The structure and intermolecular interactions of a creatinine designed–receptor complex, studied by *ab initio* methods

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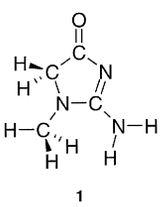
Structural and energetic features of the intermolecular interactions of a creatinine designed–receptor complex are investigated using *ab initio* electronic structure methods. Both the host and receptor can adopt different tautomeric forms and it is found that in the complex both molecules are considerably different from their gas-phase structures. A polar environment has an important role in determining the binding energy of the complex and may lead to proton transfer in the complex.

Introduction

Creatinine is an important end product of nitrogen metabolism in vertebrates and appears in the urine of healthy individuals.[1] The search for a suitable host complexing this guest molecule has led to experimental studies of the mode of binding of creatinine to hosts ranging from quite small molecules such as pyrimidine derivatives[2] to large polycyclic molecules.[3] Of particular interest is the recent report of an artificial receptor which can possibly be used for creatinine assays.[3]

There are two possible tautomers of creatinine, the amine **1** and imine **2** forms. In addition, four possible protomeric forms



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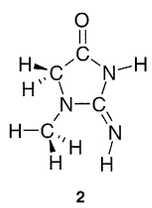

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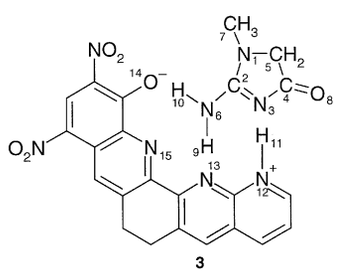

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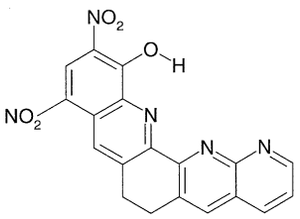
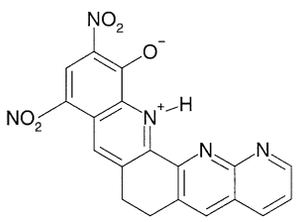
(**R1** ⟶ **R4**) of the receptor can be envisaged, the hydroxy form **R1** and three zwitterions (**R2**, **R3** and **R4**). The crystal structure of the receptor[3,4] showed the hydrogen atom to be disordered over two positions corresponding to tautomers **R1** and **R2**. A crystal structure of the complex **3** between the receptor and creatinine[3,4] shows that the tautomeric form, **R4**, of the receptor was formally involved in interacting with the amine form of creatinine. We describe here *ab initio* electronic structure calculations of the different tautomeric forms of the receptor, of the complex with creatinine and the effect of a polar environment on the energetics of complex formation. These calculations are designed to contribute to understanding the structural and energetic features of complex formation.

Computational details

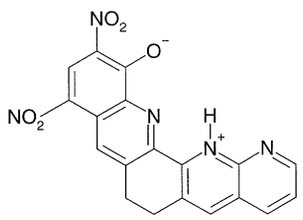
Conventional *ab initio* calculations of the structures and energetics of the four tautomeric forms of the receptor (**R1** ⟶ **R4**), of the amine and imine forms of creatinine and of the



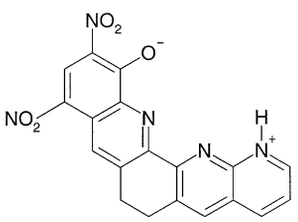
R1



R2



R3



R4

complex between **R4** and the amine form of creatinine, were carried out at the 3-21G split valence level.[5] for the guest–host complex the basis set size was 369. In view of the size of these calculations the stationary points were not characterised as minima. However, we believe them to be minima rather than transition states in view of the resultant structural parameters. Energy calculations at these optimised structures were then carried out employing the large cc-pVDZ basis of Dunning,[6] a basis at the double zeta level and including polarisation functions giving 608 basis functions for the guest–host complex. These calculations were carried out using a parallel version of GAUSSIAN92[7] implemented by us on the CRAY T3D at the Edinburgh Parallel Computing Centre (EPCC).

The solvation energies of these optimised structures were estimated using a continuum model of solvation within an *ab initio* framework. We have used the polarisable continuum model (PCM) as developed by Tomasi and co-workers,[8] and implemented within GAUSSIAN94[9] as the SCIPCM method. These calculations employed a relative permittivity of 78.4 to model water, and a 0.001e isodensity surface.

Computational results

The energies of the various structures are summarised in Table 1. Turning first to the energies of the four structures of the receptor, in the gas phase, hydroxy form (**R1**) is the most stable, with the three zwitterionic forms being of higher energy. The stability of the zwitterionic form progressively decreases as the separation between the positive and negative centres increases, presumably reflecting the decreasing electrostatic interaction.

