

Co-operative electrostatics for understanding crown ether hydration patterns

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A prototype problem in supramolecular chemistry is: Would it be possible to understand qualitative trends in hydration process of crown ether from simple considerations at the molecular level? An answer is offered for the hydration of 18-crown-6 (18C6) in terms of co-operative electrostatic effects. These effects are monitored by mapping the molecular electrostatic potential topography of 18-crown-6 as well as various intermediate hydrated species, followed by electrostatic modelling. All model calculations have been done at *ab-initio* HF/6-31G level. The trends of these hydration patterns are in good agreement with the corresponding fully optimized *ab-initio* ones. Final structure of 18C6·4H₂O is quite similar to the corresponding experimental crystal structure. Such an electrostatics-based method seems to be an excellent general tool for understanding weak interactions in supramolecular chemistry.**

SUPRAMOLECULAR chemistry, defined by Lehn¹ as the chemistry of the intermolecular bond, deals with entities formed by complexation of two or more molecular units. This subject covers a wide variety of molecular recognition processes including enzyme-receptor binding¹, hydration of proteins and DNA, catalyst-substrate as well as cation- π interactions² etc. The importance of electrostatics in these processes has been widely recognized²⁻⁴. For instance, *ab-initio*⁵ studies as well as computer simulations, despite being computer-intensive methods, are being employed for studying the hydration processes. Although a great deal of energetic and dynamic information is thereby engendered, the understanding of primitive patterns at molecular level is not directly possible by the use of these methods. We propose to present such a general approach, for gaining insights at molecular level, with a test example of crown ether hydration.

The hydration of 18-crown-6 (18C6) has been extensively studied⁶⁻⁸ experimentally as well as theoretically as a prototype problem in supramolecular chemistry. By constructing the melting diagrams of 18C6·nH₂O, the existence of several binary hydrates has been verified⁶. The detailed crystal structures of these hydrates have been probed⁶ by X-ray diffraction. The D_{3d} conformation of hydrated crown ether has also been confirmed by Raman spectroscopy⁷. Earlier investigations have indi-

cated that in aqueous solution, the predominant conformation is the centrosymmetric D_{3d}, which is favourable for complexation with water molecules.

Computational studies⁸ on the hydration of 18C6 include the Monte Carlo simulations of conformation-dependent hydration reported by Ranghino *et al.*⁸ as well as the recent work by Thompson⁸. It was noted by Ranghino *et al.*⁸ that for the D_{3d} conformation, there is a typical co-operativity between two water molecules on each face. They attempted, quite unsuccessfully, to correlate the solute-water interaction energy with the dipole moment of water. Some other correlations with the accessible molecular surface as well as the deepest energy potential around 18C6 were also tried out, although the success there was also rather limited. It was concluded that the results of Monte Carlo simulations are qualitatively explicable but hardly predictable and could not be extrapolated to other systems. Earlier, Hori *et al.*⁸ had concluded from the HF/STO-3G calculations that the charge transfer and electrostatics are significant for cation-crown ether interactions. However, considering that no ionic species or strong polarization effects are involved, it is intuitively felt that for the hydration process, electrostatics alone would dominate.

Recent molecular dynamic simulations by Kowall and Geiger⁸ have also indicated that a water molecule is strongly bound to ether oxygens, two on each face of the ring, whereas the third ether oxygen, one on each face is coordinated by a singly-bound and rapidly-fluctuating water molecule. Thus the question asked by Ranghino *et al.*⁸ is still unanswered viz. **would it be possible to understand (or predict) at least trends in hydration processes from simple considerations?**

It is the purpose of this communication to analyse, qualitatively as well as semiquantitatively, the pattern of hydration of 18C6, based on the cooperative electrostatic effects due to the lone pairs of oxygens of 18C6, and those of water molecules. We shall limit the present work to 18C6·4H₂O, although further extensions to the higher hydrates are readily possible.

The lock and key mechanism for understanding the hydration process of D_{3d} conformers of 18C6 is offered by mapping of the topography of the Molecular Electrostatic Potential (MESP) of 18C6 as well as the various intermediate hydrated species. MESP has been widely used^{9,10} in the chemical literature as a tool for probing electron-rich sites, although MESP topography-mapping is a more recent development. The *ab-initio* calculations reported in this work are carried out with the help of GAMESS¹¹ and GAUSSIAN¹¹ packages at HF/6-31G** level. The individual MESP features of 18C6 and water have been mapped by employing indigenously developed packages UNIPROP and UNIVIS¹² (Figure 1). It may be expected that the 18C6···H₂O interaction is stronger than the H₂O···H₂O interaction, since 18C6 MESP

