
MP3	− 0.27638	− 0.37984	− 0.41012	− 0.41978	− 0.430 (97.4)
MP4	− 0.28194	− 0.39079	− 0.42240	− 0.43268	− 0.440 (100.0)
MP5	− 0.28239	− 0.38907			
CCSD	− 0.27897	− 0.38154	− 0.41144	− 0.42104	− 0.428 (96.9)
CCSD(T)	− 0.28226	− 0.38978	− 0.42096	− 0.43105	− 0.438 (99.5)
CISD	− 0.26898	− 0.36799	− 0.39675	− 0.40599	− 0.412 (92.6)

Table 11.20 Bond distance (Å) in FOOF. Experimental values are 1.217 and 1.575 Å

	R_{OO}			R_{FO}		
	cc-pVDZ	DZP	TZ(2d)	cc-pVDZ	DZP	TZ(2d)
HF	1.304	1.308	1.301	1.368	1.362	1.361
MP2	1.210	1.266	1.140	1.581	1.521	1.728
MP3	1.302	1.320	1.301	1.455	1.449	1.450
CCSD	1.276	1.307	1.278	1.494	1.474	1.482
CCSD(T)	1.216	1.261	1.216	1.637	1.571	1.614
CISD	1.304	1.316	1.301	1.416	1.412	1.407
SVWN	1.202	1.222	1.186	1.556	1.536	1.573
BLYP	1.224	1.243	1.207	1.622	1.604	1.643
BPW91	1.211	1.231	1.119	1.612	1.589	1.623
B3LYP	1.240	1.264	1.222	1.523	1.502	1.540
B3PW91	1.229	1.254	1.217	1.517	1.491	1.524

Table 11.20 sourced from Ref. 15.

Table 11.21 Dipole moment (Debye) for CO; the experimental value is 0.122 D

	aug-cc-pVDZ	aug-cc-pVTZ	aug-cc-pVQZ	aug-cc-pV5Z
HF	-0.255	-0.263	-0.265	-0.265
MP2	0.296	0.280	0.275	0.273
MP3	0.076	0.047	0.036	0.032
MP4	0.220	0.222	0.216	0.214
CCSD	0.097	0.070	0.059	0.055
CCSD(T)	0.141	0.127	0.118	0.115
CISD	0.050	0.023	0.011	
SVWN	0.232	0.226	0.229	
BLYP	0.187	0.184	0.185	
BPW91	0.221	0.217	0.218	
B3LYP	0.091	0.086	0.087	
B3PW91	0.119	0.114	0.116	

QM/MM Modeling Approach

- Couple quantum mechanics and molecular mechanics approaches (e.g. QM/MM)

- QM treatment of the active site

  - reacting center

  - excited state processes (e.g. spectroscopy)

  - problem structures (e.g. complex transition metal center)

- Classical MM treatment of environment

  - enzyme structure

  - explicit solvent molecules

  - bulky organometallic ligands
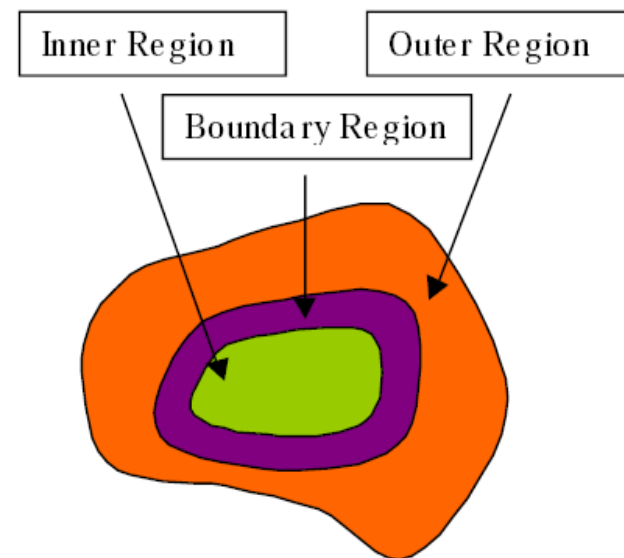
General QM/MM Methodology

- The QM/MM potential energy is implemented via solving the Schrödinger equation with an effective Hamiltonian

$$H_{eff} \; \Psi(r, R_a, R_M) = E(R_a, R_M) \; \Psi(r, R_a, R_M)$$

- Where H_{eff} and $H_{QM/MM}$ are defined as....

$$H_{eff} = H_{QM} + H_{MM} + H_{QM/MM}$$

$$H_{QM/MM} = -\sum_{i,M}\left(\frac{q_M}{r_{iM}}\right) + \sum_{A,M}\frac{Z_A\,q_M}{R_{A,M}} + \sum_{A,M}\left(\frac{A_{A,M}}{R_{A,M}^{12}} - \frac{B_{A,M}}{R_{A,M}^{6}}\right)$$

