

Dimerisation of urea in water solution: a quantum mechanical investigation

Fabio Ramondo,^{*a} Luigi Bencivenni,^b Ruggero Caminiti,^b Andrea Pieretti^c and Lorenzo Gontrani^c

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The effect of water solvation on the structure and stability of cyclic dimers of urea has been investigated with the aid of density functional theory at the B3LYP/6-311++G** level. Several hydration models have been discussed. Specific solvent effects have been simulated through single and multiple water–urea interactions involving all the hydration sites of urea. The bulk solvent effects have been estimated through polarised continuum models. Under all the hydration patterns cyclic dimers continue to be stable structures although the solvent weakens the urea–urea interaction. Single and multiple specific urea–water interactions are competitive with urea dimerisation. The anticooperative nature of the two intermolecular interactions is largely due to the changes on σ - and π -electron density of urea caused by hydrogen bonding with water. The stability of the dimer is however, lost within a few ps when the hydrated dimer is described by a quantum mechanical molecular dynamics approach (ADMP). The cyclic dimer evolves towards structures where urea molecules are linked not more directly but through water molecules which have a bridge function.

Introduction

Urea is one of the simplest molecules of biological interest. Whereas structural features of the molecule in the gas phase¹ as well as solid state² are largely known, the structure of aqueous urea solutions continues to attract research interest. The motives for such attention are due to some intriguing properties of concentrated aqueous urea solutions. Urea increases the solubility of many hydrocarbon gases in water,³ affects the stability of proteins^{4,5} and inhibits micelle formation.⁶

Understanding such important effects at the molecular level has led to controversial microscopic descriptions of aqueous solutions. Two models have been suggested. The first mechanism⁷ modelled water as a two phase system: a structured, ice-like domain with lower density and a less organised and more dense domain. According to this model, the presence of urea shifts the equilibrium between the two phases in favour of the structureless domain since hydrogen bonds between water molecules are destroyed by the introduction of urea molecules. A different approach^{8–10} suggested that the molecular aggregation between urea plays an essential role in determining properties of urea solutions also at low concentration.

Many experiments have been carried out to investigate the validity of these models. NMR,¹¹ Raman¹² and infrared¹³

studies gave indirect evidence about the first model. The formation of urea dimers and higher aggregates was instead derived from osmotic pressure measurements¹⁴ and infrared spectra of urea–water solutions.¹⁵ Diffraction studies of urea in water can instead determine more directly the structure of urea–water solutions. Some evidence of urea–urea pairing in solutions emerged at high concentrations from an earlier X-ray study¹⁶; however neutron diffraction experiments¹⁷ concluded that urea does not cause significant perturbation of the water structure. A more recent neutron diffraction investigation¹⁸ of urea–water solutions at a molar ratio of 1 : 4 found that urea mixes with water molecules simply replacing water on a more or less random basis consistently with the hydrogen bonding sites. The high number of hydration sites of urea allows the formation of urea chains or clusters with the solution. From neutron diffraction observations it was also concluded that there is a negligible tendency of urea to segregate from water.

Self association of urea in water has also been the subject of a wide number of theoretical investigations. Several molecular dynamics simulations were carried out to clarify the stability of urea dimers in solution, however no definitive conclusions were obtained. Some simulations indicated that dimers are not stable in water,^{19,20} some studies did not find substantial aggregation^{21,22} whereas other molecular dynamics studies^{23,24} evidenced the formation of urea dimers of cyclic structure by increasing concentration. Other MD simulations indicated that no long-lived cyclic dimers were observed at any concentration.²⁵ Lastly, a theoretical study²⁶ proposed that the tendency to aggregation of urea is determined only by its high number of hydrogen bonding sites. Therefore the molecular dynamic simulations as well as the experiments did not end the

^a Dipartimento di Chimica, Ingegneria Chimica e Materiali, Università dell'Aquila, I-67100 L'Aquila, Italy. E-mail: framondo@univaq.it; Fax: +39 0862 433753

^b Dipartimento di Chimica, Università degli Studi di Roma "La Sapienza", P. le A. Moro 5, 00185 Roma, Italy

^c CASPUR, Consorzio interuniversitario per le Applicazioni di Supercalcolo per Università e Ricerca, Via dei Tizii, 6/b, 00185 Roma, Italy

controversy. The tendency to form dimers in solution, although quite weak, seems to depend critically on the potential functions used in the simulations.²⁷

Most recently the structure of the urea–water system has been investigated through molecular dynamics simulations and analysis of Raman spectral band shapes.^{28,29} It was concluded that urea molecules are solvated by water through several hydrogen bonding sites and the radial distribution of urea molecules in the solution is almost uniform. The high density of hydrogen bonds between urea and water also emerged from a previous theoretical study (reference interaction site model-self-consistent-field).³⁰ This model predicts that urea adopts a nitrogen pyramidal structure in water, as well as it occurs in the gas phase, and is surrounded on average by more than seven water molecules.

On the basis of the whole theoretical work published to date, it emerges that a correct parametrisation for urea is fundamental but probably not sufficient for an accurate evaluation of the urea dimer stability in water. Quantum mechanical methods are necessary to give a more complete and appropriate description of all the intermolecular interactions occurring in urea–water solutions. The main aim of the present work is to investigate by means of quantum mechanical calculations, density functional theory (DFT), the structural features of molecular aggregates both *in vacuo* and in solution. A previous DFT theoretical study³¹ has already investigated the stability of the urea dimer by increasing the number of water molecules. The present study now focuses attention on how the stability of the cyclic dimer of urea is affected by different solvation patterns. The hydration models proposed here are chosen with the careful aim to study systematically and separately the role of each specific urea–water interaction on the structure and stability of urea dimers. The solvent effect in our models is simulated both through specific interactions of water molecules and through bulk effects described by polarisable continuum methods. However similar models are still static descriptions of the aggregates eventually formed in solutions. It is worth investigating again the lifetime of the molecular complexes proposed by dynamic models at the quantum mechanical level. Therefore, some selected aggregates have been analysed using a quantum mechanical molecular dynamics approach called Atom-centered Density Matrix Propagation (ADMP).^{32–34} The evolution of the molecular aggregates over time gives useful information on the tendency of urea in water solution to form dimers with well-defined structures, such as double-hydrogen bonded dimers, or flexible aggregates.