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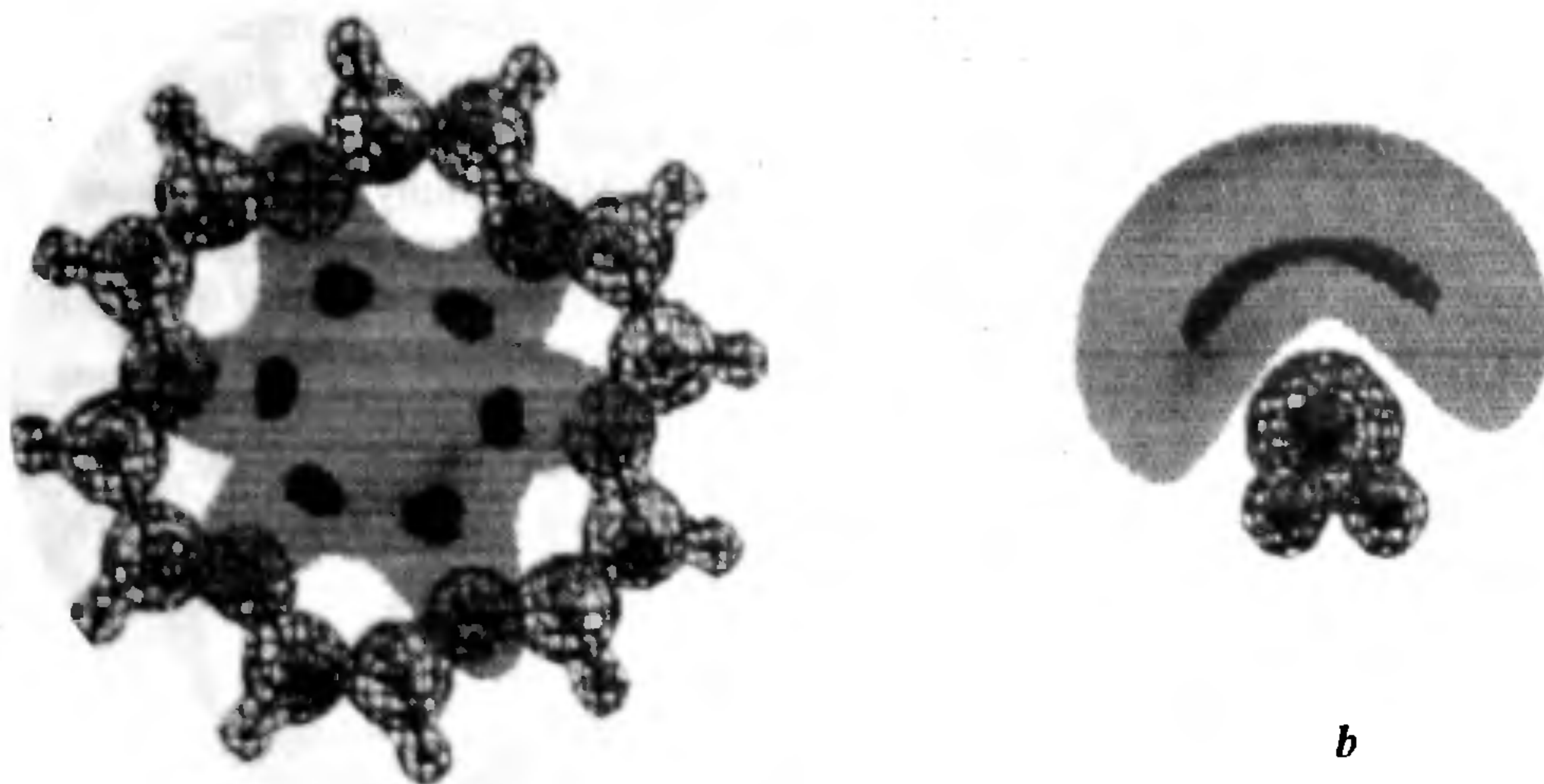


Figure 1. *a.* 1575.3 kJ mol⁻¹ MESP mesh wire plot and -157.5 kJ mol⁻¹ (light) and -288.8 kJ mol⁻¹ (dark) isosurfaces of 18C6. The MESP minima values are -318.9 kJ mol⁻¹; *b.* 2362.9 kJ mol⁻¹ MESP mesh wire plot and -131.3 kJ mol⁻¹ (light) and -252.1 kJ mol⁻¹ (dark) isosurfaces for the water molecule. The MESP minima correspond to -261.2 kJ mol⁻¹.

