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Published on Web 08/25/2006

Microsolvation of Formamide: A Rotational Study

Susana Blanco, Juan C. López,* Alberto Lesarri, and José L. Alonso

Contribution from the Grupo de Espectroscopía Molecular (GEM), Departamento de Química Física y Química Inorgánica, Facultad de Ciencias, Universidad de Valladolid, 47005 Valladolid, Spain

Received March 17, 2006; E-mail: jclopez@qf.uva.es

Abstract: Microsolvated formamide clusters have been generated in a supersonic jet expansion and characterized using Fourier transform microwave spectroscopy. Three conformers of the monohydrated cluster and one of the dihydrated complex have been observed. Seven monosubstituted isotopic species have been measured for the most stable conformer of formamide$\cdots H_2O$, which adopts a closed planar ring structure stabilized by two intermolecular hydrogen bonds (N—H$\cdots$O(H)—H$\cdots$O=C). The two higher energy forms of formamide$\cdots H_2O$ have been observed for the first time. The second most stable conformer is stabilized by a O—H$\cdots$O=C and a weak C—H$\cdots$O hydrogen bond, while, in the less stable form, water accepts a hydrogen bond from the anti hydrogen of the amino group. For formamide$\cdots (H_2O)_2$, the parent and nine monosubstituted isotopic species have been observed. In this cluster the two water molecules close a cycle with the amide group through three intermolecular hydrogen bonds (N—H$\cdots$O(H)—H$\cdots$O(H)—H$\cdots$O=C), the nonbonded hydrogen atoms of water adopting an up–down configuration. Substitution (r_s) and effective (r_0) structures have been determined for formamide, the most stable form of formamide$\cdots H_2O$ and formamide$\cdots (H_2O)_2$. The results on monohydrated formamide clusters can help to explain the observed preferences of bound water in proteins. Clear evidence of σ-bond cooperativity effects emerges when comparing the structures of the mono- and dihydrated formamide clusters. No detectable structural changes due to π-bond cooperativity are observed on formamide upon hydration.

Introduction

The evolution of molecular properties from isolation to solution is a central subject to Chemistry since solvation can affect the structure, function, and reactivity of chemical species. Many phenomena controlled by the subtle noncovalent interaction forces responsible for solvation can be found in the field of biomolecules. Molecular shape and protein folding,[1] charge stabilization,[2] and conformational[3] and tautomeric[4,5] equilibria constitute only a few examples. Understanding the role of these forces at the molecular level is a formidable task which requires the isolation of molecules from their condensed phase environment and their study in gas phase with varying degrees of hydration. The environment in which an isolated molecule is associated with a defined number of water molecules is usually called microsolvation and can be created in a supersonic jet.[6] The expansion of a gas mixture of the solute and water diluted in a light carrier gas into a high vacuum allows the production of such microsolvated clusters, which are frozen in the postexpansion collisionless flow regime and can be monitored by spectroscopic means in conditions of virtual isolation. Rotational spectroscopy is ideal for this purpose since it has an inherent high resolution and it is exceptionally sensible to the molecular mass distribution and geometry. As a consequence, it can provide very detailed structural information even when there are several coexisting species in the jet, like isomers, conformers, or isotopomers.

Water is an essential component of macromolecular biological systems. The crystals of proteins resemble highly concentrated solutions where 20% to 50% of the crystal volume can be occupied by water molecules.[7] Its small size and double-donor double-acceptor capacities give water a peculiar flexibility to form a variety of hydrogen bonds. Bound water molecules have been observed inserted between the carbonyl and amino groups in α-helices and involved in different turns and folding processes.[8] A detailed survey in globular proteins[9] revealed that water molecules can establish hydrogen bonds to the main chain through the C=O and N—H groups of the peptide unit or to the side chains through other polar groups. Bound water molecules were found to be linked to the peptide carbonyl