Computational details

Most calculations were run using the GAUSSIAN 03, revision C.01 package.³⁵

Geometries and vibrational frequencies of the monomer and dimer in the gas-phase were obtained by an analytical gradient based technique using the density functional theory, employing the B3LYP (Becke's three parameter exchange³⁶ and Lee, Yang, Parr correlation³⁷) potentials, combined with the 6-311 + G** basis set. Geometry optimisations were carried

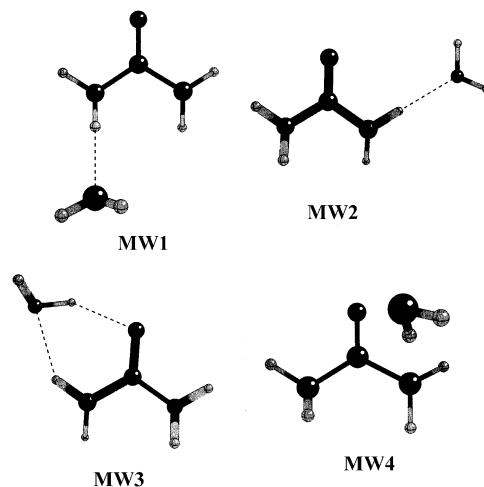


Fig. 1 Urea–water complexes.

out without any symmetry constraints however the final structure of the dimer showed C_2 symmetry.

To investigate the effects of specific solute–solvent interactions, we have selected some complexes formed by interaction of urea with a small number of water molecules. Three complexes were firstly considered to describe hydration separately of each NH (MW1 and MW2) and C=O (MW3) site of urea (see Fig. 1). A third interaction has also been taken into account adding one water molecule pointing the OH bond towards the nitrogen lone pair (MW4) (Fig. 1). The hydration sites considered for the monomer were also studied for the cyclic dimer by connecting one water molecule for each monomer unit (DW1, DW2, DW2', DW3 and DW4), as shown in Fig. 2. Then, multiple hydrations were investigated both for the monomer and dimer. The NH groups of urea monomer (MW5) and dimer (DW5) were solvated simultaneously by three waters (Fig. 3). MW5 and DW5 were finally further hydrated by allowing them to interact with one water molecule through the C=O group (MW6 and DW6) and with two additional water molecules pointing towards the nitrogen lone-pairs (MW7 and DW7) (see Fig. 3). All the complexes were investigated at the B3LYP/6-311 + G** level by geometry optimisations and were characterised by frequency calculations. The urea dimer was optimised without any symmetry constraints whereas the water molecules were oriented under a local C_2 symmetry model. Under the above constraints, the dimer urea showed slight deviations from C_2 symmetry localised only in the intermolecular geometrical parameters.

The electronic structure of the previous complexes was then discussed by analysing the topological properties of the electron density distribution $\rho(r)$ as developed by Bader³⁸ using the subroutine implemented in GAUSSIAN 03 at the B3LYP/6-311 + G** level.

The stability of all the dimers proposed here was evaluated from the values of energy interaction calculated as the difference between the energy of the dimer and that of the monomer both considered at the same hydration level. Basis set superposition error (BSSE) corrections were performed using the counterpoise method³⁹ and all the interaction energies were

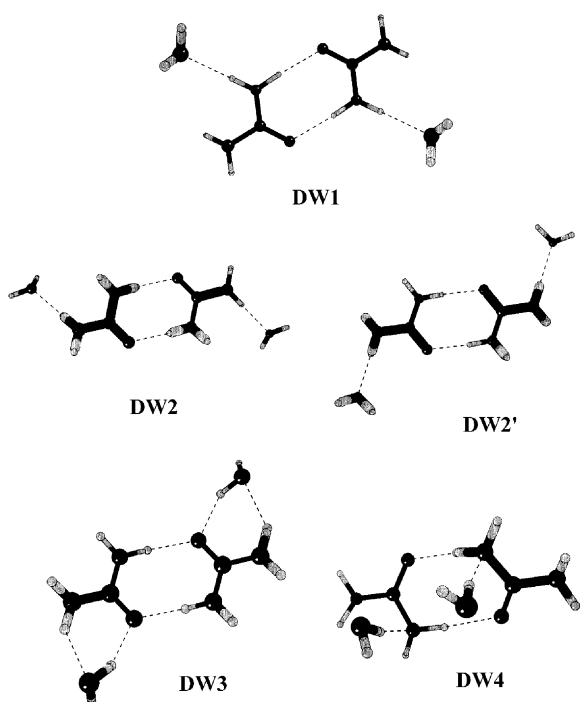


Fig. 2 Structures of the urea cyclic dimer interacting with water through the amino groups (DW1, DW2 and DW2'), the carbonyl group (DW3) and the nitrogen atom (DW4).

calculated in the full basis set of the corresponding cluster. Hydration energies were similarly evaluated as the difference between the energies of the aquo-complexes and those of the isolated molecules.

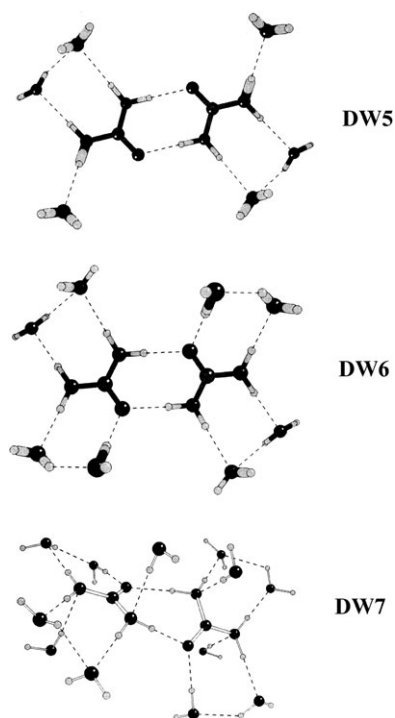


Fig. 3 Structures of multiple hydrations of the urea cyclic dimer.

According to the energy decomposition analysis (EDA) of Morokuma^{40–42} the binding energy of the interacting systems, urea–urea and urea–water, can be decomposed into the following components: the electrostatic interaction term (ES), reflecting the interaction between the undistorted electron distribution of the two systems; the polarisation interaction term (PL), accounting for the electron distribution in the two interacting systems; the charge transfer of electron delocalisation interaction term (CT) and a coupling term (MIX), accounting for higher order interactions. These energy decomposition terms were evaluated on the binding energy of urea–urea and urea–water systems by the EDA procedure implemented in the GAMESS package⁴³ at the HF/6-31G**//B3LYP/6-311++G** level.