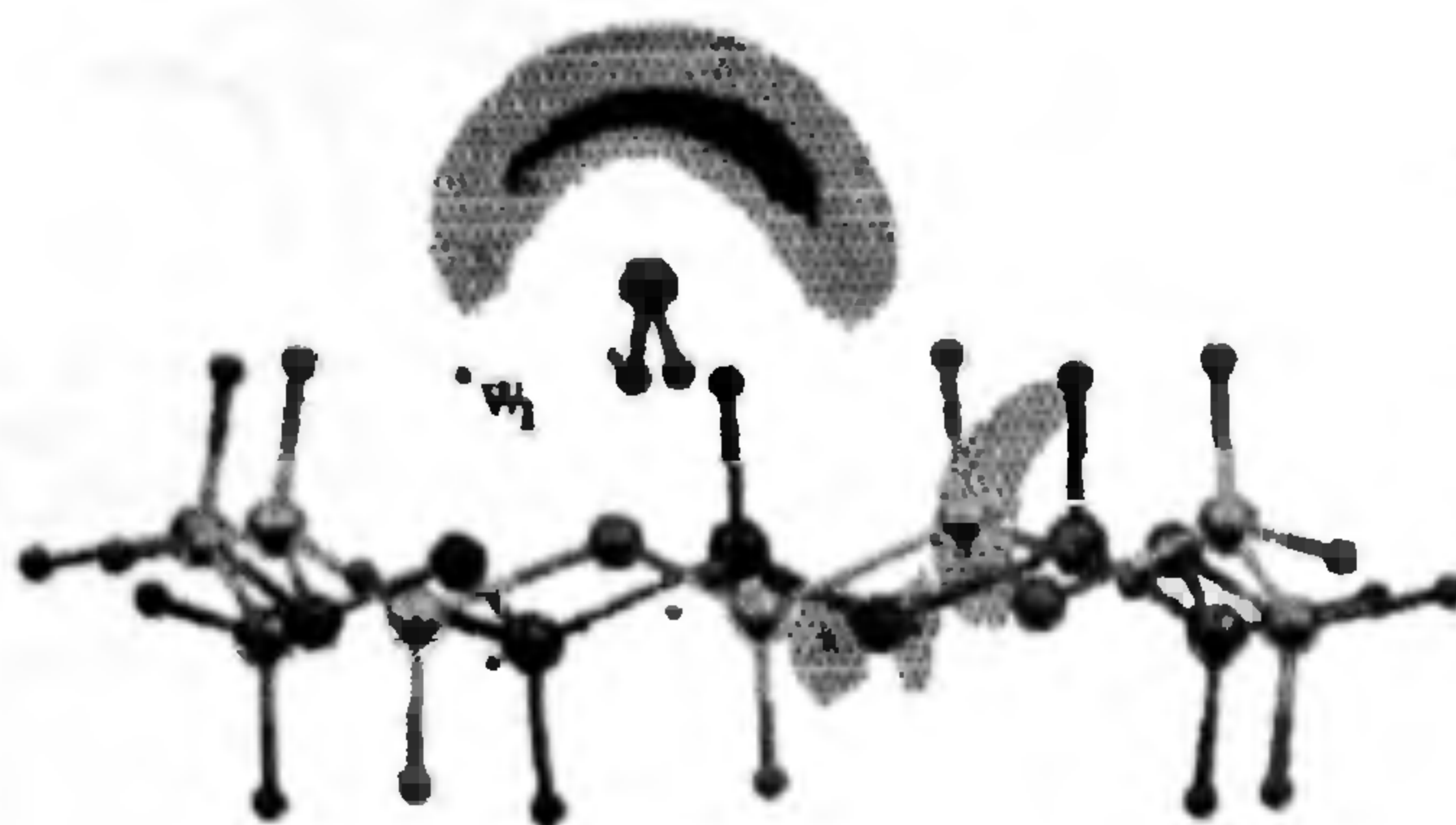


Figure 2. *Ab-initio* optimized structure of 18C6-H₂O (the water molecule shown as W₁), with crown ether MESP CPs shown as dots, MESP isosurfaces of values -270.4 (light) and -359.7 (dark) kJ mol⁻¹. The two deepest lone pair MESP minima for W₁ are -386.5 and -369.7 kJ mol⁻¹.

minimum is -318.9 kJ mol⁻¹ as against the corresponding value of -261.2 kJ mol⁻¹ for water.

Where the first water molecule binds to 18C6 is qualitatively decided by the MESP topography. An electrostatic model developed in the author's laboratory viz. Electrostatic Potential for Intermolecular Complexation (EPIC)¹³ has been employed for obtaining structures and energetics of 18C6 hydrates. This model utilizes the entire three-dimensional MESP distribution as well as atom-centered charges derived from the respective MESP's¹⁴. The binding energy of the first water molecule (W₁) to 18C6 within EPIC model is 41.0 kJ mol⁻¹, and an *ab-initio* optimization carried out starting from this geometry yields an interaction energy of 49.4 kJ mol⁻¹ (all *ab-initio* values refer to HF/6-31G** level). On the basis set superposition energy (BSSE) correction it turns out to be 36.1 kJ mol⁻¹, 73% of that without the BSSE correction. The MESP topography of 18C6-H₂O has been