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10.1021/ja0618393 CCC: $33.50 © 2006 American Chemical Society

groups in a proportion (42%) comparable to that found for the side chains (44%). In contrast, a low percentage (14%) of water molecules was found to hydrate the peptide amino groups. The preference of water to be bound to peptide oxygen atoms was attributed[9] to several factors, including the ability of carbonyl oxygen to form more than one hydrogen bond, the less stringent geometrical constraints of carbonyl groups as acceptors compared to the amino groups as donors and the tendency of water molecules to act as proton donors. This contrasts with the results of gas-phase investigations on water clusters which indicate that water is stronger as a proton acceptor (i.e., base) than as a proton donor (i.e., acid).[7b] Gas-phase investigations of microsolvated model systems carrying the peptide group but without the restrictions imposed by the protein structure are of interest to explain the observed preferences of bound water in proteins.

Formamide (NH_2COH) can be considered as a prototype substrate for such gas-phase studies since it can establish the same hydrogen bond interactions with water as the backbone of proteins. Previous microwave[10] and infrared[11] studies of monohydrated formamide detected only the most stable conformer (Ia in Figure 1) in which water is simultaneously acting as a proton donor to the carbonyl group oxygen atom and as a proton acceptor from the amino group, bridging the peptide functional group in a close cyclic structure. This conformer can be taken as a model for the interactions of water with the *cis*-peptide group. However, in nature the amide links within peptides have mostly trans arrangements, with the amino and carbonyl groups opposing each other. In such cases water could form hydrogen bonds through either the carbonyl or the amino groups as they occur for formamide$\cdots H_2O$ complexes Ib and Ic of Figure 1, formed through $C{=}O\cdots H{-}O$ or $NH\cdots O$ interactions, respectively. These conformers have been predicted[12] to have much higher energy ($>$10 kJ mol^{-1}) with respect to the Ia global minimum and have never been observed. The present work was addressed to the experimental observation of all these conformers of formamide$\cdots H_2O$ to obtain structural information through the analysis of their rotational spectra.

Hydrogen bond cooperativity has been identified as one important factor contributing to the stabilization of hydrated biomolecules.[12] σ-Bond cooperativity is associated to chains or cycles of hydrogen bonds between OH or any other group acting simultaneously as donor and acceptor.[7] Sequential cycles, also called homodromic, are particularly stable and characterized by a shortening of the hydrogen bond distances and an increase of hydrogen bond energy.[13] In this context both conformer Ia of monohydrated formamide (see Figure 1) and the predicted global minimum of dihydrated formamide[12] (see Figure 2) can be considered as models of sequential cycles. A comparison of the hydrogen bond structures in these two systems may provide interesting information about the extension of σ-bond cooperativity effects. In addition π-bond cooperativity[7] in the amide group should cause a polarization of the electron distribution, enhancing its donor/acceptor capabilities. In the conventional valence bond description, solvation by a water bridge should favor the ionic resonant form ($H_2N^+{=}CO^-H$) of formamide, and the possible effects of the polarization of the electron distribution could be detectable as small changes in the $C{-}N$ and $C{=}O$ bond lengths (Chart 1). Despite the fact that the pure rotational spectra of dihydrated clusters have been observed only in a few exceptional cases,[14] we could extend our study of the microsolvated formamide clusters to the formamide$-(H_2O)_2$ complex. Aiming to observe possible structural changes due to the effects of both σ- and π-bond cooperativities, detailed information on the structure of formamide, formamide$\cdots H_2O$, and formamide$\cdots(H_2O)_2$ has been obtained.