Table 1 Relative energies (E/kcal mol^{-1}) and dipole moment (μ/Debye) of different forms of receptor

Receptor structure	3-21G// 3-21G [a,b]	cc-pVDZ// 3-21G	cc-pVDZ(PCM)// 3-21G, $\varepsilon = 78.4$
R1	0 [c] (13.6)	0 [d]	0 [e]
R2	1.2 (19.9)	8.1	−2.3
R3	9.1 (26.2)	16.9	−2.0
R4	28.1 (32.3)	34.6	1.4

[a] Dipole moment in parentheses. [b] Absolute energies. [c] −1364.48394 au. [d] −1372.33273 au. [e] −1372.37325 au.

Table 2 RHF/3-21G optimised geometries (d/Å) for creatinine and guest–host complex

	Creatinine + host			Creatinine	
	Partial opt [a]	Fully opt	Expt.[4]	Amine	Imine
N^1–C^2	1.348	1.336	1.292	1.357	1.376
C^2–N^3	1.346	1.363	1.411	1.304	1.396
N^3–C^4	1.358	1.377	1.357	1.387	1.359
C^4–C^5	1.548	1.535	1.498	1.554	1.528
C^5–N^1	1.465	1.464	1.421	1.458	1.451
N^1–C^7	1.461	1.471	1.505	1.453	1.451
C^2–N^6	1.295	1.280	1.282	1.334	1.250
C^4–O^8	1.218	1.203	1.234	1.205	1.207
N^{12}–H^{11}	1.004	1.836			
N^3–H^{11}	1.569	1.022	1.64		
N^{13}–H^9	2.066	1.921	2.08		
N^{15}–H^{10}	2.783	2.527			
O^{14}–H^{10}	1.652	1.575	1.84		
N^{15}–H^9	2.469	2.484			
N^3–H^{12}	2.566	2.854	2.75		
N^6–O^{14}	2.645	2.610	2.69		

[a] N^{12}–H^{11} constrained at 1.004 Å.

The ordering of these structures is the same at both the 3-21G and extended basis set levels, although the energy separations are greater for the larger basis. Solvation, as modelled by the PCM treatment has a profound effect on the relative energetics of the four tautomers of the receptor. The solvation energies are in the order **R4** > **R3** > **R2** > **R1**, in line with the order of the molecular polarities as reflected in the dipole moments. Such differential solvation has the effect of drastically reducing the energy spread of the four species in aqueous solution. Indeed, within the accuracy of our calculation, the four structures are essentially iso-energetic in water.

The structural parameters of the creatinine–receptor complex, optimised at the 3-21G level are shown in Table 2 (see structure **3** for atom numbering). In one important aspect, our calculated minimum energy structure differs from that found experimentally in the solid state. We find that proton transfer has occurred from the host molecule to N_3 of the creatinine molecule. Although the experimental evidence is strong that proton transfer has not occurred, we note that the hydrogen atom bonded to N^{12} was located in a difference Fourier map and refined with no constraints. The U value was 0.13 Å^2, the N–H bond length was 1.06(13) Å and the hydrogen was positioned in a trigonal position.[4] We have investigated this structural aspect further by optimising the structure of the guest–host complex keeping this proton attached to the host molecule, with a N^{12}–H^{11} distance of 1.004 Å. This calculation confirmed that proton transfer was energetically favourable, by 15 kcal mol^{-1} (1 cal = 4.184 J) at the cc-pVDZ//3-21G level (Table 3). We note that our constrained structure has a larger dipole moment (22.2 D), than the fully optimised one (18.7 D) suggesting that a polar environment might favour the former. A calculation of the relative energies of these two guest–host structures in water using the PCM approach, confirms that the structure having no proton transfer is preferentially stabilised, although

Table 3 Binding energies (E/kcal mol^{-1}) of creatinine–receptor complexes [a]

Complex structure	3-21G// 3-21G	cc-pVDZ// 3-21G	cc-pVDZ(PCM)// 3-21G, $\varepsilon = 78.4$
Fully optimised	83.5	59.8	13.6
Constrained (N^{12}–H^{11}, 1.004 Å)	68.6	45.1	6.2

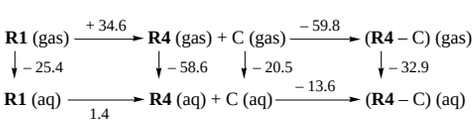
[a] With respect to **R4** and creatinine (amine).

the structure in which proton transfer has occurred is still preferred (by 7 kcal mol^{-1}).