The bulk water solvent effects on the molecular properties of urea were taken into account by means of the polarisable continuum model (PCM)^{44,45} initially on the monomer and dimer. Their geometries were obtained using the same level, B3LYP/6-311++G**, applied for the molecules in the gas-phase. The PCM model was then applied to the monohydrated complexes to further estimate the solvation effects on the stability of the dimer. Free energies of monomer and dimer in water were obtained from PCM calculations at the optimised geometries for DW1, DW2, DW2' and DW3. Within the PCM framework,⁴⁴ the free energy of a system in solution, G , may be decomposed in the following contributions: an electrostatic contribution, G_{el} , a non-electrostatic contribution, G_{nonel} , comprising a cavitation term, a dispersion free energy term due to dispersion interactions between solute and solvent and a repulsion term, and a thermal contribution, G_{therm} . The first two contributions are directly calculated with the PCM procedure, G_{PCM} , whereas the third contribution can be evaluated applying the standard methods of statistical mechanics. In our case the free energy dimerisation of urea, ΔG , is therefore evaluated by summing ΔG_{PCM} , the difference between G_{PCM} of the dimer and those of the monomer, and ΔG_{therm} , the difference between G_{therm} of the dimer and G_{therm} of the monomers calculated by considering the motions of the gas phase molecular species in the classical approximations of the harmonic vibrations and free rigid rotations. As a matter of fact, six vibrational modes of the dimer are substantially intermolecular vibrations which are not adequately described by the harmonic approximation. However the value of ΔG_{therm} has shown little sensitivity to the frequencies of the intermolecular modes. Scale factors ranging from 0.7 to 0.9 were arbitrarily applied to the frequencies of these intermolecular modes and the consequent decreases of ΔG were calculated within 4 kJ mol⁻¹. The BSSE is another cause which could affect the values of the intermolecular frequencies but this effect is indeed negligible on the evaluation of ΔG .⁴⁶ The second source of error in the classic description of the molecular motion is found in the fact that the translational and rotational contributions are calculated by assuming free motions of the solute as in the gas phase. As a matter of fact, the solvent is made up of individual molecules characterised by their internal and external motions. When the translating, rotating and vibrating solvent molecules collide with the solute, they can influence the motion of the solute exerting a sort of friction upon it. The resulting solute–solvent

interaction can be thought of as a “medium hindrance” which can be described using the Pitzer model.⁴⁷ The effect is similar to the friction expected for the internal rotations of molecules. In that case the increase in free energy was calculated to be about 10 kJ mol⁻¹.⁴⁸ In our case, the net result on ΔG can be estimated to be about -10 kJ mol⁻¹. In conclusion the ΔG value of dimerisation obtained from PCM calculations by including thermal contributions derived from mechanical statistics can be corrected with estimated values of about -14 kJ mol⁻¹.

The dynamics of the cyclic dimer were then simulated using the molecular dynamics approach Atom-centered Density Matrix Propagation (ADMP) as implemented in the Gaussian packages. Three sets of ADMP simulations were performed. In the first calculation the dynamics of the dimer and monomer *in vacuo* were investigated using the B3LYP/6-31G* method; the system was simulated under constant temperature conditions (300 K) for a trajectory of 16 ps duration with a time step of 0.25 fs. A second simulation was performed in the same conditions for the dimer and monomer applying the PCM model for a trajectory of 9 ps. A third simulation was then carried out on the hydrated dimer. The starting structure in these ADMP simulations was the complex at higher hydration degree (DW7) and simulations were performed at 300 K at time steps of 0.25 fs for a trajectory of 9 ps.

Calculations were run on a cluster of six HP (ES40) servers, each one equipped with four ev6 CPU at 500 MHz and 2 GB of RAM, and on a cluster of eight HP (ES45) servers, each one equipped with four ev68 CPU at 1.25 GHz and 8 GB of RAM.

Results and discussion

Dimer *in vacuo*

Microwave spectroscopy¹ and theoretical calculations⁴⁹ indicate undoubtedly that urea has a non planar structure in the gas phase. High level calculations⁴⁹ lead us to conclude that deviations from planarity can be obtained through two stable structures (C_s and C_2 symmetry) which can easily convert to each other through a non-planar C_1 symmetry transition state. More recent calculations,^{50–52} revealed that urea also possesses a non-planar structure when it self associates to form oligomers of different structures and size (from dimers to eptamers). In particular two dimers (C_1 and C_2 symmetry) formed through two equivalent C=O...HN hydrogen bonds were found to be the most stable dimeric structures. Both can be obtained from aggregation of two C_2 symmetry monomers; the dimers produced can differ from each other in the relative orientation of the four non planar NH₂ groups. Since these dimers show very similar stability,⁵⁰ in the present study we have considered only the cyclic structure of the C_2 symmetry. In addition, since B3LYP/6-311++G** and higher *ab initio*⁵¹ levels reproduce consistently the structural properties of urea and its aggregates, we decided to study the dimerisation process at the B3LYP/6-311++G** level.

The molecular properties calculated for the monomer and C_2 symmetry dimer are compared in Table 1. The energy interaction values indicate firstly that dimerisation in the gas phase is a process energetically favourable (-54 kJ mol⁻¹).

Table 1 Selected geometrical parameters, dimerisation energy, ΔE (kJ mol⁻¹) and dimerisation free energy, ΔG_{PCM} (kJ mol⁻¹) and ΔG (kJ mol⁻¹), of the monomer (M) and cyclic dimer (D) of urea obtained from B3LYP/6-31++G** calculations

| | <i>In vacuo</i> | | PCM | |
|--------------------------------------------------|-----------------|-------|-------|-------|
| | M | D | M | D |
| $r(\text{C}=\text{O})/\text{\AA}$ | 1.217 | 1.233 | 1.240 | 1.248 |
| $r(\text{C}-\text{N})^a/\text{\AA}$ | 1.386 | 1.361 | 1.367 | 1.356 |
| $r(\text{C}-\text{N})/\text{\AA}$ | 1.386 | 1.385 | 1.367 | 1.366 |
| $\angle(\text{N}-\text{C}-\text{N})^\circ$ | 114.2 | 115.9 | 115.9 | 116.8 |
| $\tau(\text{C}-\text{NH}_2)^{ab}/^\circ$ | 140.0 | 152.7 | 150.9 | 162.4 |
| $\tau(\text{C}-\text{NH}_2)^b/^\circ$ | 140.0 | 141.0 | 150.9 | 150.8 |
| $r(\text{NH}\cdots\text{O}=\text{C})/\text{\AA}$ | | 1.869 | | 1.919 |
| ΔE | | -53.9 | | |
| ΔG_{PCM} | | | | -11.7 |
| ΔG | | | | 20 |

^a Hydrogen bonded amino group. ^b Angle between the NH₂ plane and the CN bond.