- The total energy is then:

$$E_{tot} = \frac{\langle \Psi | \hat{H}_{QM} + \hat{H}_{QM/MM} | \Psi \rangle}{\langle \Psi | \Psi \rangle} + E_{MM}$$

Warshel, A.; Levitt, M. *J. Mol. Biol.* 1976, 103, 227-249.
Singh, U. C.; Kollman, P. A. *J. Comp. Chem.* 1986, 7, 718-730.
Field, M.J.; Bash, P.A.; Karplus, M. *J. Comp. Chem.* 1990, 11, 700-733.
Lyne, P.D.; Hodoscek, M.; Karplus, M. *J. Phys. Chem. A* 1993, 103, 3462-3471.
Eurenius, K.P.; Chatfield, D.C.; Brooks, B.R.; Hodoscek, M. *Int. J. Quant. Chem.* 1996, 60, 1189.

Implementations of QM/MM

- Semi-empirical
  - AM1
  - PM3
  - MNDO
  - PDP3 (PDDG/PM3)
  - PDMN (PDDG/MNDO)
  - SCCDFTB

- Pros:
  - Fast
  - Simpler than *ab initio* QM methods
  - In many cases describes system(s) correctly

- Cons:
  - Reduced accuracy
  - Only restricted wavefunctions (caveat...)
  - Parameters
  - Ground state methods
  - Only valence electrons treated explicitly

Implementations of QM/MM

- *Ab initio*
  - HF
  - DFT
    - Pure: BLYP
    - Hybrid: B3LYP
    - RI methods
  - MP2
    - Local methods
    - RI methods
  - CCSD
  - Multireference methods
    - CASSCF
    - Spin-flip
    - EOM

- Pros:
  - Accuracy
    - Much better description of wavefunction (e.g. correlation)
  - Flexibility
- Cons:
  - Performance
    - Speed
    - System size limitations
  - More complex than semi-empirical methods

Additional Implementations of QM/MM

- Empirical Valence Bond (EVB)
  - Approximates QM interactions
  - Mixes valence bond configurations
    - Must define bonding patterns in "QM" system
  - Requires parameterization

- SCCDFTB
  - Empirical approximation to DFT (B3LYP)
  - QM/MM implementation via CHARMM
  - Approximately the same cost as AM1, PM3
    - But better accuracy
  - Actively being developed
    - Q. Cui
    - M. Elstner

Additional Implementations of QM/MM

- ONIOM: Morokuma *et al.*

  - QM/MM, QM/QM, QM/QM/MM and QM/QM/QM

  - Subtractive method

$$E^{\mathrm{ONIOM2}} = E^{\mathrm{high}}_{\mathrm{model}} - E^{\mathrm{low}}_{\mathrm{model}} + E^{\mathrm{low}}_{\mathrm{real}}$$

$$E^{\mathrm{ONIOM3}} = E^{\mathrm{high}}_{\mathrm{small\ model}} - E^{\mathrm{medium}}_{\mathrm{small\ model}} + E^{\mathrm{medium}}_{\mathrm{intermediate\ model}} -$$
$$E^{\mathrm{low}}_{\mathrm{intermediate\ model}} + E^{\mathrm{low}}_{\mathrm{real}}$$

  - Pro: Easy to use!

  - Widely available: Gaussian, Q-Chem 3.0

Additional Implementations of QM/MM

- CPMD: Car-Parrinello Molecular Dynamics
  - Employs DFT
    - Mostly restricted to pure DFT functionals
  - QM wavefunction is propagated through the dynamics
  - Electronic motion can become coupled to the nuclear motion
    - Should not happen in the Born-Oppenheimer approximation
  - Employs plane wave basis functions
    - Needs a lot of them to describe the wave function accurately
  - Employs Effective Core Potentials (ECP)

QM/MM Boundary Treatments

- **Electrostatic interactions:**
  - Mechanical Embedding
    - in vacuo QM calculation coupled classically to MM via point charges at QM nuclear sites
  - Electrostatic Embedding
    - MM atoms appear as centres generating electrostatic contribution to QM Hamiltonian
  - Polarised Embedding
    - MM polarisability is coupled to QM charge density

QM/MM Boundary Treatments

- Single Link Atom (Singh and Kollman)

- Double Link Atom (Brooks and coworkers)

  - Gaussian Blur

- Generalized Hybrid Orbital (GHO) Approximation

  - Gao and coworkers

- Local Self-Consistent Field (LSCF)

  - Rivail and coworkers

- Frozen Orbital Approximation

  - Friesner and coworkers

- Pseudobond Methods

  - Yang and coworkers

Amara and Field; Theor Chem Acc (2003)109:43–52