Turning now to the predicted structure of the guest–host complex (Table 2), there are major hydrogen bonding interactions involving the amine hydrogens (H^9, H^{10}) and the hydrogen (H^{11}) bound to nitrogen atom N^{12} of the zwitterionic form of the receptor (**R4**). The two amine hydrogens (H^9, H^{10}) have primary hydrogen bonds with N^{13} and O^{14} of the receptor, the latter being particularly short (*ca.* 1.6 Å). In addition there are secondary hydrogen bonds with both H^9 and H^{10} interacting with N^{15} of the receptor. In both of the guest–host structures studied, there are primary hydrogen bonding interactions involving hydrogen, H^{11}, and either N^{12} of the host (in the minimum energy structure) or N^3 of creatinine, in the higher energy structure, corresponding to the crystal structure. In the latter, this distance is particularly short (1.6 Å), suggesting that this proton (H^{11}) may be somewhat mobile. The competing nature of these various intermolecular hydrogen bonding interactions is evident in our two structures. Thus, for example, for the fully optimised structure, corresponding to protonation of the creatinine guest molecule, the N^3–N^{12} intermolecular distance is 2.85 Å, whilst in the structure in which the host is protonated, this value is 2.57 Å. In the former complex, the intermolecular distances involving the amine hydrogens (H^9, H^{10}) are correspondingly shorter than in the latter structure. All the predicted intermolecular distances are in line with the corresponding experimental values (Table 2).

The intermolecular hydrogen bonding interactions lead to important polarisation of the guest molecule, seen by a comparison of the optimised structures of the amine and imine tautomers of creatinine with the structure of creatinine in the host complex (Table 2). High level *ab initio* calculations of the structure and energetics of the two tautomers of creatinine in the gas phase show that the imine form is preferred (by 2 kcal mol^{-1}), but that in polar media, such as water, the amine form is dominant.[10] In both of the complexes studied, the structure of creatinine is seen to be intermediate between that of the free amine and imine tautomers. This reflects the intermolecular hydrogen bonding interactions which will aid protonation of N^3 and deprotonation of N^6 of creatinine. That the structure of the guest molecule is between that of the two possible tautomers is well illustrated by the C^2–N^6 and C^2–N^3 bond lengths. In the free amine tautomer C^2–N^6 is longer than C^2–N^3 as expected, whilst in the imine form this order is reversed. However, in both structures of the complex, C^2–N^3 is longer than C^2–N^6 in agreement with the experimental values, showing the imine character of the complexed guest molecule.

The effect of solvation on the binding energetics of creatinine to the receptor is summarised in Scheme 1. The values of the



Scheme 1 Energetics (E/kcal mol^{-1}) of binding of creatinine (C) to receptor structure **R4** in the gas and aqueous phase

overall binding energy with respect to the receptor structure **R1** are favourable both in the gas phase (25.2 kcal mol^{-1}) and in

water (12.2 kcal mol^{-1}). A reduction of the binding energy in the aqueous phase occurs in spite of the considerable stabilisation in water of the receptor form **R4** actually involved in the binding. This is due to the lower solvation energy of the complex compared with that of the guest plus host. The inclusion of basis set superposition effects, 3.0 and 3.3 kcal mol^{-1}, for creatinine and receptor (**R4**), respectively, reduces the binding energy to 18.9 kcal mol^{-1} in the gas phase and 5.9 kcal mol^{-1} in water.

Discussion

The calculations we have carried out have identified important structural and energetic features of the interaction between creatinine, and an artificial receptor. In the gas phase the favourable intermolecular interactions in the guest–host complex stabilise a higher energy zwitterionic form (**R4**) of the receptor. In solution all of the polar zwitterionic forms of the receptor are preferentially stabilised by solvation and it is not clear which form of it is favoured in an aqueous environment. This agrees with the colour responses observed for the receptor in different solvents.[3] The neutral form **R1** predominates in the light yellow dichloromethane ($\varepsilon = 9.1$) solution, whereas the reddish colour of methanol ($\varepsilon = 32.6$) solutions indicates the presence of a dipolar tautomer. As is usual in guest–host interactions, the effect of a polar environment is to reduce the effective binding energy. Our calculations predict that the complex is still bound in water, by *ca.* 6 kcal mol^{-1}. This is in line with the measured dissociation constant of the complex being 0.5 μM in water-saturated chloroform giving a free energy of binding of less than 10 kcal mol^{-1}.

The predicted structure of the guest–host complex shows large perturbations of the guest molecule, also indicated from X-ray crystallographic studies. In particular the formally single C^2–$N(H_2)$ bond is shorter than the ring C^2–N bond having formally a large degree of double bond character. Our gas phase calculations of the complex predict proton transfer from the nitrogen atom of the zwitterionic host molecule to the creatinine nitrogen atom. This is not observed in the solid state crystal structure. However, solvation calculations show that a polar environment favours the complex having the receptor protonated rather than the guest molecule. Our calculated structure having the creatinine guest molecule protonated is for an isolated guest–host complex. The solid state polar environment may be responsible for the observed structure having the receptor protonated and that in the less polar aqueous environment proton transfer does indeed occur.

Acknowledgements

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