calculated using the block diagonal density matrix obtained by patching the corresponding individual *ab-initio* density matrices. Figure 2 presents MESP isosurfaces for 18C6-H₂O complex optimized at *ab-initio* level. The most noteworthy observation is that the MESP minimum of the bonded water molecule becomes much deeper, viz. -362.3 kJ mol⁻¹ -386.5 kJ mol⁻¹ for EPIC-patched and *ab-initio* optimized structures respectively. This feature has earlier been noticed¹⁵ for the lone pairs in the case of hydrogen-bonded DNA base pairs. The remaining 18C6 oxygen minima show somewhat higher value compared to the 18C6 minima values (typical value -288.8 kJ mol⁻¹). A significant implication of this observation is that the incoming second water molecule (W₂) perhaps binds to the deepest minimum of the first water molecule with its other hydrogen interacting with the 18C6 oxygen minimum on the same face. The EPIC and *ab-initio* interaction energies of 18C6-H₂O with the

second water molecule (second molecule coming from the side of first water molecule of 18C6, see Figure 3) turn out to be 45.7 kJ mol^{-1} and 52.2 kJ mol^{-1} respectively. The *ab-initio* interaction energy for the same with BSSE is 40.0 kJ mol^{-1} . The interaction energy, when the second water molecule attacks 18C6-H₂O from the side opposite to that of the first water molecule, turns out to be 39.1 kJ mol^{-1} and 42.8 kJ mol^{-1} with EPIC and *ab-initio* level respectively. The *ab-initio* value on BSSE correction becomes 31.6 kJ mol^{-1} . These

interaction energies reveal that the second water molecule preferentially attaches from the side of the first water molecule, according to the predictions based on the MESP study. As seen from Figure 3, the MESP of W₂ becomes substantially deeper (CP values of $-333.4 \text{ kJ mol}^{-1}$ and $-379.0 \text{ kJ mol}^{-1}$ at EPIC and *ab-initio* level respectively).

An interesting question now is: where will the next incoming water molecule (W₃) bind? Since all the sites on the top face (where the first and second water