Secondly, it induces large structural modifications mainly localised on the -N(H)-C(=O)- moiety involved in the hydrogen bonding interaction. The lengthening of the C=O and NH bonds and the simultaneous shortening of the CN bond are structural modifications well known for the amide group.^{53,54} They are largely caused from a redistribution of the π -character between C=O and CN bonds produced by hydrogen bonding. This hypothesis is substantially confirmed by analysing the topological properties of the electron density, $\rho(r)$. The values of ρ calculated in the bond critical point (BCP), ρ_c , show that electron density decreases in the C=O bond (from 0.413 to 0.398 e au⁻³) and it increases in the CN bond (from 0.310 to 0.327 e au⁻³) when the dimer is formed. The π -electron redistribution between C=O and CN is fully consistent with the variations of the ellipticity of these bonds. Correspondingly, the NCN bond angle increases (from 114.2° to 115.9°) and deviations from planarity are reduced for dimerisation; however the dimer is still non-planar.

The stability of the cyclic dimer may be alternatively tested from our molecular dynamics simulations. Starting from the equilibrium geometry, we performed a 16 ps run to investigate if the cyclic structure keeps its stability or has a tendency to change its structure. The O...H hydrogen bond distances were firstly monitored during the dynamics process. They are reported in Fig. 4a and they reveal that the cyclic dimer remains stable *in vacuo* within at least the simulation time. The mean values of the O...H distances are 2.020 Å and 2.030 Å within a standard deviation of 0.20 Å.

Dimerisation energy was then calculated again on the basis of dynamical aspects as the difference between the average energies of the dimer and monomer both obtained from ADMP simulations. The stability of the cyclic dimer is only marginally affected by dynamics. This finding provides unequivocal evidence that indeed such a structure exists at $T = 300$ K. Table 2 also reports the average intramolecular geometries of monomer and dimer. The structural changes caused by dimerisation are only slightly different from those obtained with the static description. In addition it is interesting to note that the average structure of urea continues to be non-planar, as witnessed by the values of the angle (τ) between the NH₂

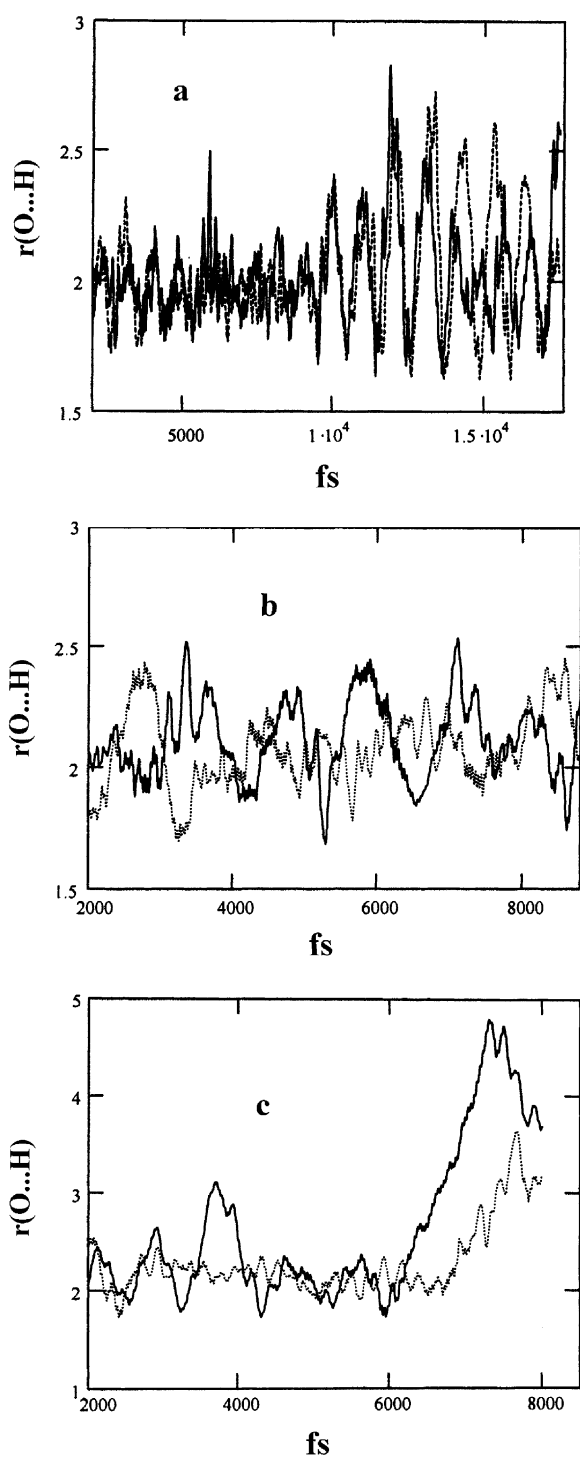


Fig. 4 Time-evolution of the O...H urea-urea distances (Å) of dimer *in vacuo* (a), in continuum water solvent, PCM, (b) and in DW7 (c) obtained from B3LYP/6-31G* simulations.

plane and CN bond which moves from 143° for the monomer to 151° for the dimer.