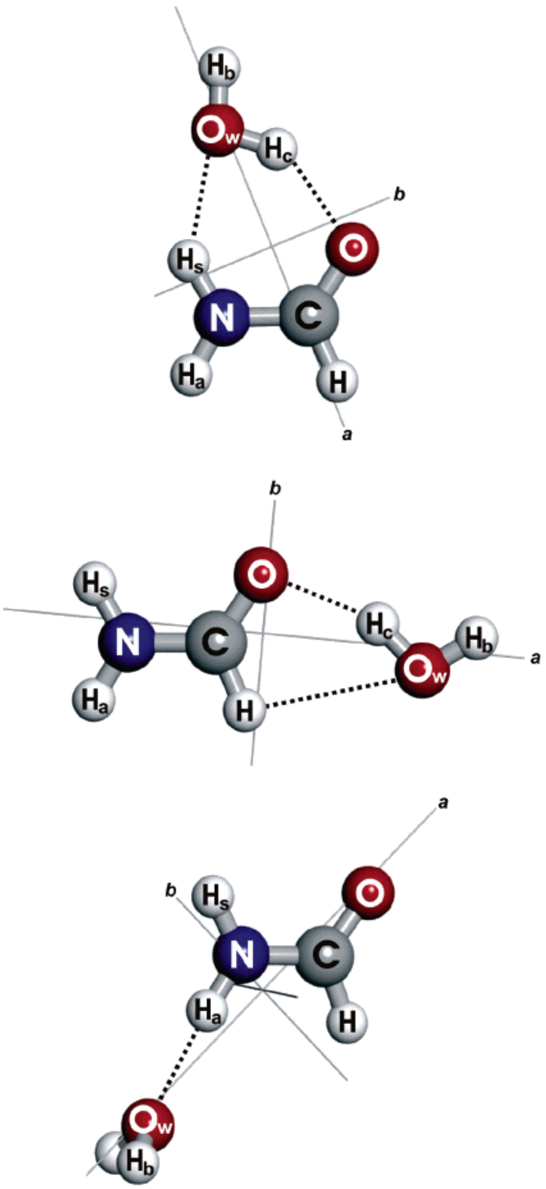

Figure 1. Conformers Ia (up), Ib (center), and Ic (down) of formamide$\cdots H_2O$ in their principal inertial axis system.

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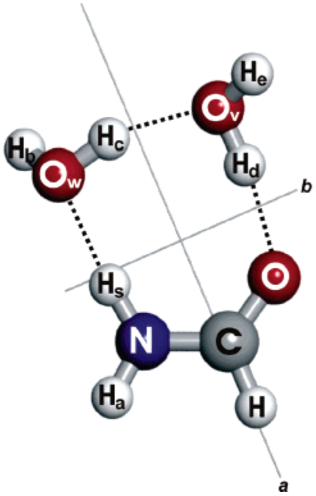

Figure 2. Conformer IIa of formamide···$(H_2O)_2$.

Experimental and Theoretical Methods

The molecular-beam Fourier transform microwave spectrometer (MB-FTMW), already described elsewhere,[15] was operated in the frequency range 6−22 GHz. In this instrument a supersonic jet is generated by expansion of a gas mixture through a small (0.8 mm diameter) pulsed nozzle into the evacuated region between two 55 cm confocal spherical mirrors forming a microwave Fabry−Pérot resonator. The sample of formamide, a viscous liquid with a boiling point of ca. 210 °C, its ^{13}C and ^{15}N enriched samples, and an enriched sample of ^{18}O-water were obtained commercially. The monodeuterated derivatives of formamide or water were produced by mixing these compounds with D_2O. To produce a jet expansion with enough concentration of formamide, the sample was placed in a heatable nozzle previously described[16] and heated to ∼50 °C. Neon at backing pressures of ∼1−1.5 bar was used as carrier gas for the observations of formamide and its isotopomers. The clusters with water were generated by inserting a water reservoir in the carrier gas line just before the nozzle and using higher (5−7 bar) backing pressures. After the supersonic expansion is formed, a very short (typically 0.3 μs, 10−300 mW) microwave pulse polarizes the species in the jet. The subsequent coherent transient emission due to molecular decay to equilibrium is later recorded in the time domain. Typically a ca. 400 μs length time domain spectrum is recorded in 40−100 ns intervals. The frequency domain spectrum is reconstructed with a Fourier transformation of the free-induction decay, which yields the resonant frequencies of the rotational transitions. Due to the collinear arrangement of the jet and resonator axis, each rotational transition is split in two Doppler components so the resonant frequencies are taken as the arithmetic mean of both components. The frequency accuracy is better than 3 kHz.