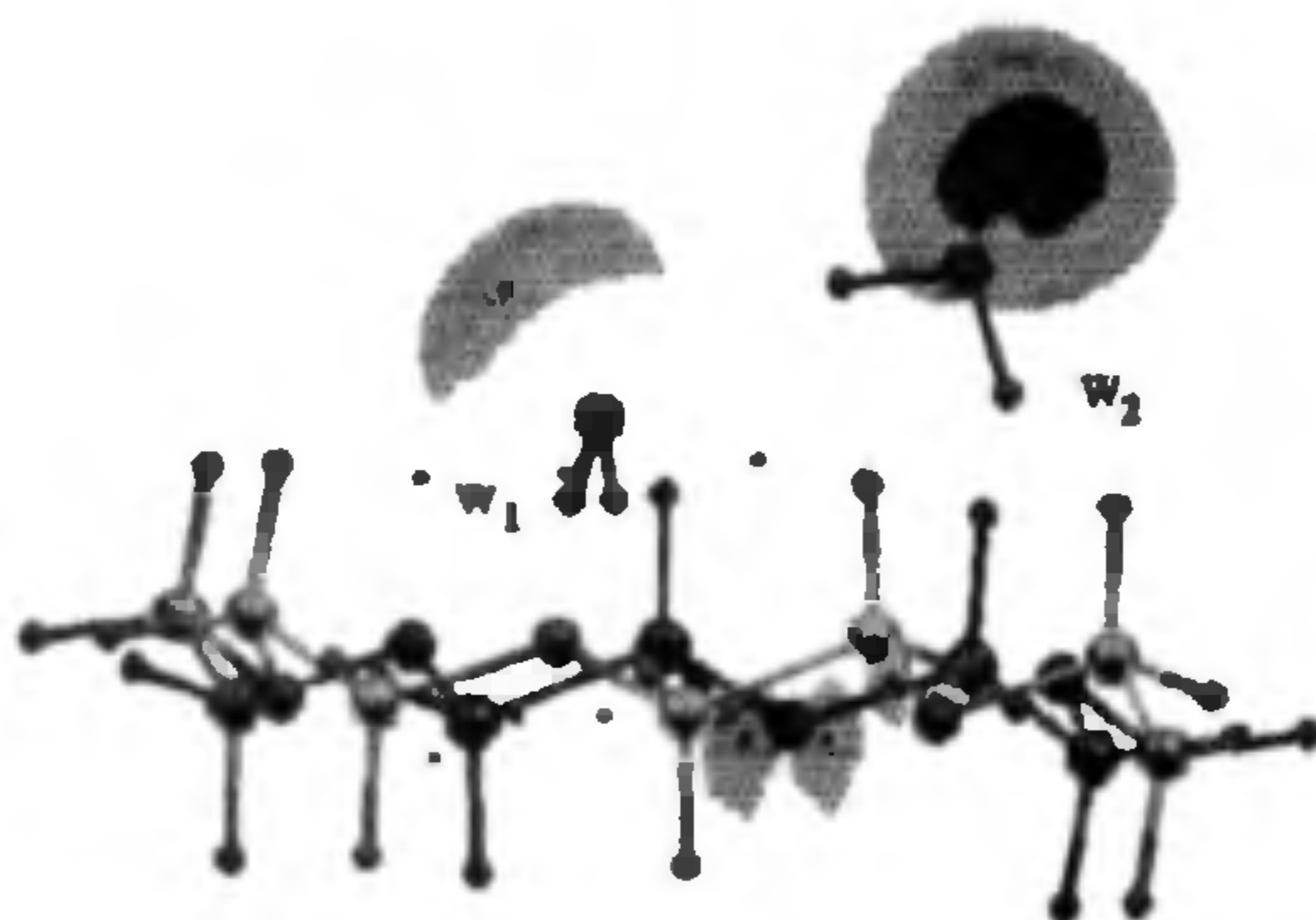


Figure 3. *Ab-initio* optimized structure of 18C6-2H₂O (water molecules as W₁ and W₂), with crown ether MESP CPs shown as dots, MESP isosurfaces of values -244.2 (light) and -341.3 (dark) kJ mol^{-1} . The two deepest lone pair MESP minima of W₂ are -379.0 and $-377.8 \text{ kJ mol}^{-1}$.

