A NEW APPROACH TO THE QUANTUM MODELLING OF BIOCHEMICALS

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We describe a new approach to the quantum chemistry of biological molecules and other systems where complex geometry and bonding patterns cause problems. Our approach combines self-consistent quantum chemistry with molecular dynamics, removing the need to define interatomic potentials in advance. The method is illustrated using serotonin (both in free space and with model receptors) as an example.

KEY WORDS: Quantum modelling, CHEMOS, serotonin

1 INTRODUCTION

We describe a new approach to the quantum chemistry of biological molecules and other systems where complex geometry and bonding patterns cause problems. It uses ideas from condensed-matter science, combining self-consistent quantum chemistry with molecular dynamics, rather than regarding these as successive steps; the dynamics can be damped for geometry optimisation. In essence, we follow molecular dynamics without the need to define interatomic potentials in advance, so that no prejudices about the character of the bonding are included. The approach has special promise for modelling complex behaviour at a molecular level, for example the dynamics of proton transfer, as in transmitter-receptor interactions, or following electron transfer, as in photo-induced processes.

We shall illustrate the method using serotonin [1–19] as an example, both in free space and with model receptors. These receptor models are of two sorts: external potentials which mimic the general shape, and specific molecular species used to build a model receptor. Such models are well-known, and form the basis of previous calculations of reaction paths and energetics. In our approach there is no need to guess critical geometries or reaction paths in advance. Indeed, a complicated reaction (of a class already known) emerged from our calculations without pre-knowledge of the mechanism and without requiring specific bonding patterns or imposing the reaction in advance. We note in particular that the process we shall discuss could not have been modelled by conventional molecular mechanics, and probably would not have been found by normal "static search" methods.

2 SELF-CONSISTENCY AND ION DYNAMICS

Our CHEMOS code (§2.2) for self-consistent quantum-chemical molecular dynamics [20–23] is based on two main linked components. One part is standard quantum chemistry (and may be carried out at various levels of sophistication), and generates forces self-consistent to a chosen degree without numerical differentiation. The other part is molecular dynamics, which gives classical ion dynamics. This second component has the particular virtue that the user does not need to define a reaction in advance, since the evolution of the system with time will identify important processes. Our code has further facilities to include external force fields and electric fields which represent less-critical or more distant parts of the molecular environment of the receptor. We have the standard routines which predict specific properties, plus others yielding scanning tunnelling microscopy images.

The idea that electronic self-consistency and molecular geometry could be done simultaneously is not new. Even in the 1960s, simple calculations were done for one-electron systems [24]. However, the paper by Car and Parrinello [25] brought important new ideas. One was the idea of regarding the coefficients in a wave function or density as dynamical variables. A second idea was to return to the use of damped dynamics, popular too in the 1960s [26], but here with its emphasis on avoiding reliance on symmetry, as well as avoiding metastable energy minima. A third idea was the use of new self-consistent methods, e.g. density functional theory. Our strategy is different, but shares many of these advantages: we exploit developments in semi-empirical methods related to density functional theory, and we bring the eletronic and atomic optimisation steps together.

2.1 *Comparison with other common methods*

In modelling biologically-important molecules, three approaches are common. First, there are electronic structure calculations for pre-selected geometries (see [7–9] for POLYATOM calculations, [15, 16] for CNDO, [17–19] for extended Hückel theory). Sophistication falls as molecular size rises, and many large biomolecule calculations are not even self-consistent. Further, most standard approaches cannot simulate the effects either of supposed receptor structure, or of any applied fields which affect the molecular conformation. Accurate and effective ways to allow for the presence of water exist [27], and could be implemented in our approach, but this has not been done.

The second standard approach is molecular mechanics, based on valence force potentials. Empirical potentials are helpful for extrapolation from simpler systems. Simple intermolecular atom-exchange interactions are allowed within some of the more complicated potentials (for example the Tersoff many-body form which has been used [28] for molecular dynamics simulations). Yet methods based solely on potentials omit much of the chemistry, for the interatomic forces do not depend on electronic state (e.g. ground versus excited state); nor do these potentials describe charge transfer well, a situation we meet in many cases, not least for the doping process in conducting polymers.

The third approach emphasises shape, and matches large rigid molecules (or their subunits) against other large rigid structues; packing (i.e. short range repulsion) is assumed to dominate, though Coulomb forces may contribute too [29, 30]. In essence, our provision of external field options in CHEMOS allows large-

scale shape factors to be incorporated. These options also allow us to couple a control group of atoms, in which electronic structure is explicitly treated, with a far larger group of atoms interacting by an interatomic potential. This is especially useful in constant temperature molecular dynamics, as in studies of friction [31].

2.2 *Methods and options for electronic structure techniques*

We proceed thus: (i) Select a starting geometry; (ii) Start calculating electronic structure, but stop at a chosen level of convergence; (iii) Calculate the forces on each atom analytically; (iv) Follow the molecule's dynamics, either undamped (standard molecular dynamics) or damped to achieve an energy minimum. In the motion, the Fock matrix is diagonalised regularly. We have found once per timestep satisfactory, but this is not compulsory, and situations where more steps are needed are encountered fairly often. This same procedure can be used for those excited states which can be maintained orthogonal to the ground state, e.g. for spin triplet excitations from a singlet ground state. Our approach is self-consistent as regards electronic structure and geometry. In the best cases, damped dynamics seem to yield a relaxed, self-consistent state about as fast as self-consistency for a fixed geometry, and the convergence is frequently very good.

Recognising the unavoidable compromises between accuracy and the level of molecular complexity which can be handled, our present implementation is at the CNDO/2 and INDO levels. Extension to MINDO and special implementations of INDO for transition metal systems is under way. For these zero differential overlap methods, forces (first derivatives of energies) can be calculated analytically. These semi-empirical methods can be derived in various ways, both as approximate forms of Hartree-Fock theory [32] and an approximation based on density functional theory [33]. In some applications we shall need matrix elements (e.g. tunnelling rates), and these methods eliminate the problems inevitable with approaches based on still simpler approaches, like valence force potentials.

