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Microsolvation of morpholine, a bidentate base – the importance of cooperativity

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The structure, relative energies, and bonding in morpholine(water)$_n$ (n = 1–4) clusters have been investigated at the Becke, three-parameter, Lee–Yang–Parr/6–311 + G(3df,2p)//Becke, three-parameter, Lee–Yang–Parr/6–311 + G(d,p) level of theory. Cooperative effects have been analyzed through the use of structural, energetic, and electron density indexes. Our analysis shows that these effects are crucial to trace the relative stability of the complexes formed. In all cases water molecules prefer to self-associate forming chains in which each individual molecule behaves as a hydrogen bond (HB) donor and HB acceptor. The chain so formed behaves in turn as HB donor and HB acceptor with respect to morpholine, being the most stable arrangements those in which the NH group of morpholine behaves simultaneously as HB donor and HB acceptor. Higher in energy lie complexes in which the HB acceptor continues to be the NH group, but the HB donor is a CH group, or alternative structures in which the HB acceptor is the ether-like oxygen of morpholine and the HB donor its NH group. Cooperativity increases with the number of solvent molecules, but there is a clear attenuation effect. Thus, whereas the additive interaction energy on going from dihydrated to trihydrated species increases by a factor of 3, this increase is about half on going from trihydrated to tetrahydrated complexes. Copyright © 2012 John Wiley & Sons, Ltd.

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Keywords: density functional theory; herterocyclic compounds; hydrogen bond; microsolvation; morpholine; Quantum Theory of Atoms in Molecules (QTAIM)

INTRODUCTION

Solvation effects are crucial in chemistry, where the huge majority of processes take place in the condensed phase. Actually the interactions between solute and solvent are rather often responsible for the reactivity trends within a certain family of compounds, and more often than not, the reactivity trends observed in the gas-phase differ from those observed in solution. Indeed, one important aspect of the problem is whether the most significant solvation effects are readily described by a small number of solvent molecules or if a bulky model is actually needed. Particularly important are these effects when the solvent is water, and the solute has several active sites. Actually, some features, such as intramolecular hydrogen bonds (HBs) as the one present in tropolone, which only manifest in the gas phase, actually disappear as such when the system interacts with a limited number of water molecules.[1] Similarly, it has been found that specific hydration environments are able to explain the observed vibrational shifts in certain molecules whereas they are not reproduced by polarized continuous models, even though simple hydrated structures are not able to explain all the shiftings.[2] Also, a reduced number of water molecules is also needed to stabilize the zwiterionic form of glycine,[3] or cysteine,[4] and to reduce the acidity gap between N1 and N3 in uracil[5] and triazepine thio derivatives.[6] Also, specific solvation involves, in some specific cases, weak HB donors, such as CH groups, as seems to be the case for instance in the hydration of 1,4-dioxirane, as revealed both by experimental[7] and theoretical studies.[8–10] This is actually facilitated by the ability of water to behave either as an HB donor or/and as an HB acceptor and the possibility of interacting with more than one center, if the solute presents more than one active site for hydrogen bonding. Related with this is also the possible competition between specific solvation of the different active sites through intermolecular solute–water HBs and the self-aggregation of water molecules through water–water interactions.[11,12]

To investigate this question, we have chosen as a suitable model morpholine because, besides its many industrial and pharmaceutical properties: morpholine is known to be a hygroscopic molecule with important industrial applications, because of its anticorrosive properties, and in the pharmaceutical industry for its anti-inflammatory and antifungal activity, this compound is a six-membered cyclic amino ether (see Scheme 1), and therefore it is able to behave simultaneously as a hydrogen bond donor, through its NH group and as a double HB acceptor by means of both its NH group and the ether-like oxygen. Eventually it

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can also act as HB donor through the CH_2 groups of the six-membered ring. On top of that the isolated morpholine presents two conformers, namely the *chair* and the *boat* or *twist* structures, whose relative stability may change upon microsolvation.

COMPUTATIONAL DETAILS

The number of possible isomers and conformers of microhydrated morpholines increases significantly with the number of the molecules of solvent. The initial guess structures were generated systematically using their molecular electrostatic potential and the AGOA 2.0 code,[13–15] which was specifically designed to explore the structures of solvents around polar solutes. The structures so detected for the different morpholine (water)$_n$ (n = 1–4) hydration clusters, have been optimized by means of the B3LYP density functional theory (DFT) approach. Previous assessments in the literature have shown that this method, which combines Becke's three parameter (B3) exchange functional[16] with the Lee–Yang–Parr (LYP) nonlocal correlation functional,[17] is able to accurately describe intermolecular and intramolecular HB[18–23] of the type expected to be formed in the aforementioned clusters. It should be mentioned however that more assessments including new generation functionals, have detected some cases in which the performance of B3LYP is questionable,[24–27] mainly when dealing with HBs in which dispersion contributions can be significant. Although this is not the case in the systems investigated in this paper, we have decided to recalculate with three of the functionals that have been shown to better perform for the description of HBs, namely X3LYP,[26,28,29] M05-2X,[27,30] and PBE0,[27] the structures and energies of the three (or four) more stable clusters for the monohydrated, dihydrated, trihydrated, and tetrahydrated-morpholine. The results obtained have been summarized in Tables S1 and S2. These results show that neither the structure nor the stability trends change significantly with the functional used. Although, the B3LYP relative energies are in general smaller than those calculated with the other three functionals, the trends, which is what matters in our survey, are the same as clearly illustrated in Figure S1, which shows that the linear correlations between B3LYP and X3LYP, M05-2X and PBE0 values have correlation coefficients of 0.9993, 0.9976, and 0.9996, respectively. The different stationary points found for these clusters were characterized as local minima by evaluating the corresponding harmonic vibrational frequencies, which were also used to calculate the zero point vibrational energies, which were used

Scheme 1. Stable isomers of morpholine

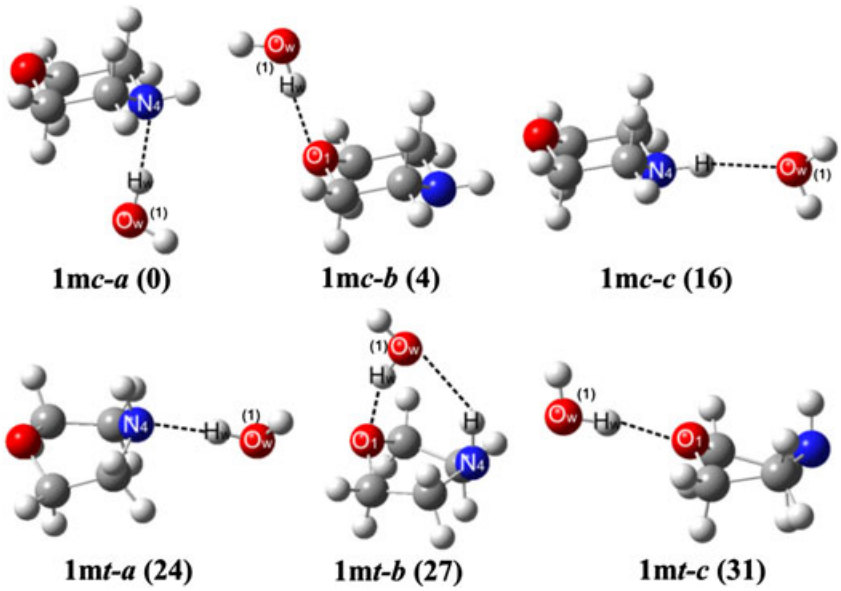

Figure 1. Optimized structures of monohydrated complexes of morpholine. Relative energies in kJ mol^{-1} are given within parenthesis