Prior to collection of the spectra on the microsolvated formamide cluster, the lines of formamide[17] and the water dimer[18] were monitored. To obtain intense spectra of formamide it was found necessary to distillate the used samples by passing the carrier gas through the heatable nozzle for about 1 h before starting measurements. Given this problem we could only employ the reduced amounts of enriched isotopic samples in the investigation of the species having the most intense spectra, namely formamide, formamide···H_2O, conformer Ia, and formamide···$(H_2O)_2$.

We extended the previous ab initio quantum mechanical calculations[12] on mono- and dihydrated formamide to predict the molecular properties relevant to the interpretation of the rotational spectra of the plausible conformers, like the rotational and ^{14}N nuclear quadrupole coupling constants and the electric dipole moments. The results of the new calculations, conducted with second-order Møller−Plesset perturbation theory and a Pople's 6-311++G(d,p) basis set,[19] are shown in Table 1. The counterpoise procedure, including fragment relaxation energy terms,[20] was used to correct the dissociation energies D_e for the basis set superposition error (BSSE).

Rotational Spectra and Structure

1. Formamide. The rotational spectra of bare formamide for the parent and enriched isotopic species were observed before investigating their water adducts. In this way, the rotational spectra of the parent, $NH_2-^{13}COH$, $^{15}NH_2-COH$, ND_sH_a-COH, and NH_sD_a-COH species of bare formamide were measured with the high accuracy provided by the MB-FTMW technique. A Watson's semirigid rotor Hamiltonian[21] in the asymmetric reduction and I^r representation, plus a term to account for the ^{14}N hyperfine structure,[22,23] was used to derive the rotational parameters and ^{14}N nuclear quadrupole coupling constants. For the parent species the observed frequencies were fitted together with those previously reported.[17c] Each line was given the weight $1/\delta^2$ according to the estimated accuracies: $\delta = 5$ kHz for the new measurements, $\delta = 0.1$ MHz for the previously reported hyperfine components, and $\delta = 0.5$ MHz for the nonresolved frequency centers. For other isotopic species the observed frequencies were fitted with the centrifugal distortion constants fixed to the parent species values. The obtained rotational parameters are collected in Table 2. The accuracy of the new parameters is improved with respect to those previously reported, and in addition the rotational constant A is now given for the ^{13}C species.

The new sets of rotational constants were combined with those previously reported[17] for isotopomers such as $NH_2-C^{18}OH$ and NH_2-COD to calculate the r_s and r_0 structures of formamide shown in Table 3. It was assumed that the molecule is planar as indicated by the values of the planar moment P_c ($= (I_a + I_b - I_c)/2 = \Sigma_i\, m_i\, c_i^2$), which gives the mass extension out of the *ab* inertial plane. All of them are close to zero, indicating that the substituted atoms are close to the *ab* inertial plane and thus that formamide is essentially planar. The r_s structural analysis was based on the Kraitchman substitution method,[24,25] which provides the squared coordinates of the substituted nuclei in the principal inertial axis system of the normal species. The substitution coordinates, calculated for each atom independently from differences in the moments of inertia of the substituted and reference species, are conceived to partially cancel the zero-point vibrational effects on the moments of inertia. The absolute values of these coordinates

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Chart 1. Possible Structural Distortions of Formamide upon Hydration Due to σ- or π-Bond Cooperativity