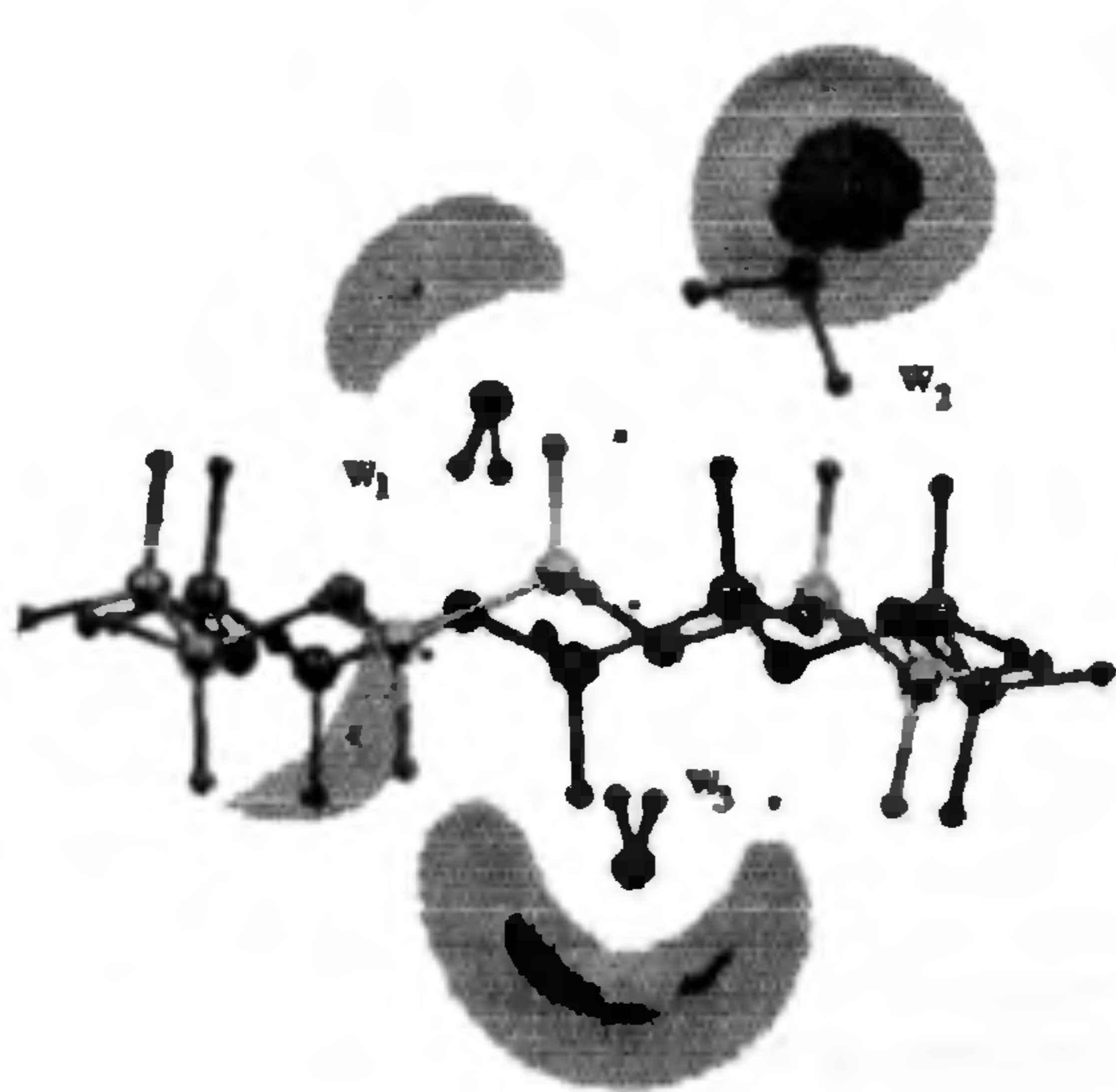


Figure 4. *Ab-initio* optimized structure of 18C8-3H₂O (water molecule denoted as W₁, W₂ and W₃), with crown ether MESP CPs shown as dots, MESP isosurfaces of values -199.5 (light) and -325.6 (dark) kJ mol^{-1} . The two lone pair minima for W₂ are -370.6 and $-369.3 \text{ kJ mol}^{-1}$ and the two lone pair MESP minima for W₃ are -351.5 and $-336.6 \text{ kJ mol}^{-1}$.

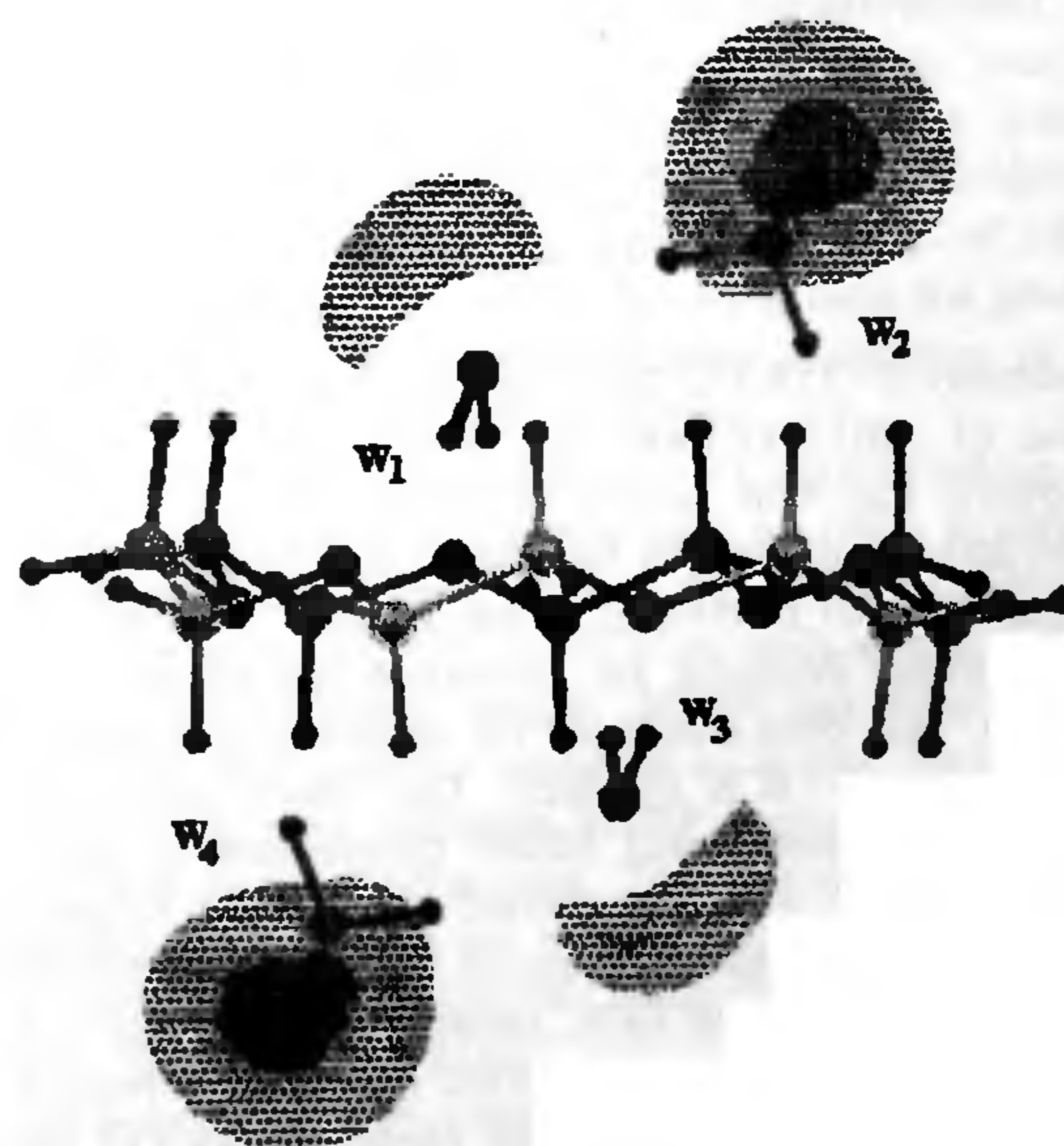


Figure 5. *Ab-initio* optimized structure of 18C6-4H₂O (water molecules represented as W₁, W₂, W₃ and W₄), with MESP isosurfaces of values -183.8 (light) and -315.1 (dark) kJ mol^{-1} . The four deepest lone pair MESP minima for W₂ and W₄ are $-356.7 \text{ kJ mol}^{-1}$.