Table 1. Interaction energy (ΔE, kJ mol^{-1}), hydrogen bonds (HBs), HB lengths (R_{YH}, Å), δR (Å), electron density at the HB critical point (ρ_b, a.u.), population of the σ_{XH}* antibonding orbital (me), and NBO second-order interaction energies ($E^{(2)}$, kJ mol^{-1}) for monohydrated morpholine complexes

Complex	ΔE	HBs	R_{YH}	δR	ρ_b	Population σ_{XH}*	$E^{(2)}$
1mc–*a*	−26.2	O_w–$H_{w(1)}$···N_4	1.924	0.876	0.0333	35	50
1mc–*b*	−22.7	O_w–$H_{w(1)}$···O_1	1.869	0.831	0.0290	21	34
1mc–*c*	−9.8	N_4–H···$O_{w(1)}$	2.145	0.555	0.0158	4	15
1mt–*a*	−27.9	O_w–$H_{w(1)}$···N_4	1.907	0.893	0.0340	32	51
1mt–*b*	−25.8	O_w–$H_{w(1)}$···O_1	1.867	0.833	0.0304	23	38
		N_4–H···$O_{w(1)}$	2.442	0.258	0.0085	0.1	3
1mt–*c*	−21.6	O_w–$H_{w(1)}$···O_1	1.876	0.824	0.0288	20	34

without scaling. The basis set expansion employed both for the geometry optimizations and the vibrational frequencies calculation was the 6-311 + G(d,p). To obtain reliable energies as far as the relative stability of the different clusters is concerned, we carried out single-point calculations, on the previously optimized structures, with a much larger 6-311 + G(3df,2p) expansion.

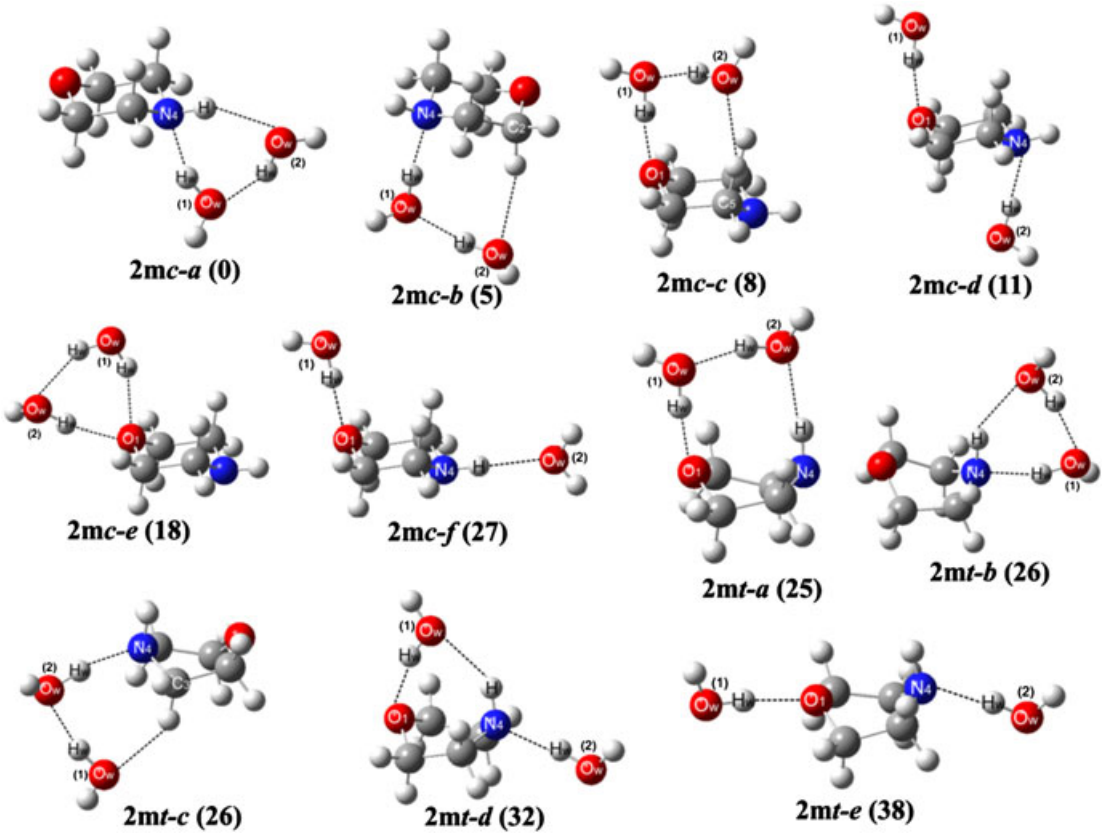

Figure 2. Optimized structures of dihydrated complexes of morpholine. Relative energies in kJ mol^{-1} are given within parenthesis

Table 2. Interaction energy (ΔE, kJ mol^{-1}), hydrogen bonds (HBs), HBs lengths (R_{YH}, Å), δR (Å) (See eq. (1)), electron density at the HB critical point (ρ_b, a.u.), population of the σ_{XH}* antibonding orbital (me), NBO second-order interaction energies ($E^{(2)}$, kJ mol^{-1}) and additive interaction energy (E_{add}, kJ mol^{-1}) for some representative dihydrated morpholine complexes[a]