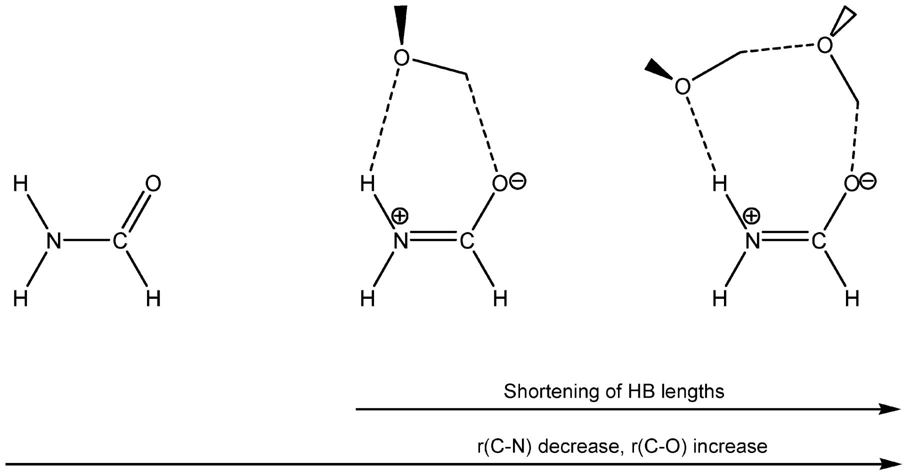

Table 1. Ab Initio (MP2/6-311++G(d,p)) Molecular Properties of the 1:1 and 1:2 Clusters of Formamide and Water

	formamide··H_2O			formamide···$(H_2O)_2$
	Ia	Ib	Ic	IIa
	Rotational Constants			
A/MHz	11 076	25 971	35 288	4405
B/MHz	4621	2685	2073	2645
C/MHz	3275	2438	1979	1663
	^{14}N Nuclear Quadrupole Coupling Constants[a]			
χ_{aa}/MHz	1.38	2.05	1.60	1.09
χ_{bb}/MHz	2.19	1.91	2.01	2.19
χ_{cc}/MHz	−3.57	−3.96	−3.62	−3.27
	Electric Dipole Moment[b]			
μ_a/D	0.85	3.52	7.22	0.89
μ_b/D	−2.07	1.17	−0.27	−1.76
μ_c/D	−0.38	−1.33	−0.23	−0.46
μ_{total}/D	2.27	3.94	7.23	2.02
	Energies			
ΔE/kJ mol^{-1}	0.	10.7	12.6	
D_e/kJ mol^{-1}	35.5	24.5	20.4	75.6

[a] Only diagonal tensor elements are given. [b] 1 D ≈ 3.3356 × 10^{-30} C m.

given in Table 3 are only consistent with reasonable structures for this molecule. The sign ambiguities for larger coordinates were easily resolved by inspection, while for the small coordinates the chosen signs were those yielding the most reasonable r_s bond lengths and angles. It is well-known that the errors derived from those of the rotational constants are low compared with possible errors arising from vibration−rotation contributions. For that reason the uncertainties, δz_i, in Table 3 were calculated according to Costain formula[25] $\delta z_i = 0.0012/|z_i|$ Å, which takes into account this fact and gives more realistic errors.

Alternatively, the effective (r_0) structure[26] of the complex was also determined from a least-squares fit of all known experimental rotational constants to determine the r_0 parameters given in Table 3.

2. Formamide···H_2O: Conformer Ia. The rotational spectrum of the parent species of conformer Ia of formamide···H_2O, already reported,[10] was used to optimize the experimental conditions. To obtain more accurate structural information on this conformer we have studied the rotational spectra of seven new isotopomers, namely $^{15}NH_2{-}COH\cdots H_2O$, $NH_2{-}{}^{13}COH\cdots H_2O$, $ND_sH_a{-}COH\cdots H_2O$, $NH_sD_a{-}COH\cdots H_2O$, $NH_2{-}COH\cdots H_2{}^{18}O_w$, $NH_2{-}COH\cdots H_bD_cO$, and $NH_2{-}COH\cdots D_bH_cO$ (notation in Figure 1), which were assigned on the basis of predicted isotopic shifts. The spectra of all the species with ^{14}N ($I = 1$) and D ($I = 1$) show the hyperfine structure due to the nuclear quadrupole coupling interaction originated by those nuclei. The small hyperfine effects due to the deuterium atom were not considered. The same Hamiltonian described for formamide was used to derive the rotational parameters and ^{14}N nuclear quadrupole coupling constants for the new species. These constants along with those reported previously for the parent species[10] are shown in Table 4.