It is not essential to use a semi-empirical method; indeed floating Gaussian (or other) methods may have advantages. However, there will always be a niche for simpler techniques for complex problems and, as we need only first-row species (H, C, N, O) for serotonin or for our other applications (to conducting polymers and [34] to STM imaging) the CNDO/2 level is especially convenient. Further, zero-differential overlap methods can be extended to describe hydrogen bonding [35] should we wish to include solvation. Perhaps more importantly, it is also well-validated, with many previous calculations for reference. We believe it essential to use a tried and tested method, where ranges of validity and accuracy are established. It is, of course, absolutely essential to avoid fitting answers: any parameters must be fixed by general considerations in advance.

3 BIOMOLECULE STRUCTURE; THE EXAMPLE OF SEROTONIN

Serotonin (5-hydroxytryptamine) acts as a neurotransmitter. It is a natural vasoconstrictor, but has wider importance in brain chemistry, influencing sleep patterns, appetite and (like the structurally-related LSD) other aspects of behaviour [1, 2, 3]. Serotonin's special versatility appears to stem from its ability to bind to at least three distinct receptors (5-HT1, 5-HT2 and 5-HT3). Recent reports [4] imply exceptional promise for drugs which interact with one of these receptors,

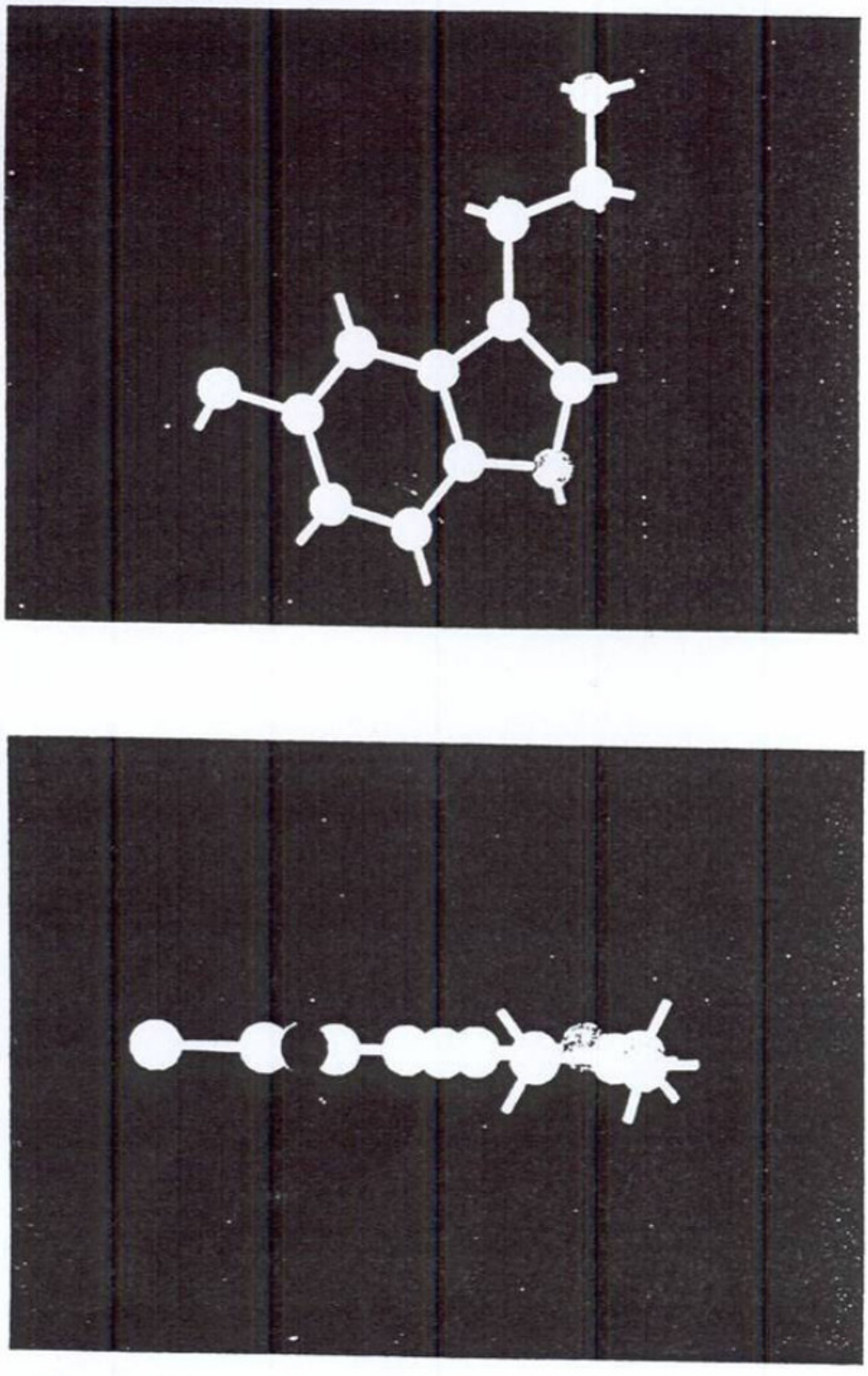
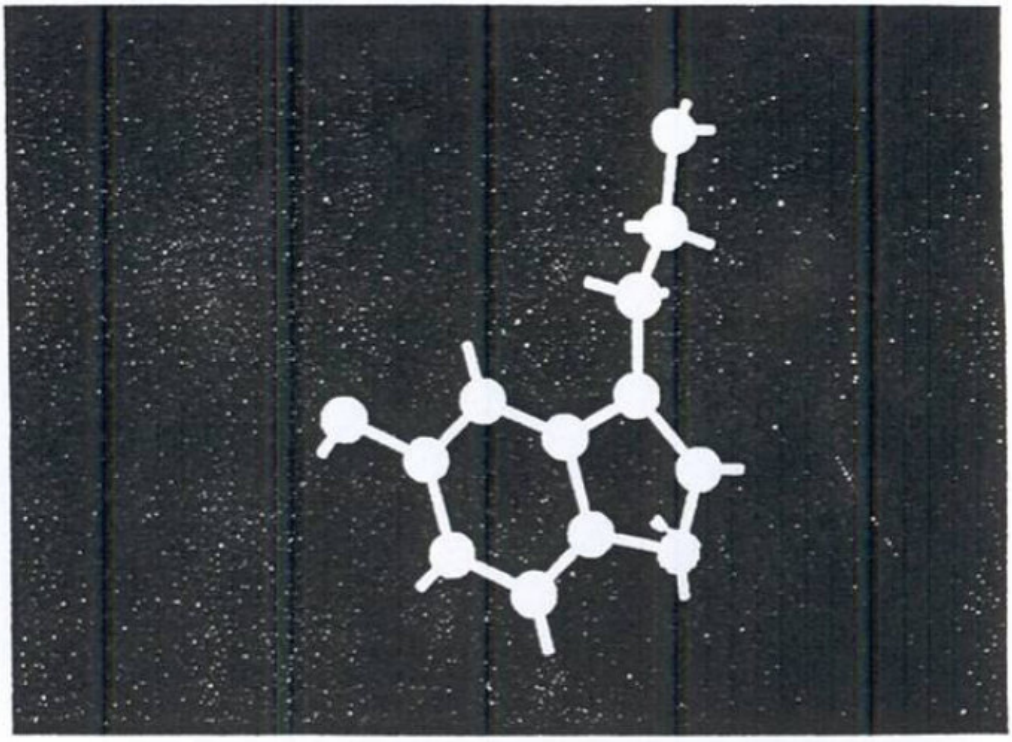