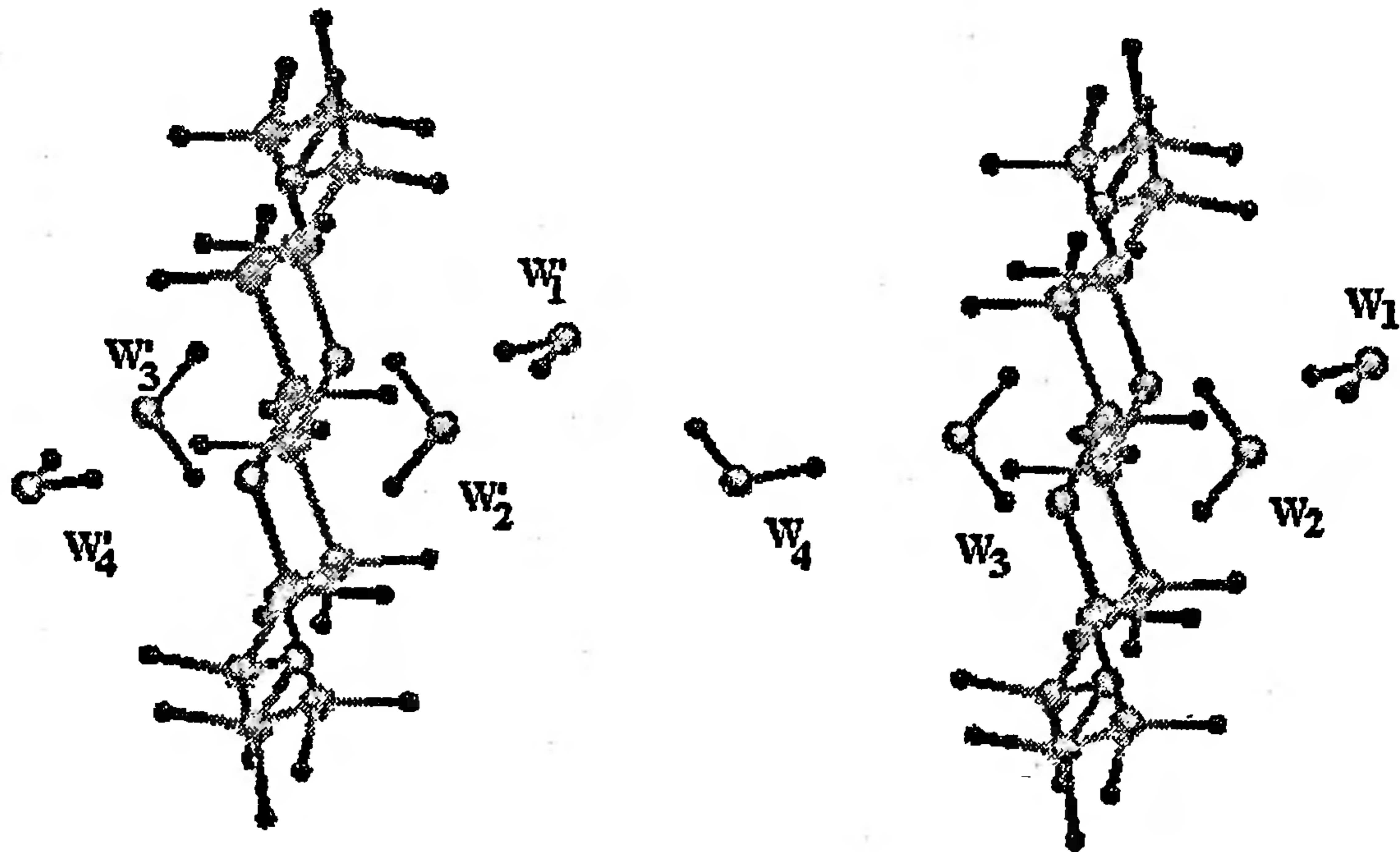


Figure 6. EPIC model optimized structure of dimer of tetrahydrate of 18C6 with flipped water molecule connecting two units viz. $18C6 \cdot 4H_2O'$ and $18C6 \cdot 4H_2O$.