Lovas et al.[10] investigate the planarity and hydrogen bond parameters of this conformer from the rotational constants of only the parent species following an effective structure (r_0) procedure. The rotational constants of the isotopomers investigated in the present work have allowed us to investigate the substitution structure (r_s) of the complex and to improve the effective structure. In agreement with the previous work,[10] the planarity of conformer Ia of formamide···H_2O can be deduced from the values planar moment P_c. As can be seen in Table 4, all the P_c values are nearly zero, indicating that the substituted atoms are close to the *ab* inertial plane and thus that this complex is essentially planar. The small increase of the planar moments with respect to bare formamide can be attributed to zero-point vibrational effects due to intermolecular motions. The slightly larger P_c value for the $NH_2{-}COH\cdots(D_bH_cO)$ isotopomer reveals that the atom of water not involved in the intermolecular hydrogen bond can be out-of-plane or involved in a large amplitude intermolecular out-of-plane vibration. The nuclear coordinates and the substitution structure (r_s) of conformer Ia of formamide···H_2O, calculated following the same procedure described above, are shown in Table 5. The poor reliability of the r_s coordinates, due to zero-point vibrational effects, becomes apparent for atoms lying near the inertial axes. This is the reason for the imaginary *c* coordinate of atoms C, N, and O_w, which were set to zero taking into account that these atoms should be close to the *ab* plane. The structural parameters involving the oxygen atom of formamide in the complex were taken from the structure of bare formamide given in Table 3. The effective (r_0) hydrogen bond parameters[26] of the complex were also

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Table 2. Rotational Parameters of Formamide

	NH_2–COH	NH_2–^{13}COH	$^{15}NH_2$–COH	ND_sH_a–COH	NH_sD_a–COH
A^a/MHz	72 716.8847(62)[g]	71 058.2060(88)	72 449.71270 (14)	61 345.5960(81)	71 180.7824(59)
B/MHz	11 373.5814(11)	11 372.5603(16)	11 054.53489(25)	11 009.9115(14)	10 473.4299(11)
C/MHz	9833.8812(11)	9801.8861(16)	9589.817 12(25)	9334.0837(14)	9132.3741(11)
$P_c{}^b$/u Å^2	−0.003 596(5)	−0.004 362(8)	−0.003 534(1)	−0.001 492(8)	0.007 047(6)
$\Delta_J{}^c$/kHz	7.977(26)	[7.977][h]	[7.977]	[7.977]	[7.977]
Δ_{JK}/kHz	−68.96(48)	[−68.96]	[−68.96]	[−68.96]	[−68.96]
Δ_K/kHz	1402.1(18)	[1402.1]	[1402.1]	[1402.1]	[1402.1]
δ_J/kHz	1.5734(10)	[1.5734]	[1.5734]	[1.5734]	[1.5734]
δ_K/kHz	35.882(57)	[35.882]	[35.882]	[35.882]	[35.882]
$\chi_{aa}{}^d$/MHz	1.9613(34)	1.9663(84)		1.9723(70)	1.9947(52)
χ_{bb}/MHz	1.8925(51)	1.8979(99)		1.902(10)	1.9084(90)
χ_{cc}/MHz	−3.8538(51)	−3.8642(99)		−3.875(10)	−3.9004(90)
σ^e/kHz	5.0	5.6	0.5	6.0	3.8
N^f	20	12	4	15	9

[a] A, B, C represent the rotational constants. [b] Planar moment $P_c = (I_a + I_b - I_c)/2 = \Sigma_i m_i c_i^2$. [c] Δ_J, Δ_{JK}, Δ_K, δ_J, δ_K are the quartic centrifugal distortion constants. [d] $\chi_{\alpha\beta}$ ($\alpha,\beta = a$, b, or c) are ^{14}N nuclear quadrupole coupling parameters. [e] rms deviation of the fit. For the parent molecule this corresponds to the lines measured in this work. The rms of the fit including the transitions reported in ref 17c is 128 kHz. [f] Number of fitted transitions. For the parent molecule this corresponds to the lines measured in this work. In this case a total of 83 transitions including those reported in ref 17c were fitted. [g] Standard error in parentheses in units of the last digit.