Figure 1 Geometry of Serotonin. The above figure gives two views the planar confirmation discussed in Reference 21, and is a metastable form, not that of lowest energy; it does not correspond to observations on this class of molecule. The figure on facing-page shows the lowest energy "out of plane" configuration from later calculations; these results are in line with experiment. (See Colour Plates)



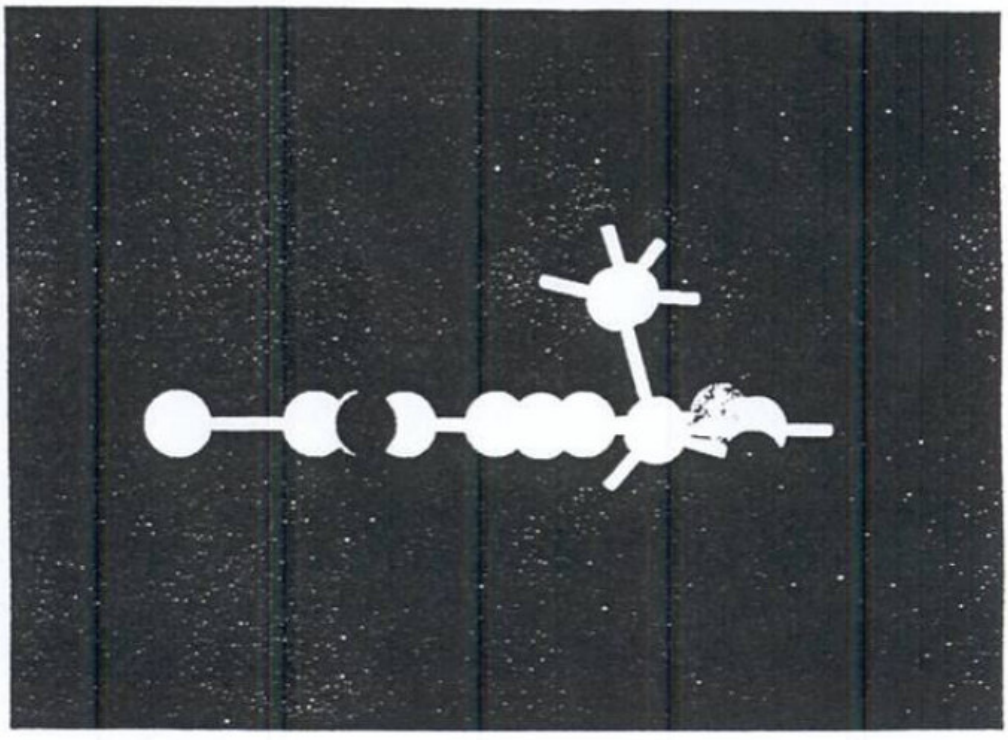


Figure 1 continued

as either an antagonist, blocking normal response, or agonist, stimulating a similar response. We do not solve any of these problems in this paper: we describe an approach which may aid their solution. In demonstrating the method, we also make substantial idealisations, notably in omitting water of solvation; this remediable omission alllows us to show some features more clearly.

3.1 *Geometry in free space*

We find serotonin is non-planar, in agreement with previous calculations [5]. Experimentally, the cation appears planar in the crystalline form, but this may be a result of crystallisation. Figure 1 shows two low-energy geometries, the lowest energy form predicted being consistent with experiment. In Section 6.1 we construct an energy surface for a number of related geometries.

We can also investigate other charge states and excited states. Thus we have compared the ground singlet and triplet excited state of serotonin. On excitation, the H atom on the five-membered ring and the N atom on the chain move towards each other, and there is electron transfer from the N to the H and its neighbouring carbon. This motion suggests significant polarisability, partly ionic and partly electronic. We might conjecture that polarisability is a significant part of