Solvated molecules

A. Continuum model. After a complete characterisation of the dimerisation process *in vacuo*, we now consider the self

aggregation of urea in water solution firstly by a simple approach which describes the solvent as a polarisable continuum medium (PCM). In order to carry out a quick comparison with the results *in vacuo*, we have also reported in Table 1 some important structural properties obtained from the PCM method. Some salient results can be summarised with the following points: (i) solvent causes structural modifications similar to that expected for dimerisation *in vacuo* and; (ii) dimerisation in water produces a further lengthening of the C=O bond and a shortening of the CN bond although the extent of the changes is less pronounced than *in vacuo*. Inspection of the stability of the dimer reveals that it decreases from -54 kJ mol^{-1} *in vacuo* to -12 kJ mol^{-1} in water if we consider the value of ΔG_{PCM} . If thermal corrections are included, ΔG_{therm} , the dimerisation free energy ΔG increases towards positive values (20 kJ mol^{-1}). It is interesting to note that the ΔG value calculated for the gas phase is still negative (-5 kJ mol^{-1}).

On the basis of these considerations it emerges that the water solvent hinders the cyclic dimerisation of urea, in agreement with that found for formamide in water.⁵⁵ Since the entropic term, which is the disfavouring factor to dimerisation, is not very different from the gas phase to the solution, we can conclude that the solvent produces sharp changes in the enthalpic factor. In particular a cyclic dimerisation, the most probable process in the gas phase, tends to be hindered in water because it leads to the formation of apolar aggregates.

The cyclic dimer optimised by considering a simple static description was reconsidered by including dynamics effects. An analysis of our ADMP calculations indicates that urea units continue to be linked to each other through a couple of O...H hydrogen bonds. However our simulations reveal the presence of a small asymmetry in the two intermolecular distances, (2.040 Å and 2.114 Å). In addition the value of ΔG_{PCM} seems to be affected from dynamics. ΔG_{PCM} relative to the static structure (-19 kJ mol^{-1}) has in fact a higher value than that of the average ΔG_{PCM} (-30 kJ mol^{-1}) obtained from dynamic simulations (Table 2). Notwithstanding the PCM model describes the solvent by considering only the simple dielectric effect, it suggests that the double hydrogen bonded dimers of urea are deeply destabilised in water. The results of our dynamic simulations therefore suggest that cyclic urea dimers (apolar aggregates) seems to evolve towards asymmetric (polar) aggregates.

B. Specific solute-solvent interactions. Specific interactions between urea and water molecules were then introduced to more accurately simulate the role of the solvent. Among the possible hydration sites, the amino groups as well as the carbonyl group can be easily involved in specific urea-water interactions through $\text{NH}\cdots\text{OH}_2$ and $\text{C}=\text{O}\cdots\text{HOH}$ hydrogen bonds, respectively. We are now interested in examining how the interacting water molecules really affect the stability of the cyclic dimer already studied *in vacuo*. We consider here the complexes reproduced in Fig. 2 and 3 starting our discussion from those in which each urea of dimer interacts with a single water molecule. The first one (DW1), where hydration occurs at the same amino group involved in the dimer formation, allows us to investigate how solvation can directly perturb the

Table 2 Selected average geometrical parameters, average dimerisation energy, ΔE (kJ mol^{-1}), and average dimerisation free energy, ΔG_{PCM} (kJ mol^{-1}) of the monomer (M) and cyclic dimer (D) of urea obtained from ADMP B3LYP/6-31G* simulations

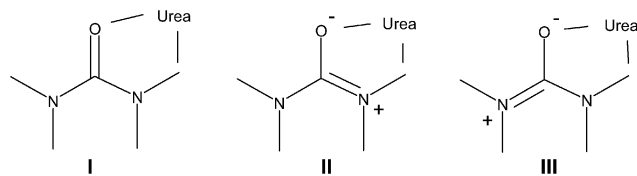
| | <i>In vacuo</i> | | PCM | |
|---------------------------------------------------|-------------------|-------------------|-------------------|-------------------|
| | M | D | M | D |
| $r(\text{C}=\text{O})/\text{\AA}$ | 1.222 ± 0.020 | 1.236 ± 0.017 | 1.240 ± 0.024 | 1.251 ± 0.030 |
| $r(\text{C}-\text{N})^a/\text{\AA}$ | 1.396 ± 0.034 | 1.373 ± 0.030 | 1.382 ± 0.031 | 1.374 ± 0.031 |
| $r(\text{C}-\text{N})/\text{\AA}$ | 1.396 ± 0.034 | 1.394 ± 0.031 | 1.383 ± 0.032 | 1.380 ± 0.031 |
| $\tau(\text{C}-\text{NH}_2)^{ab}/^\circ$ | 143 ± 18 | 151 ± 17 | 146 ± 17 | 149 ± 16 |
| $r(\text{NH}\cdots\text{O}=\text{C})/\text{\AA}$ | | 2.020 ± 0.20 | | 2.040 ± 0.14 |
| $r(\text{NH}\cdots\text{O}=\text{C})(\text{\AA})$ | | 2.030 ± 0.20 | | 2.114 ± 0.18 |
| ΔE | | -52^c | | |
| ΔG_{PCM} | | | | -30^d |

^a Hydrogen bonded amino group. ^b Angle between the CN bond and the NH_2 plane. ^c B3LYP/6-31G* value of the equilibrium structure is -51 kJ mol^{-1} . ^d B3LYP/6-31G* value of the equilibrium structure is -19 kJ mol^{-1} . The BSSE corrections were assumed equal to those calculated for the dimer at the equilibrium structure.

urea–urea bond. The second and third complexes (DW2 and DW2') instead give information on how hydration of the second amino group may affect the dimerisation process. Lastly, the fourth complex (DW3) takes into account the role of the solvation of the carbonyl group. The same patterns of hydration were also considered for the monomer by studying the $\text{NH}\cdots\text{OH}_2$ (MW1 and MW2) and $\text{C}=\text{O}\cdots\text{HOH}$ (MW3) interactions. Such monohydrated urea complexes were then hydrated further to investigate the role of multiple hydration. In particular the NH bonds (MW5 and DW5) and the $\text{C}=\text{O}$ bond (MW6 and DW6) were hydrated simultaneously.