molecules bind) of 18C6 are blocked and W_3 can anchor to only one oxygen minimum of a water molecule, it is therefore expected that W_3 will bind on the other face of 18C6 with a slightly reduced interaction energy compared to that of the first water because the 18C6 oxygen minima of the other face is more positive (typical value $-262.6 \text{ kJ mol}^{-1}$). The interaction energies of W_3 with $18C6 \cdot 2H_2O$ indeed turn out to be 40.1 kJ mol^{-1} and 43.5 kJ mol^{-1} within EPIC and *ab-initio* frameworks respectively (see Figure 4), the latter becomes 30.2 kJ mol^{-1} with BSSE correction. It is also found that three water molecules cannot bind on the top face of 18C6 in a cooperative manner as strongly as the above-mentioned arrangement. Continuing this story, the next water molecule (W_4) prefers to bind with one hydrogen, capturing an MESP minimum of W_3 molecule ($-320.3 \text{ kJ mol}^{-1}$ and $-351.8 \text{ kJ mol}^{-1}$ at EPIC and *ab-initio* levels respectively) and with another hydrogen getting attached to 18C6 minimum (cf. Figure 5). The binding energies of W_4 to $18C6 \cdot 3H_2O$ are 43.7 and 49.3 kJ mol^{-1} at EPIC and *ab-initio* levels respectively, being $37.43 \text{ kJ mol}^{-1}$ with BSSE correction. Although the *ab-initio* SCF interaction energies without BSSE correction are typically 70 to 80% for $18C6 \cdot nH_2O$ ($n=1, 2, 3$ and 4), the qualitative picture of hydration pattern of 18C6 does not change. The MESP minimum value of crown ether to which this fourth water molecule binds is about $-242.6 \text{ kJ mol}^{-1}$. Further details of energetics and structures of $18C6 \cdot nH_2O$ for $n=1$ to 6 are being published¹⁶ elsewhere.

The question now is: if two such crown ether moieties are brought together, will this fourth water molecule

flip and get attached to the MESP minimum of a water molecule bonded to the other $18C6 \cdot 4H_2O$? The answer to this question can be sought by bringing an $18C6 \cdot 4H_2O$ and an $18C6 \cdot 3H_2O$ optimally together along with a water molecule in between them with a hydrogen 'sticky end', binding to the deepest MESP minimum of $18C6 \cdot 4H_2O$ (viz. $-356.7 \text{ kJ mol}^{-1}$). EPIC model has been employed for this purpose and the binding energy of this water molecule turns out to be 56.8 kJ mol^{-1} in contrast to that for the fourth water molecule in the $18C6 \cdot 4H_2O$ viz. 43.7 kJ mol^{-1} . The corresponding EPIC structure is shown in Figure 6. It is gratifying to note that this structure is in excellent agreement with the crystal structure recently reported by Albert *et al.*⁶ In conclusion, the lock and key arrangement engendered by the MESP topography followed by electrostatic modelling seems to offer an excellent tool for understanding weak intermolecular interactions in supramolecular chemistry.

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$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} \int \frac{\rho(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} d^3 \mathbf{r}'$$

where Z_A is charge of nucleus A located at \mathbf{R}_A and $\rho(\mathbf{r})$ denotes the molecular charge density. Negative value of $V(\mathbf{r})$ provides information regarding electron-rich sites. The topographical analysis of this scalar field involves locating and characterizing the critical points (CPs), where the first-order partial derivatives of this field vanish. The nature of the function at these CPs is known by inspecting the signs of the eigenvalues of the respective Hessian matrix. These CPs are identified by the notation (rank, signature), where rank is number of nonzero eigenvalues of Hessian matrix, and signature is algebraic sum of the signs of the eigenvalues. The nondegenerate CPs of rank 3 could be any one of (3, +3) (minimum), (3, -3) (maximum) or saddles of the types (3, +1) and (3, -1). The package UNIVIS developed by Gadre and co-workers; see Limaye, A., Dattawadkar, S., Inamdar, P. V. and Gadre, S. R., *J. Mol. Graph.*, 1996, 14-19.

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pp. 219-255; In the EPIC model described in this work, rigid species A and B are moved relative to each other so as to minimize interaction energy

$$E_{int} = \frac{1}{2} \left\{ \sum_i V_{A,i} q_{B,i} + \sum_j V_{B,j} q_{A,j} \right\}$$

where, $V_{A,i}$ and $V_{B,j}$ are the MESP's due to species A and B respectively at the i^{th} and j^{th} nuclear site in species B and A respectively. Here, the MESP-derived charges are $q_{B,i}$ and $q_{A,j}$ respectively. The movement is constrained such that the van der Waals surfaces of A and B do not interpenetrate.

14. The FORTRAN program performing charge fitting to molecular electrostatic potentials was made available from C. Chipot, University De Nancy I, France. We thank Dr C. Chipot for supplying us this code. See also, Chipot, C., Ángyán, J. A., Ferenczy, G. G. and Scheraga, H. A., *J. Phys. Chem.*, 1993, **97**, 6628-6636.
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