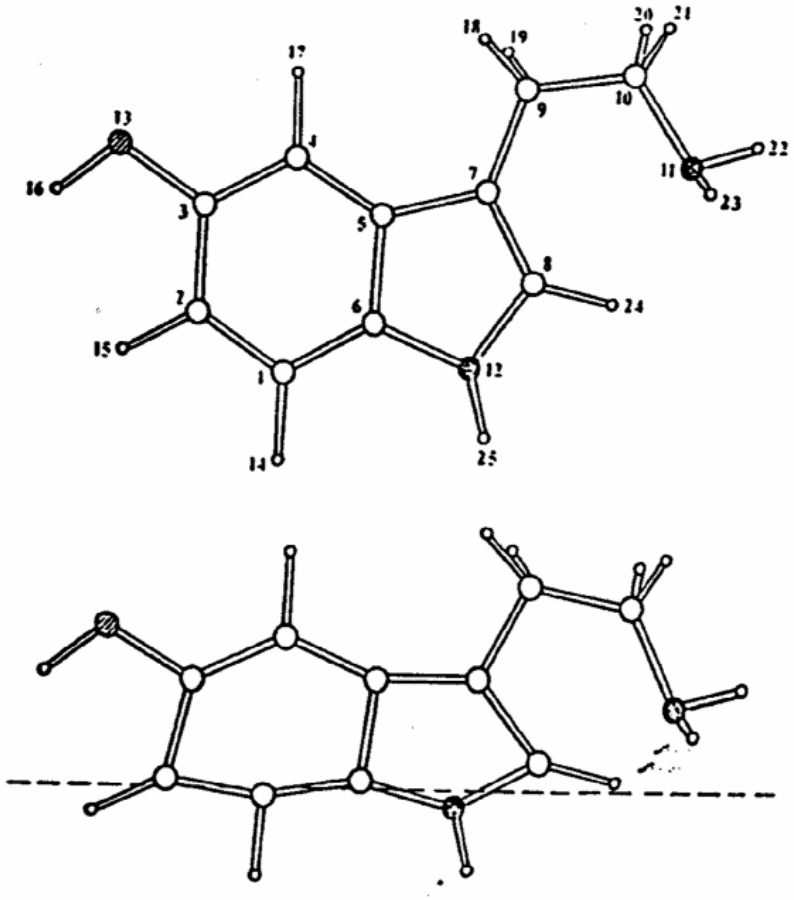


Figure 2 The effect of a constraint. Here Serotonin is deformed by a hard wall with a short-range attractive potential.

interaction with receptors, and this led us to consider several specific receptor models.

3.2 *Effects of a force field*

We show (Figure 2) the effects of a shape constraint which mimics a receptor, taking the simplest possible model, a plane with weak attraction and strong short-range repulsion. More complex, realistic, forms are straightforward. Receptor shape constraints are a basic mechanism of selectivity. Whilst many discussions assume rigid molecular shapes, it is widely appreciated that a molecule may adapt by bending or twisting to slot into the receptor. Such deformation or polarisation would be especially important when there are "floppy" chains of atoms, as for serotonin, leading to quite strong effects on the geometry. Since the electronic structure is calculated consistently at all times, we can predict relevant properties like polarisability (though, in common with all limited-basis methods, the polarisability predicted is not accurate) or response to charged units in the receptor.

One important force field is that of the tip of a scanning-tunnelling microscope. Recent observations claim to observe individual atomic positions for a variety of organic and biological molecules. Potentially, this a major development, not only as a source of geometric data, but also because the STM tip might be used as a selective problem to investigate the ease of various structural changes. However, there are two cautions. First, one should be sure that the image really is associated with the molecule, not just a modification of the subtrate signal. Secondly, we have showed elsewhere (using CHEMOS) that the tip can modify observed signals qualitatively from simple views [34]. One major factor is the distortion or reorientation induced by the non-uniform electric field of the tip.

4 WHAT TYPES OF BIOLOGICAL PROCESS?

The potential of our approach lies both in phenomena like selectivity, where only thermal processes are involved, and also in behaviour after excitation, e.g. photochemical phenomena. Biochemical selectivity has at least two key components (as Hopfield has noted [36], high selectivity may need more than one determining feature). One comes from molecular electronic structure [5–19]; the second concerns shape, and how the molecule's structure matches that of its receptors [29, 30]. We can study both aspects together in our new approach, which exploits simultaneous electronic and atomic relaxation. Simple models of the receptor can be incorporated from the start: the geometry of the biomolecule is optimised with receptor constraints present.

4.1 *Catalytic Selection as a Component of Transmitter-Receptor Interaction?*

The way a receptor can respond selectively to a transmitter raises several distinct issues. First, there is a molecular geometry issue: the transmitter must "fit" the receptor better than almost all other molecules. If, as usually assumed, no strong chemical interactions are involved, the binding will be small, typically only a few kT at body temperatures; without further selectivity, a whole range of alternative molecules would also fit a chosen receptor, often with effects quite different from the intended transmitter. How else could selection occur? We noted above that

deformation of the transmitter might be an extra factor, i.e. the right "flexibility" or "polarisability" could be as necessary as the right "shape". This idea can be investigated systematically by new methods we have developed, which are based on self-consistent quantum chemistry and damped molecular dynamics for geometry optimisation. Our recent work suggests that, at least for serotonin, flexibility is a useful, but not a dominant, factor.

A second issue is what happens when the transmitter is in place at a receptor. Clearly some reaction occurs; molecules which fit and do not react merely block a receptor, whereas the transmitter is presumably involved in charge transfer, proton transfer, or some other reaction. The reaction may be entirely within the receptor, with the transmitter simply biasing a reaction through its electric field or through the deformation it induces in the receptor itself. There may be more than one reaction. Nevertheless, the presence or absence of a reaction is a component of selectivity, in that it must be considered in assessing any synthetic molecules which might interact with the receptor.

We shall address the key question of whether the transmitter is altered (e.g. changing its charge state) or whether the changes are solely within the receptor. In an important series of calculations on a model receptor for serotonin, Weinstein and his colleagues [10–14] propose proton transfer within the receptor itself. In essence, serotonin encourages proton transfer: "as 5-HT approaches the receptor model, the indole portion of 5-HT forms a stacking complex with the imidazolium/ammonia cation and induces proton transfer from imidazolium to ammonia. Thus the stacking interaction causes the electric field at the two components of the hydrogen bond to be differentially modified, and thereby facilitates the proton transfer in one direction" [10, 11].

Our calculations were done in a similar spirit, in that we used several small molecular units to mimic key receptor units; we were also able to include force fields but, since our results were not substantially affected, we shall discuss here only behaviour in the absence of the force field. Our calculations differ from those of Weinstein *et al.* in two respects. First, we have used our self-consistent quantum-chemical molecular dynamics code. Secondly, we have not attempted to mimic the precise receptor structure in quite the same way: we have experimented with various possible receptor components, rather than seeking to represent a particular structure. This is partly because of concern over the accuracy with which atomic positions are known for actual receptors; these doubts are enhanced in relation to atomic positions in the presence of a transmitter. Our analysis should be regarded as indicative of possible behaviour, not the modelling of a specific system.