Complex	ΔE	HBs	R_{YH}	δR	ρ_b	Population σ_{XH}*	$E^{(2)}$	E_{add}
2mc–a	−60.2	O_w–$H_{w(1)}$···N_4	1.865	0.935	0.0379	46	62	15.6
		N_4–H···$O_{w(2)}$	2.175	0.525	0.0155	18	12	
		O_w–$H_{w(2)}$. . .$O_{w(1)}$	1.885	0.815	0.0282	20	37	
2mc–b	−55.8	O_w–$H_{w(1)}$···N_4	1.843	0.957	0.0402	49	72	15.8
		C_2–H···$O_{w(2)}$	2.488	0.212	0.0092	−1	8	
		O_w–$H_{w(2)}$. . .$O_{w(1)}$	1.842	0.858	0.0312	24	47	
2mc–c	−52.2	O_w–$H_{w(1)}$···O_1	1.792	0.908	0.0353	30	51	13.4
		C_5–H···$O_{w(2)}$	2.538	0.162	0.0082	−3	6	
		O_w–$H_{w(2)}$. . .$O_{w(1)}$	1.858	0.842	0.0298	22	43	
2mt–a	−61.3	O_w–$H_{w(1)}$···O_1	1.773	0.927	0.0369	31	55	15.8
		N_4–H···$O_{w(2)}$	2.103	0.597	0.0184	8	22	
		O_w–$H_{w(2)}$. . .$O_{w(1)}$	1.840	0.860	0.0309	23	45	
2mt–b	−60.9	O_w–$H_{w(1)}$···N_4	1.841	0.959	0.0400	46	70	15.8
		N_4–H···$O_{w(2)}$	2.222	0.478	0.0143	4	10	
		O_w–$H_{w(2)}$. . .$O_{w(1)}$	1.883	0.817	0.0283	21	37	
2mt–c	−60.2	O_w–$H_{w(1)}$···N_4	1.813	0.987	0.0427	48	78	14.0
		C_3–H···$O_{w(2)}$	2.521	0.179	0.0078	−6	4	
		O_w–$H_{w(2)}$. . .$O_{w(1)}$	1.847	0.853	0.0307	24	45	

[a]This information for the remaining dihydrated clusters is summarized in Table S5.

The interaction energy, ΔE, for each cluster was calculated as the difference between the total energy of the cluster and the sum of the energies of the different monomers involved in their equilibrium conformations. The reported interaction energy includes the ZPE corrections.

Because we are interested in the relative stabilities of solvation clusters of the same size, one may safely assume that they will not be affected by the basis set superposition error. However, to check that this is indeed the case, we have calculated the basis set superposition error for the two or the three stable complexes in each series (see Table S3).

When a network of HBs is formed in a chemical system, almost unavoidably cooperative effects arise because the unit that acts as an HB donor will be a better HB acceptor (and vice versa)[24] with respect to a third molecule. One of the consequences of cooperativity is that the interaction energy in *n*-mers is not an additive property. A good estimation of these effects, which might be critical to understand the relative stability of clusters of the same size, can be carried out in terms of geometrical, energetic, force field, and electron density parameters. In the first case, these effects should be reflected in a shortening of the HB bond length, but this index cannot be used in a straightforward manner, because it strongly depends on the nature of the atoms involved. Hence, we will use instead the δR parameter,[31–33] which for an X–H···Y HB can be defined as,

$$\delta R = R_H^{vdW} + R_Y^{vdW} - R_{Y\cdots H} \quad (1)$$

where R_H^{vdW} and R_Y^{vdW} are the van der Waals radii of H and Y, respectively, and $R_{Y\cdots H}$ is the bond length of the HB.

Also, very reliable from a quantitative viewpoint is the so-called additive interaction energy, which can be defined, in general as follows[18]:

$$E_{add} = E_{cluster} - \sum_k E_k(\text{dim}) \quad (2)$$

where $E_{cluster}$ is the interaction energy of the cluster (i.e., for a morpholine (water)$_n$ it will be given by the energy of the cluster minus the energy of morpholine and n water molecules) and ΔE_k(dim) is the dimerization energy of all dimers (k), which can be defined within the cluster, and with the geometries they have within the cluster. Cooperativity will result in a

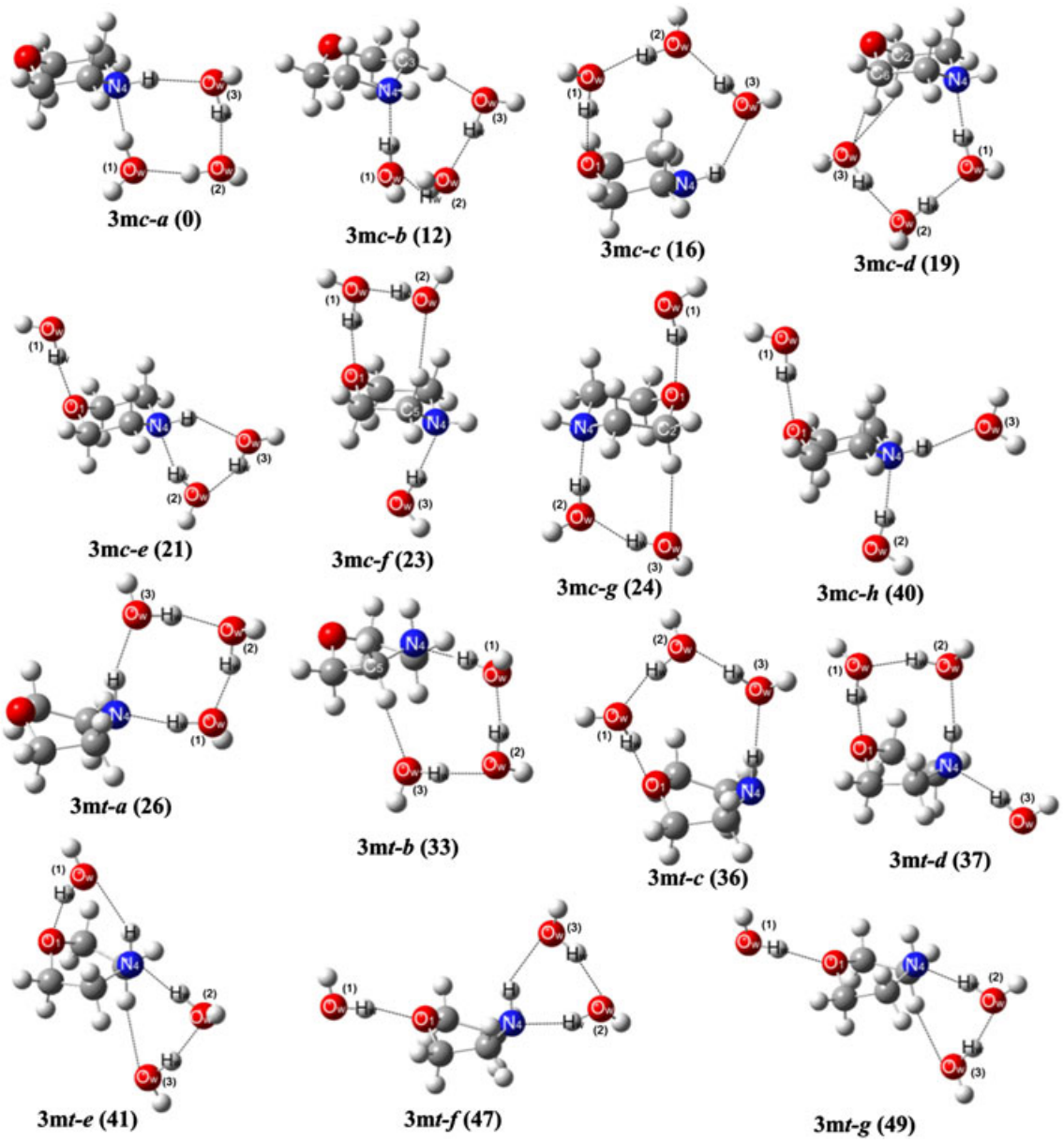

Figure 3. Optimized structures of trihydrated complexes of morpholine. Relative energies in kJ mol^{-1} are given within parenthesis

negative value of E_{add} because in those cases $\Delta E_{cluster}$ should be greater, in absolute value, than $\sum_k \Delta E_k(\text{dim})$ in Eqn (2).