Significant structural parameters of all the complexes are reported in Table 3. Comparing this data with that of the dimer *in vacuo* some interesting points quickly emerge. Firstly, water induces a further modulation of π -electron density in the urea molecule which follows different pathways in the various hydration patterns. The second salient result is that all the hydration trends considered here do not reinforce the urea–urea interaction but cause a small destabilisation of the dimer. All these complexes show in fact smaller binding energies and longer hydrogen bond lengths with respect to the values found for the dimer *in vacuo*. In addition to the destabilising effect due to solvation an increase is found with the degree of hydration. The third interesting aspect emerges by observing the intermolecular distances $\text{NH}\cdots\text{OH}_2$ involving water in the hydrated species (monomer and dimer). Urea dimerisation produces a lengthening of the urea–water distances accompanied by a weakening of the urea–water interaction. The energy of these interactions is in fact smaller for dimers than for monomers for all the complexes described above. The effect is similar to the weakening of the urea–urea interaction observed when the dimer is hydrated. The present results therefore reveal an anticooperative nature of the two intermolecular interactions.

The structural deformations produced by the different hydration patterns discussed above can be rationalised with the following arguments starting with a discussion of the DW2 and DW2' complexes. Urea can be considered as a special case of a n - π conjugated heteroallylic system. The extension of conjugation leads to a Y-delocalised hetero π -system, the



Scheme 1 Canonical forms of urea.

$\text{N}-\text{C}(\text{O})-\text{N}$ skeleton, described by the following mesomeric forms Scheme 1.

Whereas the changes of the structural and electronic properties caused by dimerisation *in vacuo* are largely consistent, as discussed below, with an important contribution of the polar canonical form II, the hydration of the second NH_2 group (DW2 and DW2') increases the role of the form III and decreases that of the form II. As well substantiated by the AIM results shown in Table 3, this hydration pattern therefore polarises further the $\text{C}=\text{O}$ bond and moves π -electron density from one CN bond (structure II) to the other one (structure III). As a consequence, the polar form II which strengthens hydrogen bonding in the urea dimer, decreases its role when the second NH_2 group is hydrated with a consequent destabilisation of the dimer. The analysis of Morokuma decomposition terms confirms this point (Table 4). Concerning the urea–urea interactions, the highest contributions to the binding energy obviously come from the electrostatic interaction and exchange repulsion terms for all the dimers considered. The EDA procedure provides evidence that the small destabilisation of DW2 and DW2' is due to the decrease of the magnitude of the electrostatic, polarisation and charge-transfer terms.⁵⁶ These results substantiate the fact that the hydration of the second amino group produces a modulation of the electron distribution of the urea dimer which decreases the electrostatic interactions between the couple of urea molecules. Therefore it is reasonable to conclude that the lesser role of the polar canonical form II in this hydration is the main cause of destabilisation of the urea dimer. As far as the urea–water interaction is concerned, the single contributions of EDA undergo similar but smaller changes when urea self

Table 3 Selected geometrical parameters, results of the topological analysis, dimerisation energy, ΔE_{dim}^a (kJ mol⁻¹), dimerisation free energy, $\Delta G_{\text{dim}}(\text{PCM})^b$ (kJ mol⁻¹) and hydration energy, ΔE_{hydr}^c (kJ mol⁻¹), obtained from B3LYP/6-31 + G** calculations

| | D | DW1 | DW2 | DW2' | DW3 | DW4 | DW5 | DW6 | DW7 |
|----------------------------------------------------|--------|--------------------|--------|--------|--------|------------------|--------------------|--------------------|--------------------|
| $r(\text{C}=\text{O})/\text{\AA}$ | 1.233 | 1.234 | 1.236 | 1.235 | 1.249 | 1.229 | 1.242 | 1.257 | 1.250 |
| $r(\text{C}-\text{N})^d/\text{\AA}$ | 1.361 | 1.356 | 1.364 | 1.366 | 1.355 | 1.379 | 1.365 | 1.356 | 1.371 |
| $r(\text{C}-\text{N})/\text{\AA}$ | 1.385 | 1.393 | 1.380 | 1.379 | 1.363 | 1.377 | 1.366 | 1.355 | 1.357 |
| ρ_{b}^e | | | | | | | | | |
| CN ^d | 0.327 | 0.331 | 0.324 | 0.324 | 0.329 | 0.318 | 0.323 | 0.328 | 0.322 |
| CN | 0.311 | 0.307 | 0.315 | 0.316 | 0.323 | 0.316 | 0.319 | 0.329 | 0.328 |
| CO | 0.398 | 0.397 | 0.395 | 0.396 | 0.385 | 0.401 | 0.391 | 0.378 | 0.384 |
| ε^f | | | | | | | | | |
| CN ^d | 0.162 | 0.168 | 0.155 | 0.154 | 0.170 | 0.142 | 0.158 | 0.162 | 0.148 |
| CN | 0.132 | 0.122 | 0.136 | 0.138 | 0.159 | 0.140 | 0.154 | 0.166 | 0.166 |
| CO | 0.080 | 0.077 | 0.077 | 0.076 | 0.071 | 0.083 | 0.077 | 0.064 | 0.074 |
| $\nabla^2 \rho_{\text{b}}$ | | | | | | | | | |
| NH ^{dg} | -1.687 | -1.677 | -1.679 | -1.680 | -1.696 | -1.667 | -1.668 | -1.676 | -1.655 |
| $r(\text{NH}\cdots\text{O}=\text{C}) (\text{\AA})$ | 1.869 | 1.902 | 1.873 | 1.879 | 1.870 | 1.877 | 1.899 | 1.903 | 1.916 |
| | | 1.903 | 1.877 | 1.878 | 1.868 | 1.877 | 1.906 | 1.904 | 1.913 |
| ΔE_{dim} | -53 | -47 | -50 | -48 | -47 | -56 ^h | -38 | -36 | -46 |
| $\Delta G_{\text{dim}}(\text{PCM})^i$ | -11.7 | -10.0 | -11.6 | -11.1 | -11.9 | -8.5 | | | |
| $r(\text{NH}\cdots\text{OH}_2)/\text{\AA}$ | | 2.074 ^d | 2.060 | 2.014 | 2.075 | | 2.103 | 2.010 | 1.948 |
| | | | | | | | 2.103 | 2.010 | 1.948 |
| | | | | | | | 2.235 ^d | 2.152 ^d | 2.089 ^d |
| $r(\text{OH}\cdots\text{NH}_2)/\text{\AA}$ | | | | | | 2.209 | | | 2.261 |
| ΔE_{hydr} | | -32 | -30 | -35 | -70 | -25 ^j | -106 | -236 | -296 |
| F^k | | 1.7 | 1.8 | 1.9 | 1.9 | 1.9 | 1.7 | 1.9 | 1.9 |