4.2 *Model receptors II: Molecular dynamics of proton release*

What we find is a proton transfer reaction between transmitter and model receptor, stimulated by the catalytic effect of a component in our model receptor. Our receptor model is, of course, hypothetical, but we do believe it is not eccentric. The model and process may well be typical of an interesting class of transmitter-receptor systems. Our present purpose, however, is to demonstrate that our new theoretical approach has the power to identify reactions which might be hard to recognise in other approaches.

The main result we find is that a proton is transferred from the serotonin to the receptor through the cooperative influence of receptor units. The simplest reaction one might invoke involves a group R1 of the receptor and a group T1 of the

transmitter, these reacting to yield product species R1", T1" and perhaps other products. We shall generalise this merely by requiring components R2, R3 of the receptor which catalyse the reaction for the intended transmitter, but which do not encourage responses from similar molecules.

We shall construct a model receptor for serotonin to include three components: two are simple molecules (ammonia and acetic acid, these being on opposite sides of the receptor, corresponding to R2 and R3 above). A third possible component (not relevant for the present discussion) is a force field which represents the other geometric features of the receptor. We shall also presume there is an unspecified fourth group (effectively R1) which can accept a proton; this could correspond to the proton acceptor considered by Weinstein *et al.*

We find by explicit calculation for the initial geometries we use (with final geometries optimised automatically by CHEMOS) that neither of the simple molecules (ammonia, acetic acid) individually reacts significantly with serotonin, though the acetic acid does cause charge redistribution. This lack of substantial effect is still true, at least for any configuration close to those we have tried, when the force field is applied. When both molecules are present, a reaction occurs (dramatically in molecular dynamics) which can be regarded as catalytic removal of a proton from the serotonin. This proton (or its hydrated form in more realistic work) would react with the undefined group R1 to yield R1'.

The sequence of the reaction (Figure 3) is interesting and unexpected. The three key atoms are the N of ammonia and the nearby O and H of serotonin. Their behaviour involves three steps. First there is a slow relaxation of the H away from the N, with a small charge transfer (about 0.1 electrons, based on Mulliken charges) from O to N. Secondly, the H moves rapidly back again towards the N (step 6 in the figure); in this step, the N transfers charge back to O (about 0.25 electrons) so that the oxygen has a large negative charge. Thirdly, the H loses most of its electronic charge to N (about 0.4 electrons are transferred) and detaches itself rapidly from the molecule as a proton (steps 7–10 in the figure).

In all, the reaction removes a proton from the OH group adjacent to the ammonia of our model receptor. In terms of our reaction description, R2 is ammonia and R3 is acetic acid; T1 is the OH group, and the group R1 (not identified here, nor affecting selectivity in this model) accepts the proton. We could have ensured the proton was captured by water, or extended our model receptor to have an explicit third component which captured the proton, but these sophistications would distract from the main point.

5 EXTENSIONS TO ELECTRON TRANSPORT: REORGANISATION AFTER EXCITATION

Interactions between biomolecules involve chemical changes, the simplest being (a) change of ionisation state and (b) gain or loss of a proton. For serotonin (which we use purely as an illustration) we find added electrons accumulate mainly in the ring of 6 carbons, which expands slightly; the chain "opens up" slightly. Removal of electrons has the opposite affect. Adding a proton to the NH_2 group also causes the structure to open up.

In principle we can study more dramatic changes, e.g. those following core or valence excitation during radiolysis [37]. The major problem is how to maintain the