Cooperative effects can be also analyzed through the cooperativity factor A_b defined as[34]:

$$A_b = \Delta\upsilon_{XH}/\Delta\upsilon'_{XH} \quad (3)$$

where $\Delta\upsilon_{XH}$ and $\Delta\upsilon'_{XH}$ represent the frequency shift undergone by the XH stretching frequency of the HB donor (XH) in the trimer and in the dimer with respect to the monomer, respectively. Unfortunately, this index, which can be readily applicable for trimers,[18,20,35–37] is not so easy to apply for larger clusters, so in our analysis, we will just explore the vibrational shifts to complement the information provided but other indexes of more general application.

Among the electron density parameters[38] the one that better describes cooperative effects is the electron density evaluated at the corresponding bond critical point (BCP).[39] It has been shown that there is a clear correlation between this electron density and the strength of the linkage,[39–42] and, as a matter of fact this index has been proposed as a criterion to classify the HBs as weak, strong, or very strong.[43]

A complementary picture of the relative strength of an HB and on the relative effects of cooperativity can be also obtained through the use of the natural bond orbital (NBO) theory,[44] which describes the bonding of a molecule in terms of atomic hybrids, and permits to estimate the

Table 3. Values of the interaction energies (ΔE) for some trihydrated complexes as compared with the energy obtained (ΔE_{total}) by adding the interaction energies of the dihydrated (ΔE_d) and monohydrated (ΔE_m) clusters, in which they can be decomposed. All values in kJ mol^{-1}

Trihydrated complex	ΔE	Dihydrated complex	ΔE_d	Monohydrated complex	ΔE_m	ΔE_{total}
3mc–*e*	82	**2mc–*a***	60	**1mc–*b***	23	83
3mc–*f*	80	**2mc–*c***	53	**1mc–*a***	26	79
3mc–*g*	79	**2mc–*b***	56	**1mc–*b***	23	79
3mt–*d*	92	**2mt–*a***	61	**1mt–*a***	30	91
3mt–*e*	88	**2mt–*c***	60	**1mt–*b***	26	86
3mt–*f* [a]	82	**2mt–*b***	61	**1mt–*b***	26	87

[a]For this trihydrated complex the agreement between ΔE and ΔE_{total} is poorer because in **1mt–*b***, there are cooperative effects that do not take place in **3mt–*f***.

Table 4. Interaction energy (ΔE, kJ mol^{-1}), hydrogen bonds (HBs), HBs lengths (R_{YH}, Å), δR (Å), electron density at the HB critical point (ρ_b, a.u.), population of the σ_{XH}* antibonding orbital (me), NBO second-order interaction energies ($E^{(2)}$, kJ mol^{-1}), and additive interaction energy (E_{add}, kJ mol^{-1}) for some representative trihydrated morpholine complexes[a]

Complex	ΔE	HBs	R_{YH}	δR	ρ_b	Population σ_{XH}*	$E^{(2)}$	E_{add}
3mc–*a*	−103.4	O_w–$H_{w(1)}$···N_4	1.791	1.009	0.0454	61	89	46.6
		N_4–H···$O_{w(3)}$	2.006	0.694	0.0222	11	31	
		O_w–$H_{w(2)}$···$O_{w(1)}$	1.761	0.939	0.0378	35	66	
		O_w–$H_{w(3)}$···$O_{w(2)}$	1.798	0.902	0.0347	30	58	
3mc–*b*	−91.5	O_w–$H_{w(1)}$···N_4	1.815	0.985	0.0430	55	82	35.6
		C_3–H···$O_{w(3)}$	2.320	0.380	0.0123	2	11	
		O_w–$H_{w(2)}$···$O_{w(1)}$	1.770	0.930	0.0370	33	65	
		O_w–$H_{w(3)}$···$O_{w(2)}$	1.822	0.878	0.0326	26	52	
3mc–*c*	−87.0	O_w–$H_{w(1)}$···O_1	1.795	0.905	0.0358	34	53	33.4
		N_4–H···$O_{w(3)}$	2.351	0.349	0.0122	0	5	
		O_w–$H_{w(2)}$···$O_{w(1)}$	1.805	0.895	0.0330	27	53	
		O_w–$H_{w(3)}$···$O_{w(2)}$	1.855	0.845	0.0298	23	44	
3mt–*a*	−103.3	O_w–$H_{w(1)}$···N_4	1.764	1.036	0.0482	62	97	47.6
		N_4–H···$O_{w(3)}$	2.007	0.693	0.0220	11	29	
		O_w–$H_{w(2)}$···$O_{w(1)}$	1.759	0.941	0.0381	35	67	
		O_w–$H_{w(3)}$···$O_{w(2)}$	1.805	0.895	0.0342	30	56	
3mt–*b*	−96.8	O_w–$H_{w(1)}$···N_4	1.773	1.027	0.0471	57	94	41.0
		C_3–H···$O_{w(3)}$	2.466	0.234	0.0090	−6	5	
		O_w–$H_{w(2)}$···$O_{w(1)}$	1.756	0.944	0.0383	35	68	
		O_w–$H_{w(3)}$···$O_{w(2)}$	1.819	0.881	0.0330	28	53	
3mt–*c*	−93.4	O_w–$H_{w(1)}$···O_1	1.746	0.954	0.0387	33	61	38.9
		N_4–H···$O_{w(3)}$	2.035	0.665	0.0209	10	29	
		O_w–$H_{w(2)}$···$O_{w(1)}$	1.780	0.920	0.0347	28	55	
		O_w–$H_{w(3)}$···$O_{w(2)}$	1.805	0.895	0.0339	29	56	

[a]This information for the remaining trihydrated clusters is summarized in Table S6.

interaction between occupied and empty orbitals through a second-order perturbation approach. Hence, the strength of an X–H···Y HB can be measured by the interaction energy between the lone-pair orbital of the HB acceptor, Y, and the σ_{XH}* antibonding orbital of the HB donor.[44] Alternatively, this strength should be reflected in the population of the σ_{XH}* antibonding orbital, because the larger the interaction the greater the charge transfer from the lone pair to the empty orbital. Actually, one of the signatures of the strength of an HB is the lengthening of the X–H bond, triggered by the population of the σ_{XH}* antibonding orbital.