^a $\Delta E_{\text{dim}} = E$ dimer (*in vacuo*/hydrated) - 2 E monomer (*in vacuo*/hydrated). ^b $\Delta G_{\text{dim}}(\text{PCM}) = G$ dimer (PCM) (*in vacuo*/hydrated) - 2 G (PCM) monomer (*in vacuo*/hydrated). ^c $\Delta E_{\text{hydr}} = E(\text{monomer/dimer})(\text{H}_2\text{O})_n - E(\text{monomer/dimer}) - n E(\text{H}_2\text{O})$. ^d CN and NH bonds of the NH₂ group involved in urea-urea interaction. ^e Electron density (e au⁻³) at the bond critical point. ^f Ellipticity at the bond critical point. ^g The value for the monomer is -1.641. ^h Dimerisation energy in DW4 is the result of urea-urea (-49 kJ mol⁻¹) and water-water (-7 kJ mol⁻¹) interactions. ⁱ ΔG_{therm} calculated for D is 32 kJ mol⁻¹. ^j Hydration energy in DW4 is the result of urea-water (-18 kJ mol⁻¹) and water-water (-7 kJ mol⁻¹) interactions. ^k $F = \Delta E_{\text{hydr}}(\text{dimer})/\Delta E_{\text{hydr}}(\text{monomer})$.

associates. As for the urea-urea interactions, the electrostatic contributions are the main cause of the fact that the NH \cdots OH₂ hydrogen bonding is weaker for the dimer than for monomer. Since such an interaction is favoured when the polar canonical form III increase its importance, we can conclude that the competition between the two polar forms II and III weakens both the C=O \cdots HN and NH \cdots OH₂ interactions.

An even more outstanding destabilisation was observed when hydration occurs directly at the NH₂ group involved in the urea-urea interaction (DW1). However in this case the solvent effect can be ascribed to the general tendency of the amino group to avoid forming two hydrogen bonds where NH₂ acts twice as the proton donor. There is an anticoooperative aspect similar to that observed for water⁵⁷ in so far as acting as a donor weakens the capability to act as another

Table 4 Morokuma energy decomposition terms for urea-urea and urea-water hydrogen bonding (kJ mol⁻¹) from HF/6-31G**//B3LYP/6-311 + + G** calculations: electrostatic interaction term (ES), exchange repulsion term (EX), polarisation interaction term (PL), charge transfer interaction term (CT), coupling term for higher order interactions (MIX) and total interaction energy (E_{total})

| | ES | EX | PL | CT | MIX | E_{tot} |
|-----------------------------|---------|-------|--------|--------|-------|---------------------|
| C=O \cdots HN | | | | | | |
| D | -94.64 | 72.22 | -14.31 | -21.76 | -4.22 | -53.4 ^a |
| DW1 | -85.02 | 66.15 | -13.10 | -20.13 | -4.69 | -47.1 ^a |
| DW2 | -91.29 | 71.63 | -14.02 | -21.71 | -4.73 | -50.2 ^a |
| DW4 | -103.93 | 72.51 | -15.10 | -24.81 | -4.06 | -57.6 ^b |
| NH \cdots OH ₂ | | | | | | |
| MW1 | -31.21 | 17.82 | -2.68 | -6.57 | -0.13 | -22.77 |
| DW1 | -28.62 | 16.86 | -2.26 | -6.57 | -0.21 | -20.80 |
| DW2 | -30.00 | 17.24 | -2.47 | -6.44 | -0.08 | -21.75 |
| N \cdots HOH | | | | | | |
| MW4 | -19.83 | 18.20 | -2.01 | -6.15 | 0.33 | -9.46 |
| DW4 | -21.63 | 17.36 | -1.92 | -6.36 | 0.21 | -12.34 ^c |

^a BSSE corrected values. ^b Dimerisation energy in DW4 is the result of urea-urea (-48 kJ mol⁻¹) and water-water (-9.7 kJ mol⁻¹) interactions. ^c Hydration energy in DW4 is the result of urea-water and water-water interactions.

donor. The topological data analysis therefore reveals two effects in DW1 hydration. On the one hand this hydration pattern enhances the role of the polar form II even more than that observed for the dimer *in vacuo*. On the other hand, AIM results suggest that the polarity of the NH bonds involved in the urea–urea interaction decreases when solvation occurs confirming the anticooperative effect. The bond critical point of such an NH bond is in fact less close to nitrogen when hydration is considered (DW1). Another sensitive probe to identify subtle spatial changes of charge concentrations is the Laplacian of $\rho(r)$. The NH covalent bonds have negative $\nabla^2\rho(r)$ values at the bond critical point since $\rho(r)$ is locally concentrated there. The fact that $\nabla^2\rho(r)$ moves from -1.687 (D) to -1.677 (DW1) reveals a small increase of charge concentration along the NH bond; it means that this bond is more polar *in vacuo* than in solvent. Therefore the DW1 solvation pattern produces two contrasting effects: a larger π -polarisation, which should strengthen urea–urea coupling, and a smaller σ -polarisation of the NH bond, which instead weakens the intermolecular hydrogen bonding. Once again the superposition of these effects leads to a net destabilisation of the dimer which according to the EDA results, may be mainly attributed to a decrease of the magnitude of the electrostatic, polarisation and charge-transfer terms of urea–urea interaction.

The third pattern of solvation (DW3) involves, as previously described, the formation of C=O \cdots HOH hydrogen bonding. Orientation of the water molecule allows however a simultaneous and weaker interaction with the second NH₂ group. This effective bridge hydration produces structural perturbations very similar to those already observed for DW2. The increased role of the canonical form III may thus be again invoked to explain the lesser stability of this hydrated dimer.