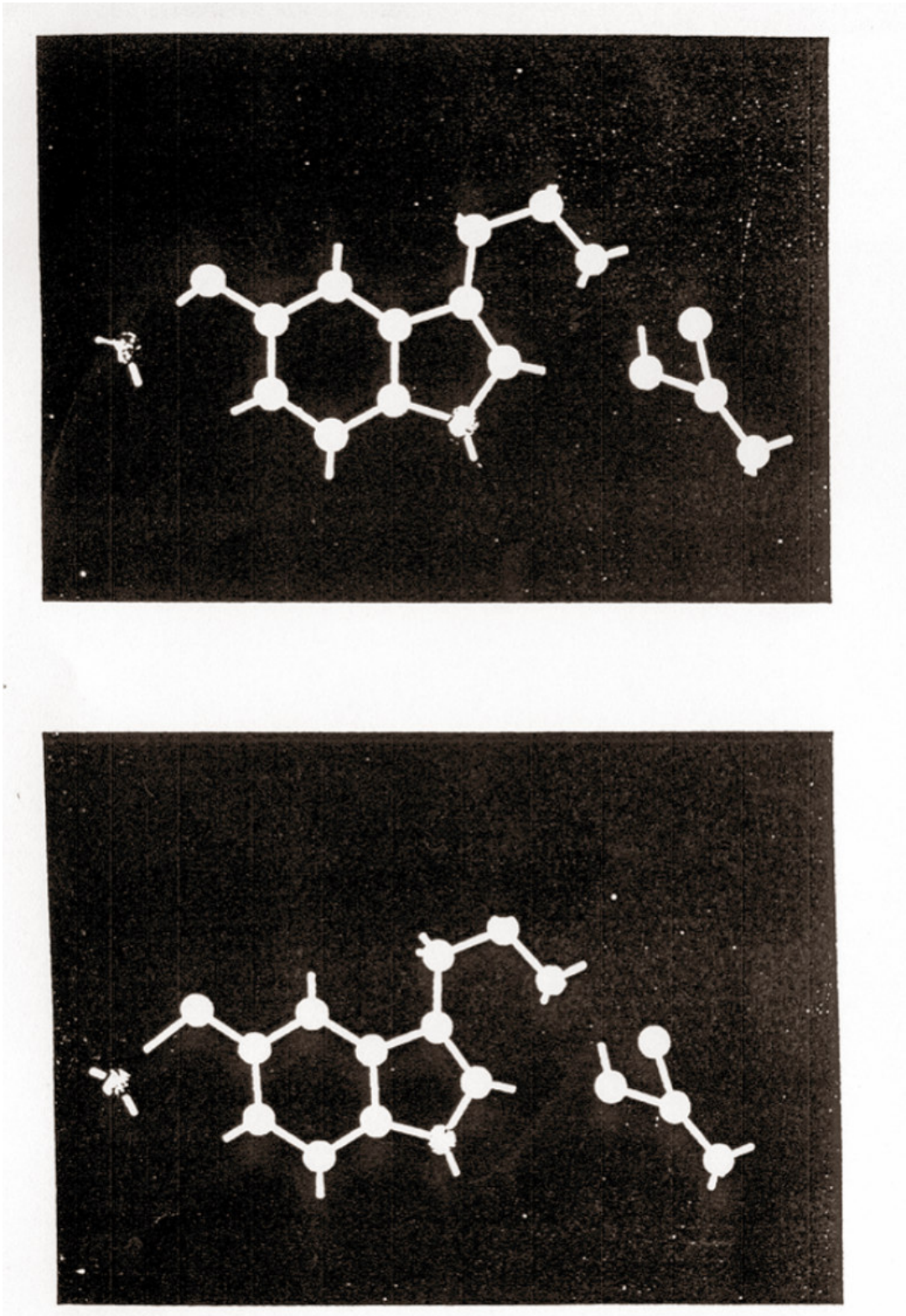
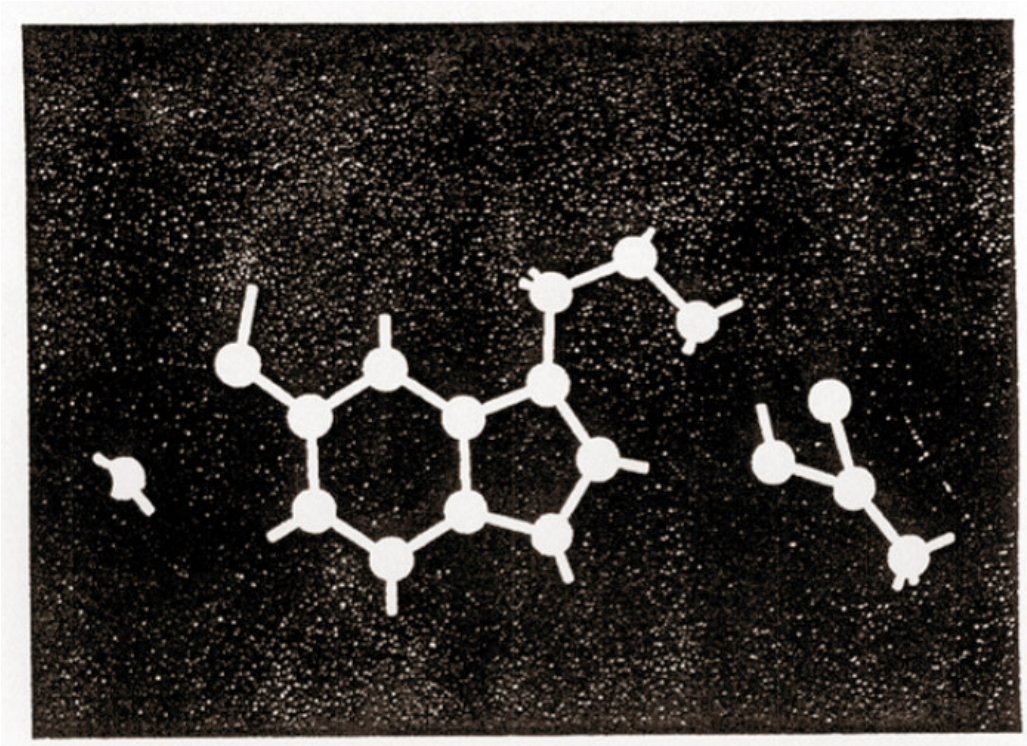


Figure 3 Detachment of hydrogen by the combined effects of ammonia and acetic acid. Neither of these molecules gives major effects by itself. The "bond" for the proton which is detached is shown for clarity, and does not imply chemical binding. (See Colour Plates)