The calculations of local topological properties of the electron charge density at the critical points were performed with the AIM2000 package.[45] The natural bond orbital analysis was performed with the NBO 3.1 program[46] as implemented in the GAUSSIAN 03 programs.[47] All calculations were carried out using the GAUSSIAN 03 suite of programs.[47]

RESULTS AND DISCUSSION

As has been previously reported in the literature, two morpholine conformers, *chair* (**mc**) and *twist* (**mt**) are stable in the gas phase, the **mc** conformer being 26 kJ mol^{-1} more stable than the **mt**, at the B3LYP/6-311 + G(3df,2p)//B3LYP/6–311 + G(d,p) level of theory used in this work.

For the sake of consistency, from now on the different morpholine(water)$_n$ clusters will be named by adding as a prefix to the acronym of the solvated conformer, **mc** or **mt**, a number indicating the number of water molecules included in the cluster. This acronym will be followed by ***a***, ***b***, ***c***. . . to name the different conformers of the cluster in decreasing stability order, hence **4mc–*a*** will designate the most stable tetrahydrated

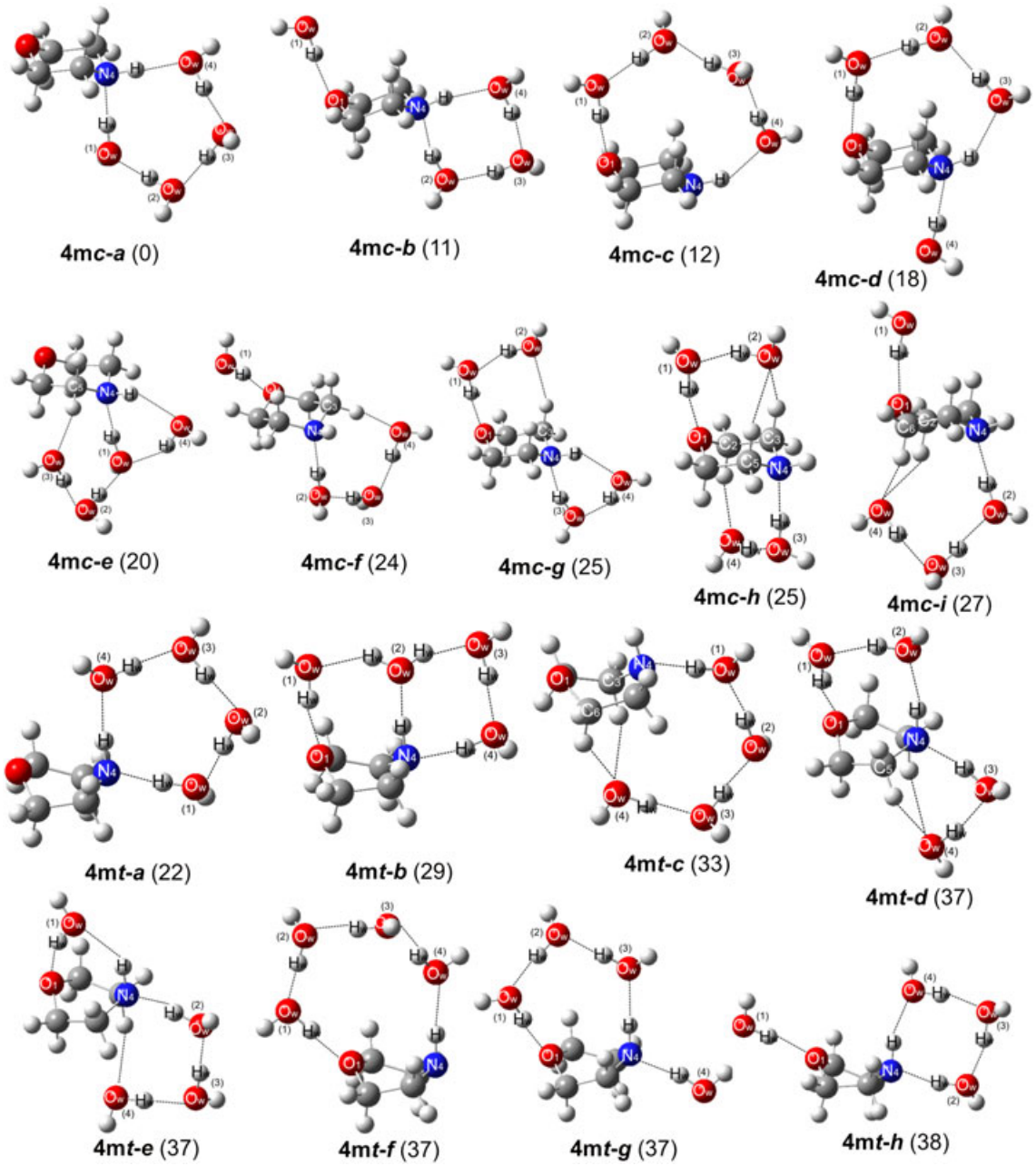

Figure 4. Optimized structures of tetrahydrated complexes of morpholine. Relative energies in kJ mol^{-1} are given within parenthesis

complex of the chair conformer of morpholine, whereas **2mt–a** will name the most stable dihydrated cluster of the twist conformer of this compound.

Monohydrated complexes

As can be easily anticipated, the morpholine monohydrated complexes present three different isomers (see Fig. 1). In two of them the water molecule behaves as an HB donor with respect to NH group (**1mc–a** and **1mt–a**) or the ether oxygen (**1mc–b** and **1mt–b**) of the solute, and a third one in which water behaves as an HB acceptor of the NH group of morpholine (**1mc–c** and **1mt–c**). It is worth noting that in the **1mt–b** isomer, because of the favorable position of the NH group of morpholine, the water molecule behaves simultaneously as an HB acceptor with respect to this group and as an HB donor with respect to the ether oxygen. For both conformers the most stable monohydrated complex corresponds to the one in which the NH group acts as the HB acceptor, in agreement with the Fourier Transform Microwave (FTMW) study of Indris *et al.*,[48] and reflecting the large intrinsic basicity of this functional group, much larger than that of the ether oxygen. Coherently, the less stable complex is that in which the NH group behaves as an HB donor, where the low intrinsic acidity of the NH group coincides with the low intrinsic basicity of the water molecule.

It is worth noting that the HB in complex **1mt–a** is slightly stronger than that in **1mc–a** as indicated by the values of the electron density at the BCP (ρ_b) and the value of δR, and the NBO second-order interaction energies (see Table 1), even though the lengthening of the NH bond is equal in both complexes. This slight difference actually reflects the higher basicity of the *twist* conformer of morpholine, whose proton affinity calculated at the B3LYP/6-311 + G(3df,2p)//B3LYP/6-31 + G(d,p) level of theory is 6.4 kJ mol^{-1} larger than that of the *chair* conformer. This implies that the monohydration of the molecule has a very small effect, less than 2.0 kJ mol^{-1}, on the relative stability of both conformers.