A more accurate description of specific solute–solvent interactions should lastly take into account that the structure of urea also continues to be non-planar in water.³⁰ A pyramidal nitrogen gives rise to electron density from its lone-pair which allows additional interactions with water. Each amino group can therefore not only donate two hydrogen bonds but simultaneously accept one from the water molecules. The N \cdots HOH interaction was thus discussed firstly for the monomer (MW4) and then for the dimer (DW4). Hydration energies as well as intermolecular bond distances (Table 3) indicate that water interacts quite weakly with nitrogen because of the smaller electrostatic interactions (Table 4). The different strength of hydrogen bonding is consistent with the fact that the amino group of urea is a better donor than acceptor of hydrogen bonds. The effects of this interaction on the structure of urea are different from those observed in the previous complexes. The topological data reveal in fact that in this case the nitrogen lone-pair is partially subtracted from π -conjugation. The electron density on the CO and CN bonds is therefore consistently modulated and the polar canonical forms decrease in their importance. Similarly the location of bond critical points on the NH and CO bonds as well as the values of the $\nabla^2\rho(r)$ along the corresponding bond paths indicate that the degree of polarisation of both the CO and NH bonds decrease when water interactions are included. On the basis of the spatial changes of electron density we can predict that, as

for the previous solvation patterns, such a nitrogen hydration weakens the urea–urea interaction. As a proof the NH \cdots O=C distances lengthen on moving from *vacuo* to DW4.

As a matter of fact the energies of dimerisation and hydration reported in Table 3 seem to indicate that urea–water and urea–urea interactions reinforce each other in DW4. However this is more apparent than real. BSSE calculations of the interaction energy performed on the four molecular units which form DW4 reveal in fact that a couple of water molecules show a small (-7 kJ mol⁻¹) attractive interaction. The net dimerisation energy in DW4 is therefore again lower than *in vacuo*. For the same reason the water–urea interaction seems to be stronger for DW4 than MW4 (Tables 3 and 4). However the strengthening is again only apparent because it is originated by the presence of this favourable water–water interaction in DW4. The values of dimerisation and hydration energy corrected for BSSE also reveal anticooperative effects between the urea–urea and urea–water interactions also when the hydration occurs at nitrogen.

Therefore all the hydration patterns considered here have a destabilising effect on the urea cyclic dimer. The single specific water–urea interactions therefore seem to be competitive with the dimerisation process.

When multiple hydrations were considered in the remaining DW5, DW6 and DW7 complexes some concluding considerations can be made. The urea–urea distances increase progressively with the degree of solvation and indifferently from the hydration site. An anticooperative effect between urea–urea and urea–water interactions is therefore present when solvation involves only the amino groups. When instead water interacts with the carbonyl group (DW6) and with nitrogen (DW7), cooperative effects are observed for the NH \cdots OH₂ interactions. This is well witnessed by the shortening of the corresponding distances observed in DW6 and DW7. The origin of such a cooperation is found in their structure which allows the formation of hydrogen bonds between water molecules. Therefore cooperative strengthening of hydrogen bonding can indeed be found in urea hydration however it involves only the urea–water and water–water interactions.

The PCM model was lastly applied to the DW1, DW2, DW2', DW3 and DW4 complexes and, as for the non hydrated dimer, the values of ΔG_{PCM} indicate that the effect of the bulk water is again destabilising towards cyclic urea dimers.

C. Dynamics of dimer in solution. All the computational models discussed up to now reveal that the urea cyclic dimer also continues to be a stable aggregate in the presence of a few numbers of water molecules, notwithstanding the specific interactions with H₂O play a destabilising role. It is more interesting to follow the evolution of the cyclic dimer and its stability in time. Within this aim we have focused our attention on DW7, the complex at a higher degree of hydration, and we performed ADMP simulations at 300 K starting from the B3LYP/6-31G* optimised geometry. By monitoring the H \cdots O hydrogen bond distances (Fig. 4c) we found that the cyclic dimer seems to be stable within a few ps. The molecules remained attached through only one NH \cdots OC bond for

another 2 ps and 7–8 ps later urea tends to be definitely surrounded only by water molecules. ADMP simulations indicate therefore that the cyclic dimer breaks up very quickly into urea units solvated by water molecules. These conclusions are confirmed by the fact that the conformations obtained in the last part of the simulation had potential energies lower than the starting point. From one of these conformations, B3LYP/6-31++G** geometry optimisations led to structures where water–water and water–urea interactions were observed.

Conclusions

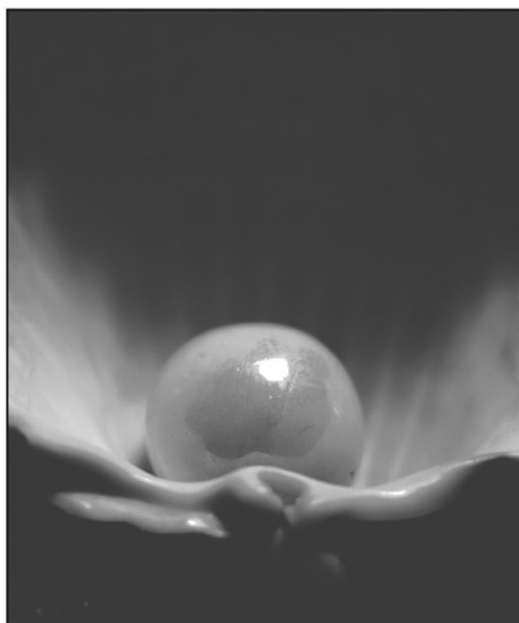
The present investigation points out the destabilising role that water plays on the cyclic dimer of urea. Water disfavours the cyclic aggregation of urea through both bulk effects and through the effects of the specific solute–solvent interactions. The bulk effect of water, described by our PCM study, hinders the formation of double hydrogen bonded dimers simply because they are apolar and thus less favourably solvated than the monomer. On the other hand, specific interactions with water cause a progressive weakening of the binding energy of the cyclic dimer. The competition between urea–water and urea–urea interactions is the main cause of its progressive destabilisation. All the cyclic dimers proposed here, even that of the 12 fold hydrated one, are stable structures *in vacuo*. This local stability is however quickly lost when dynamic aspects are considered. MD simulations indicate in fact that the cyclic dimer remains cyclic *in vacuo* but decays rapidly into separated and completely hydrated monomers in the presence of water molecules. This provides conclusive evidence that urea does not have a tendency to form well defined double hydrogen bonded pairs in low concentrations of water solutions. The fact that the 12 fold hydrated cyclic dimer (DW7) has an energy quite close to complexes in which aggregation occurs through urea–water and water–water interactions suggests that urea clustering must be seen as a dynamic process. If cyclic dimers were formed in water solution instantaneously, they would evolve towards asymmetric structures where the urea–water interactions would be the dominant feature. At higher concentrations urea could perhaps show a more pronounced tendency to dimerise through the formation of cyclic structures or more probably through collective urea-solvated aggregation where water has a bridge function between urea units.

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