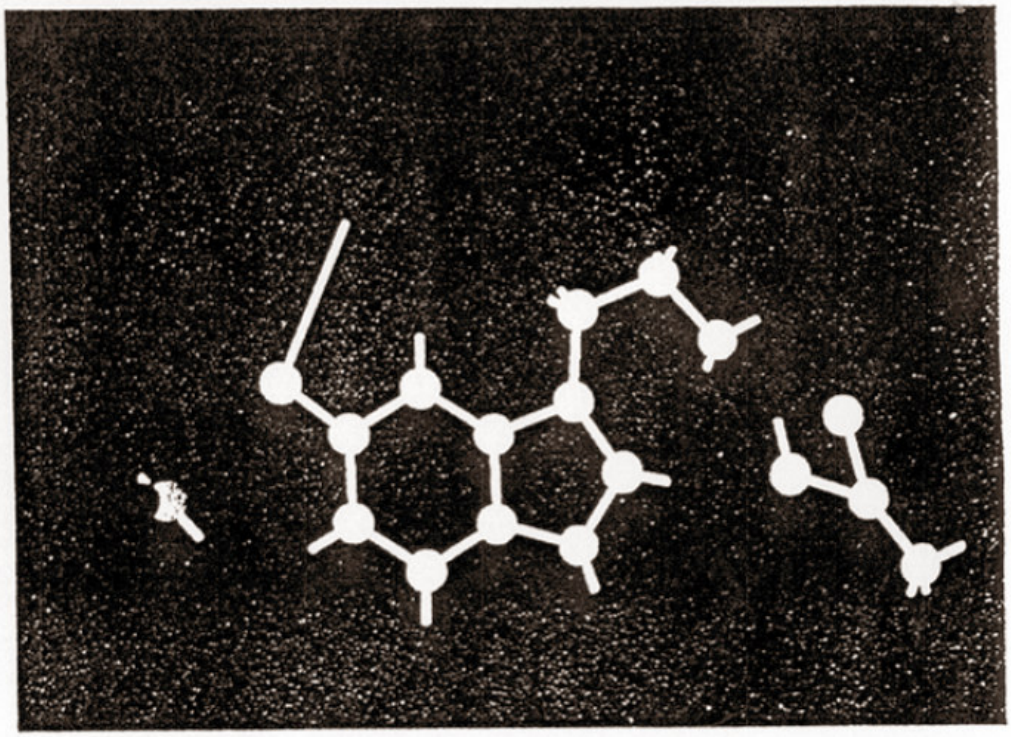


Figure 3 continued

molecule in the right eigenstate, since there will usually be no symmetry to help. The evolution can be followed in certain cases – e.g. those where the critical state is the lowest triplet state of a molecule with a singlet ground state. We have demonstrated how our approach can follow molecular dynamics usefully in a study of soliton motion in trans-polyacetylene [20, 23].

6. FURTHER COMMENTS

6.1 *Other applications: activation energies and saddle point location?*

Our approach also lends itself to novel methods for finding saddle points of energy

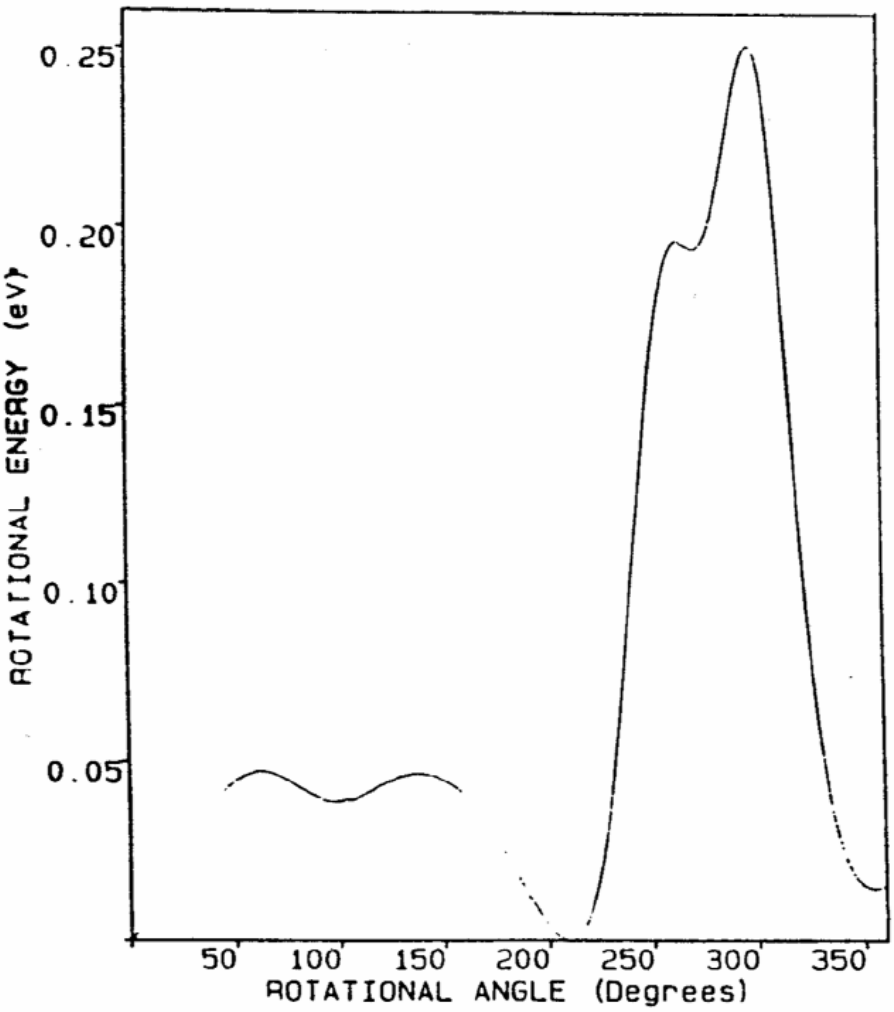


Figure 4a

Figure 4 (a) Energies for Serotonin as the tail is rotated against the two rings about the aromatic-aliphatic bond. At each stage all atomic positions are relaxed. The planar configuration (the upper diagram in Figure 1) corresponds to the local minimum at about 100°, the absolute minimum thus involves a rotation of about 100° from planar. The slight energy diference between 0° and 360° is because the damped relaxation associated with the hydrogens was not complete for the conditions we chose. Such problems are easily solved by a more detailed look at particular regions of the energy surface. (b) Conformation of serotonin for a rotational angle of 270°, where the potential energy surface is complicated by interactions beween the hydrogens on the aliphatic tail with those on the aromatic rings.