Dihydrated complexes

The most stable conformers of the morpholine dihydrated complexes are shown in Fig. 2. Two types of solvated structures can be recognized, cyclic and noncylic clusters. The latter, namely **2mc–d**, **2mc–f**, and **2mt–f**, correspond to local minima in which the two water molecules do not interact with each other, and only behave as HB donor and HB acceptor of the two active sites of the solute. The formation of the cyclic structures indicates that the two water molecules prefer self-interact, favoring the formation of a larger number of HBs and the appearance of cooperative effects, triggered by the fact that in all these cyclic structures the two water molecules behave simultaneously as HB donors and HB acceptors, with the only exception of **2mc–e**, in which one of the water molecules acts as a bi-donor, which is mirrored in its low relative stability.

The first conspicuous fact is that for the noncyclic clusters, where cooperativity cannot take place, the calculated interaction energy follows a clear additivity rule. For instance the interaction energy for cluster **2mc–d** (49.2 kJ mol^{-1}) is almost equal to the sum of the interaction energies of clusters **1mc–a** and **1mc–b** (48.9 kJ mol^{-1}). Similarly, the interaction energy of **2mc–f** (33.5 kJ mol^{-1}) is close to the sum of the interaction energies of **1mc–b** and **1mc–c** (32.5 kJ mol^{-1}).

For the **mc** conformer among the cyclic structures the most stable one (**2mc–a**) is that in which the NH group of morpholine behaves simultaneously as an HB acceptor and an HB donor with respect to the water dimer. It is important to note that the additive interaction energy amounts to 15.6 kJ mol^{-1} (see Table 2), indicating the great significance of cooperative effects, which should result in a strengthening of the O_w–H_w···N HB. In fact, the δR value, population of antibonding σ_{OH}* orbital, and the second-order interaction energies, $E^{(2)}$ for complex **2mc–a** (see Table 2) are significantly larger than for complex **1mc–a**. Conversely, for the **mt** conformer, the analogues to **2mc–a**, namely **2mt–b**, lies 0.7 kJ mol^{-1} above complex **2mt–a**, in which the water dimer behaves as an HB acceptor of the NH group of morpholine and as an HB donor to its ether oxygen. The

Table 5. Values of the interaction energies (ΔE) for some tetrahydrated complexes as compared with the energy obtained (ΔE_{total}) by adding the interaction energies of the trihydrated (ΔE_t) and monohydrated (ΔE_m), or the dihydrated (ΔE_d , $\Delta E'_d$) clusters in which they can be decomposed. All values in kJ mol^{-1}

Tetrahydrated complex	ΔE	Trihydrated complex	ΔE_t	Monohydrated complex	ΔE_m	ΔE_{total}
4mc–b	125	**3mc–a**	103	**1mc–b**	23	126
4mc–d	119	**3mc–c**	88	**1mc–a**	26	114
4mc–f	113	**3mc–b**	91	**1mc–b**	23	114
4mc–i	109	**3mc–d**	84	**1mc–b**	23	107
4mt–e	126	**3mt–b**	97	**1mt–b**	26	123
4mt–g	125	**3mt–c**	94	**1mt–a**	28	122
4mt–h	125	**3mt–a**	104	**1mt–c**	22	126
Tetrahydrated complex	ΔE	Dihydrated complex	ΔE_d	Dihydrated complex	$\Delta E'_d$	ΔE_{total}
4mc–g	112	**2mc–a**	61	**2mc–c**	52	113
4mc–h	111	**2mc–b**	56	**2mc–c**	52	108
4mt–d	126	**2mt–a**	62	**2mt–c**	61	123
Tetrahydrated complex	ΔE	Trihydrated complex	ΔE_t	Monohydrated complex	ΔE_m	ΔE_{total}
4mc–b	125	**3mc–a**	103	**1mc–b**	23	126
4mc–d	119	**3mc–c**	88	**1mc–a**	26	114
4mc–f	113	**3mc–b**	91	**1mc–b**	23	114
4mc–i	109	**3mc–d**	84	**1mc–b**	23	107
4mt–e	126	**3mt–b**	97	**1mt–b**	26	123

enhanced stability of the structure in which the two water molecules bridge between the two active sites of morpholine, **2mt–*a***, is essentially because of the relative position of the NH group in the *twist* conformation pointing inwards of the six-membered ring. Also interestingly, the second stable complex for the *chair* conformer, **2mc–*b*** corresponds to a structure in which the water dimer HB donates to the NH group of morpholine, and HB accepts from a CH group of the latter. In all these cyclic complexes the cooperative effects measured by the additive interaction energy are rather similar, the largest difference being 0.2 kJ mol^{-1}. Still, the different indexes indicate that the HB's in which the NH acts as an HB acceptor are stronger for the *twist* conformer of morpholine.

Trihydrated complexes

The most stable trihydrated complexes are shown in Fig. 3. The first conspicuous fact is that as in the case of dihydrated species, noncyclic structures, such as **3mc–*h*** are among the less stable. Some of the clusters, namely **3mc–*e***, **3mc–*f***, **3mc–*g***, **3mt–*d***, **3mt–*e***, **3mt–*f***, can be viewed as the result of the solvation of the dihydrated species discussed in the previous section, by a third water molecule, which interacts with an active site nonsolvated in the dihydrated complex. It should be mentioned that in all these cases the additivity of the interaction energies is fulfilled to a large extent, as shown in Table 3.

The remaining structures included in Fig. 3 correspond to cyclic clusters involving the three water molecules. Within these cyclic structures the three water molecules behave simultaneously as HB donors and HB acceptors, enhancing cooperativity. As it was the case for the dihydrated species, the most favorable situation corresponds to that in which the NH group of morpholine behaves simultaneously as an HB donor and an HB acceptor (structures **3mc–*a*** and **3mt–*a***). These two local minima have identical interaction energies (see Table 4), which means that the energy gap between them is identical to the energy gap between the unsolvated conformers. It is worth noting, however, that a closer inspection of the network of HBs, shows that the O_w–H_w···N HB in the *twist* conformation is still stronger than in the *chair* conformation, ratifying similar findings for the monohydrated and dihydrated clusters. This effect is however counterbalanced by the slightly weaker N–H···O_w and

Table 6. Interaction energy (ΔE, kJ mol^{-1}), hydrogen bonds (HBs), HBs lengths (R_{YH}, Å), δR (Å), electron density at the HB critical point (ρ_b, a.u.), population of the σ_{XH}* antibonding orbital (me), NBO second-order interaction energies ($E^{(2)}$, kJ mol^{-1}) and additive interaction energy (E_{add}, kJ mol^{-1}) for some representative tetrahydrated morpholine complexes[a]