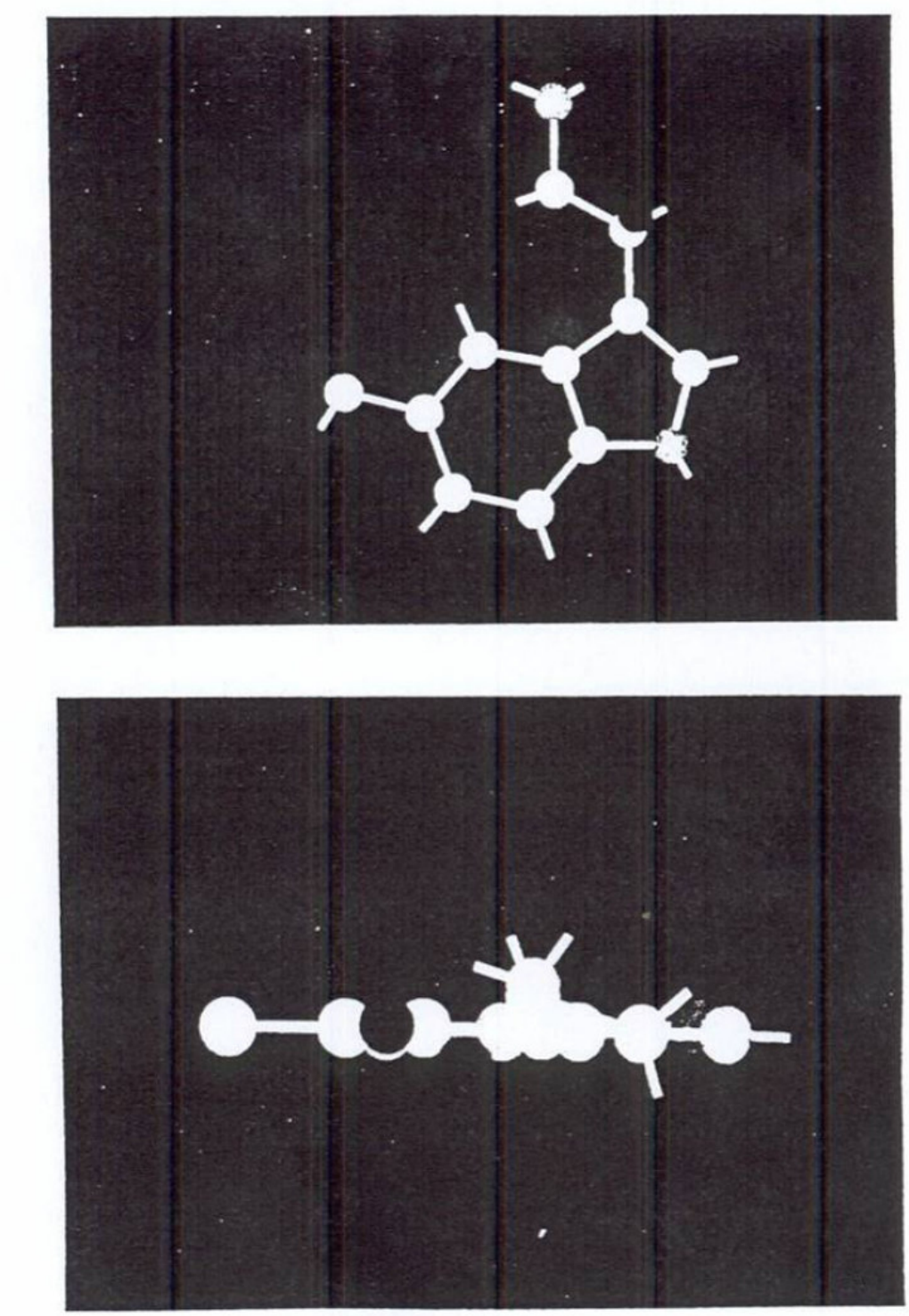


Figure 4b (See Colour Plates)

surfaces, even in the absence of symmetry. It therefore has potential for studies of enzyme action. The technique [38] is illustrated in Figure 4. In essence, the aliphatic CCN tail is rotated about the aromatic-aliphatic bond which links the tail to the 5-atom ring. Typical rotations are 0.05° per timestep: in translational motion,

similar values would be about 0.1 pm per timestep. In many cases 1 iterations per timestep is sufficient, but here – as in quite a few other examples – several iterations are needed. There is a strong steric interation between the aliphatic group and the phenyl hydrogen, so that the non-planar configuration should be stable when intermolecular interactions can be ignored.

We should comment on the character of proton transfer, since activation energies here are not just adiabatic path energies. It is often presumed that even quite large barriers in the adiabatic energy surface (perhaps even 1–2 eV) are no special obstacle to proton transfer, even when thermal energies are only a few hundredths of an eV. It also seems widely held that an adiabatic energy surface (with relaxed geometries for nearby atoms) defines the appropriate barrier for proton motion. We doubt both views. In our mechanism in section 4.2 (which is, we stress, illustrative rather than a precise model) there is no barrier to proton motion. Even if there were, the well-established assessments of mechanism for proton transport in other systems make it clear that the adiabatic barrier is not the energy determining activated motion (see e.g. [39]). Instead, the energy needed is usually the minimum energy to deform the system so that the fast-moving proton has the same energy in this geometry at its initial and final sites. We shall discuss this aspect in more detail elsewhere.

6.2 *Accuracy*

One limit on accuracy is the CNDO method itself. In particular, we have found the oxygen-oxygen interactions can cause problems in systems like silica or water. The errors are not gross, but can give qualitatively incorrect results. Clearly, one might go to more sophisticated methods though there is usually cost, either in evaluating the forces or in the greater complexity elsewhere (though MINDO seems to avoid the oxygen problems and, because of its simpler form for the two-electron integrals, is quicker). A further problem is energy conservation, and especially transfer of energy between electrons and ions during dynamics (damped dynamics will still yield the correct geometry). We have discussed this aspect elsewhere (appendix to [23]); it is usually straightforward to avoid difficulties in biological applications. Whether one can go further and usefully calculate rates of energy transfer (e.g. non-radiative transitons) is a matter we are investigating.

7 LIMITS ON THE METHOD

The ultimate limit comes from diagonalisation of the Fock matrix. Among the other molecules for which our approach may prove useful, we note these are molecules of a suitable size: various neurotransmitters, e.g. dopamine, adrenaline; hallucinogenic drugs e.g. LSD (which has structural features in common with serotonin); steroid hormones, e.g. progesterone; ATP; and a number of messengers [40, 41]. It should also be practical to treat the molecules of photosynthesis, e.g. [42] phycoyanobilin. Whether all the key molecular processes of photosynthesis can be handled – which seems likely – remains to be tested.

In summary, we have developed a new approach to self-consistent molecular dynamics. We believe it has potential for biological molecules, including the identification of transmitter-receptor interaction processes. Thus we have found striking behaviour of a well-known transmitter in the presence of a simple model receptor. The model is, of course, entirely hypothetical, and mechanisms related to

the one we describe have been proposed before. What is interesting is that the mechanism was not specified in advance (indeed was not familiar to the authors when the calculations were done) and is of some complexity, yet consistent with such views as exist about the nature of receptors. We conjecture that catalysis of reactions between receptor and transmitter is a general mechanism of ensuring selectivity when this cannot be guaranteed by shape factors alone.

Acknowledgements

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