Complex	ΔE	HBs	R_{YH}	δR	ρ_b	Population σ_{XH}*	$E^{(2)}$	E_{add}
4mc–*a*	−136.6	O_w–$H_{w(1)}$···N_4	1.770	1.030	0.0479	68	99	72.1
		N_4–H···$O_{w(4)}$	1.971	0.729	0.0240	14	36	
		O_w–$H_{w(2)}$···$O_{w(1)}$	1.731	0.969	0.0407	39	76	
		O_w–$H_{w(3)}$···$O_{w(2)}$	1.762	0.938	0.0370	33	64	
		O_w–$H_{w(4)}$···$O_{w(3)}$	1.772	0.928	0.0366	32	63	
4mc–*c*	−124.7	O_w–$H_{w(1)}$···O_1	1.757	0.943	0.0387	37	61	54.3
		N_4–H···$O_{w(4)}$	2.102	0.598	0.0185	6	19	
		O_w–$H_{w(2)}$···$O_{w(1)}$	1.773	0.927	0.0357	31	60	
		O_w–$H_{w(3)}$···$O_{w(2)}$	1.777	0.923	0.0358	31	61	
		O_w–$H_{w(4)}$···$O_{w(3)}$	1.810	0.890	0.0327	25	50	
4mc–*e*	−116.9	O_w–$H_{w(1)}$···N_4	1.722	1.078	0.0537	80	118	52.2
		N_4–H···$O_{w(4)}$	2.263	0.437	0.0134	0	8	
		C_5–H···$O_{w(3)}$	2.369	0.331	0.0113	1	9	
		O_w–$H_{w(2)}$···$O_{w(1)}$	1.805	0.895	0.0342	29	57	
		O_w–$H_{w(3)}$···$O_{w(2)}$	1.840	0.860	0.0313	24	48	
		O_w–$H_{w(4)}$···$O_{w(1)}$	1.972	0.728	0.0235	15	22	
4mt–*a*	−140.8	O_w–$H_{w(1)}$···N_4	1.741	1.059	0.0511	67	111	72.7
		N_4–H···$O_{w(4)}$	1.951	0.749	0.0255	18	41	
		O_w–$H_{w(2)}$···$O_{w(1)}$	1.726	0.974	0.0411	40	77	
		O_w–$H_{w(3)}$···$O_{w(2)}$	1.746	0.954	0.0391	36	71	
		O_w–$H_{w(4)}$···$O_{w(3)}$	1.776	0.924	0.0363	32	63	
4mt–*b*	−133.6	O_w–$H_{w(1)}$···O_1	1.876	0.824	0.0282	20	32	44.2
		O_w–$H_{w(4)}$···N_4	1.820	0.980	0.0415	51	76	
		N_4–H···$O_{w(2)}$	1.891	0.809	0.0306	26	56	
		O_w–$H_{w(2)}$···$O_{w(1)}$	1.993	0.707	0.0220	12	21	
		O_w–$H_{w(2)}$···$O_{w(3)}$	1.909	0.791	0.0271	20	36	
		O_w–$H_{w(3)}$···$O_{w(4)}$	1.816	0.884	0.0329	28	53	
4mt–*f*	−125.3	O_w–$H_{w(1)}$···O_1	1.748	0.952	0.0380	32	55	57.9
		N_4–H···$O_{w(4)}$	2.024	0.676	0.0211	9	28	
		O_w–$H_{w(2)}$···$O_{w(1)}$	1.756	0.944	0.0371	32	63	
		O_w–$H_{w(3)}$···$O_{w(2)}$	1.757	0.943	0.0381	35	69	
		O_w–$H_{w(4)}$···$O_{w(3)}$	1.798	0.902	0.0342	28	56	

[a]This information for the remaining tetrahydrated clusters is summarized in Table S7.

O_w–$H_{w(3)}$···O HBs, explaining the identical interaction energies for both complexes. Importantly, cooperativity increases with the number of water molecules in the cluster, and whereas for the analogous dihydrated complexes, the E_{add} was around 15 kJ mol^{-1}; for the trihydrated complexes its value is close to 46 kJ mol^{-1} (Table 4). Not surprisingly, for the O_w–H_w···N HB in **3mc–*a*** and **3mt–*a*** the values of ρ_b, δR, and $E^{(2)}$ or the population of the σ_{OH}* antibonding orbital are significantly larger than for **2mc–*a*** and **2mt–*a*** (see Tables 2 and 4).

Also interestingly, for both kinds of conformers, the following stable complexes, namely **3mc–*b*** and **3mt–*b***, which lie about 12 kJ mol^{-1} higher in energy than the global minima, correspond to structures in which the NH group of morpholine behaves only as an HB acceptor, the HB donor to water being a neighbor CH group of the solute. Still ~4 kJ mol^{-1} higher in energy, there are two cyclic clusters (**3mc–*c*** and **3mt–*c***) in which the NH group of morpholine behaves as an HB donor and the ether-like oxygen as an HB acceptor. The relatively low stability of clusters **3mc–*c*** and **3mt–*c***, in which the water molecules bridge between the two active sites of morpholine, is in contrast with the high stability of the dihydrated analogues. As a matter of fact, as we have discussed above, the dihydrated complex in which the water molecules bridge between both active sites of the solute, **2mt–*a*** is slightly more stable than that in which the NH group behaves as HB donor and HB acceptor, **2mt–*b***. This low stability of **3mt–*c*** actually is a consequence of weaker cooperative effects, which are reflected in a value of the additive interaction energy 9 kJ mol^{-1} smaller, and smaller values of the δR values.

Tetrahydrated complexes

The optimized structures of the most stable tetrahydrated clusters for both conformers of morpholine are plotted in Fig. 4. Among them three different types of complexes can be identified: (i) those that correspond to the most stable trihydrated complexes discussed in the previous section, solvated by a fourth water molecule that interacts with the nonsolvated site of morpholine trihydrated complex (**4mc–*b***, **4mc–*d***, **4mc–*f***, **4mc–*i***, **4mt–*e***, **4mt–*g***, **4mt–*h***); (ii) those that may be considered as a result of the combination of two dihydrated clusters (**4mc–*g***, **4mc–*h***, **4mt–*d***); (iii) cyclic structures in which the four water molecules participate in the cycle, behaving simultaneously as HB donors and HB acceptors (**4mc–*a***, **4mc–*c***, **4mt–*a***, **4mt–*c*,** **4mt–*f***), with the only exception of clusters **4mc–*e*** and **4mt–*b***, in which one of the water molecules behave as a double acceptor and as a double donor, respectively.

Similarly to what was found for dihydrated and trihydrated species, for the clusters within the first two groups, the additivity of the interaction energies is fulfilled to a large extent as shown in Table 5.

Among the remaining structures in which the four water molecules are involved in the cycle, once more the most stable correspond to those in which the NH group of morpholine behaves as an HB donor and acceptor (**4mc–*a*** and **4mt–*a***), for which the E_{add} is as large as 72 kJ mol^{-1}, and about 18 kJ mol^{-1} larger than for the other cyclic analogues, in which the four water molecules bridged between the two active sites of the solute (complexes **4mc–*c*** or **4mt–*f***) (Table 6). For the tetrahydrated systems there are two additional structures in which the NH group also behaves as an HB donor and acceptor, namely **4mc–*e*** and **4mt–*b***. However, these structures lie higher in energy than **4mc–*a*** and **4mt–*a***, respectively, because in the former the water molecules behave as a double HB acceptor, and in the latter as a double HB donor, leading to smaller cooperative effects.

Again, cooperativity increases with the number of water molecules, but there is a clear attenuation of the effect. Whereas the ratio between the E_{add} value for trihydrated and dihydrated species is about 3, the ratio between these values for tetrahydrated with respect to trihydrated is only ~1.6. Consistently however the O_w–H_w···N HB in **4mc–*a*** and **4mt–*a*** are the strongest in all the series considered as shown by the calculated values for ρ_b, δR, and $E^{(2)}$ or the population of the σ_{OH}* antibonding orbital (Table 6). Again the O_w–H_w···N HB in the **4mc–*a*** cluster is weaker than in the **4mt–*a*** conformer.

In general, the red-shifting of the X–H stretching frequency of the HB-donor is a good experimental estimation of the strength of the HB. It is worth noting that this is indeed one of the signatures of the global minima of the different hydrated complexes considered, because they nicely reflect the cooperativity effects discussed above and their increase with the number of water molecules. As is illustrated in Table 7 and Table S4, where the most relevant stretching frequencies of the complexes investigated are summarized, the symmetric stretching frequency of the O_wH_w, which acts as an HB donor in the different global minima, is strongly red-shifted with respect to the isolated water molecule. More importantly, this red-shifting increases as the number of water molecules increase being therefore a good probe of cooperative effects. However, because in the global minima for clusters with more than one water molecule, the NH group behaves as HB acceptor but also as HB donor; a red-shifting of the NH stretching frequency is also observed, but the important finding is that again this red-shifting clearly show the importance of cooperativity whereas in the dihydrated complexes the shifting is only 48 cm^{-1}, in the trihydrated and tetrahydrated species increases up to 47 and 72 cm^{-1}, respectively.

Finally, it is worth mentioning that there exists a very good exponential correlation between δR and the electron density at the bond critical point, ρ_b, of the HBs investigated (see Fig. 5). This finding is not surprising because similar correlations have

Table 7. B3LYP/6–311 + G(d,p) calculated harmonic NH and O_wH_w symmetric and antisymmetric stretching frequencies (ν_{NH}, ν_{OH}(sym), ν_{OH}(asym), respectively) for the global minima of the morpholine hydrated species. All values in cm^{-1}

Complex	ν_{NH}[a]	ν_{OH}(sym)[b]	ν_{OH}(asym)[b]
1mc–*a*	3513	3464	3883
1mt–*a*	3512	3469	3885
2mc–*a*	3465	3301	3885
2mt–*b*	3473	3274	3886
3mc–*a*	3406	3108	3882
3mt–*a*	3411	3065	3884
4mc–*a*	3399	3379	3878
4mt–*a*	3386	3363	3882

[a]For the isolated chair and twist conformers of morpholine the value of ν_{NH} 3537 and 3529 cm^{-1}, respectively, at the same level of theory.
[b]For the isolated water molecule the values of ν_{OH}(sym) and ν_{OH}(asym) are 3819 and 3924 cm^{-1}, respectively, at the same level of theory.

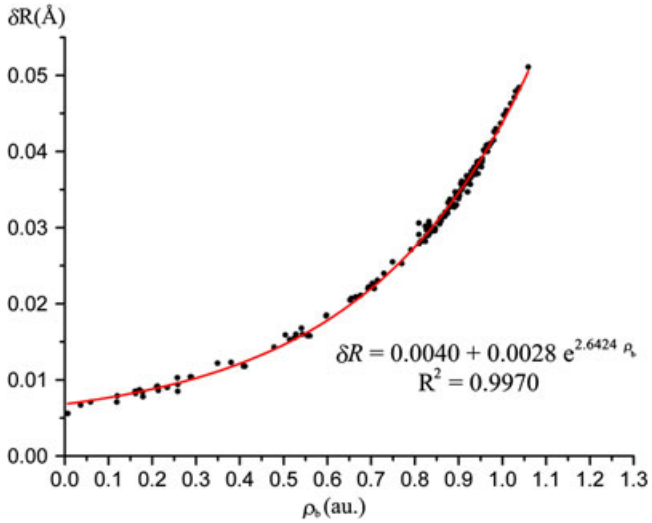

Figure 5. Correlation between δR and ρ_b for the hydrated clusters included in this study

been reported between the length of the HB and ρ_b.[41] The advantage of the correlation shown in Fig. 5 is that it is rather general because it involves HBs that differ in the HB donor, or in the HB acceptor or in both.

CONCLUSIONS

From our survey of the microsolvation of morpholine by up to four water molecules, we can conclude that for all complexes where the number of water molecules is greater than one, cooperative effects are crucial to trace the relative stability of the complexes formed. In all cases water molecules prefer to self-associate forming chains in which each individual molecule behaves as HB donor and HB acceptor. The chain so formed behaves in turn as HB donor and HB acceptor with respect to morpholine, being the most stable arrangements those in which the NH group of morpholine behaves simultaneously as HB donor and HB acceptor. Hence, although morpholine is a bidentate base, the most stable clusters, independently of the number of water molecules involved correspond systematically to those in which only the imino group is solvated. Higher in energy lie complexes in which the HB acceptor continues to be the NH group, but the HB donor is a CH group, or alternative structures in which the HB acceptor is the ether-like oxygen of morpholine and the HB donor its NH group.

Cooperativity increases with the number of solvent molecules, but there is a clear attenuation effect. Thus, whereas the additive interaction energy on going from dihydrated to trihydrated species increases by a factor of 3, this increase is about half on going for trihydrated to tetrahydrated complexes.

These cooperative effects render the O_w–H_w···N HB in the tetrahydrated species significantly stronger than in smaller clusters, and are nicely mirrored in the red-shifting of both the NH and O_wH_w stretching frequencies. Interestingly, because the NH group behaves simultaneously as an HB donor, the NH stretching frequency is also significantly red-shifted, this shifting being larger the larger are the cooperative effects. This means that in these clusters not only the O_wH_w but also the NH red-shifting should be a good experimental probe of cooperative effects.

For those clusters that can be viewed as a combination of clusters of smaller size, an almost perfect additivity scheme is followed, so the interaction energy of the larger clusters can be estimated with a rather small error, by adding the interaction energies of the smaller clusters in which it can be decomposed. A good correlation exists between the δR index and the electron density at the BCP of the different HBs investigated.

SUPPORTING INFORMATION

Supporting Information may be found in the online version of this article.

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