Table 3. Substitution Coordinates of Formamide from the Rotational Data of Table 2 and Derived Substitution (r_s) and Effective (r_0) Structures of Formamide

atom[a]	a	b	c
C	+0.069(17)[b]	+0.4075(29)	[0.000][c]
N	−1.1462(11)	−0.1646(73)	[0.000]
H_s	−1.1991(10)	−1.1653(10)	[0.000]
H_a	−1.963 36(61)	+0.3949(30)	[0.000]

	r_s	r_0
r(C=O)/Å	1.23(2)[d,e]	1.230(9)
r(C−N)/Å	1.34(2)	1.345(8)
r(N−H_s)/Å	1.002(8)	0.998(4)
r(N−H_a)/Å	0.990(7)	1.025(7)
r(C−H)/Å	1.106(4)[e]	[1.106][f]
∠(C−N−H_s)/deg	118.2(9)	118.8(6)
∠(C−N−H_a)/deg	120(1)	119.5(3)
∠(N−C=O)/deg	124.8(9)[e]	124.52(8)
∠(N−C−H)/deg	116(2)[e]	[116][f]

[a] Atom labeling as in Figure 1. [b] Error in parentheses in units of the last digit estimated according to Costain.[25] [c] Coordinates in square brackets constrained to zero. [d] Error in parentheses in units of the last digit. For the r_0 parameters these are standard errors calculated taken into account estimated errors of 0.004 Å for r(C−H) and 2° for ∠(N−C−H). [e] Derived from the data reported in ref 17b. [f] Fixed to the corresponding r_s value.

determined from a least-squares fit of the 24 experimental rotational constants of Table 4. In this fit the parameters of both monomers were assumed unperturbed and kept fixed to their isolated r_0 values (see Table 3).[27] The obtained effective structural parameters, also collected in Table 5, are consistent with those derived from the r_s coordinates and improve the r_0 structure previously determined for this conformer.[10] The errors introduced into the r_0 structural parameters by assuming unchanged monomer geometries in the complex were estimated from the ab initio predicted structural changes to be roughly one order of magnitude larger than the quoted standard errors.

3. Formamide···H_2O: Conformer Ib. Once the transitions of the most stable conformer of formamide···H_2O and its isotopomers were assigned we surveyed the microwave spectrum searching for the spectra of the other two higher-energy conformers of the 1:1 cluster labeled as Ib and Ic in Figure 1. A detailed search for the characteristic μ_a-type R-branch transitions around the predictions for the carbonyl-bonded Ib conformer allowed us to identify the $2_{0,2} \leftarrow 1_{0,1}$, $3_{0,3} \leftarrow 2_{0,2}$, and $3_{1,3} \leftarrow 2_{1,2}$ transitions of this new formamide···H_2O form. These measurements were extended to other μ_a-type R-branch transitions with $K_{-1} = 0$, 1 below 21 GHz. The spectrum of this new conformer was very weak compared to that of the Ia conformer. A notable decrease in the intensity of the observed transitions was observed in passing from $K_{-1} = 0$ to $K_{-1} = 1$ lines. This is probably due to rotational cooling given the large value of the A rotational constant. All observed transitions exhibited the expected ^{14}N nuclear quadrupole coupling hyperfine structure. Additionally, the hyperfine components of the transitions $3_{1,2} \leftarrow 2_{1,1}$, $4_{1,4} \leftarrow 3_{1,3}$, and $4_{1,3} \leftarrow 3_{1,2}$ appeared split into resolved doublets with separations of ca. 15−25 kHz (Figure 3). These small splittings could be originated by rotational transitions from two very close vibrational sublevels. Considering this possibility, separate fits for each substate to the same Hamiltonian described for formamide were done. These fits gave practically the same parameters so we constrained all spectroscopic constants to have the same values in both states except for the B and C rotational constants. The final results are collected in Table 6. Due to the weak rotational spectrum, no minor isotopomers could be measured for conformer Ib of formamide···H_2O. An unequivocal identification of the new species as the carbonyl-bonded conformer Ib resulted from the excellent agreement between the experimental rotational and nuclear quadrupole constants with the predicted values ab initio (Table 1). The utility of the nuclear quadrupole coupling constants to discriminate between different conformers has been emphasized in the study of other multiconformer systems.[28]

The value of the planar moment P_c of formamide−H_2O Ib is also close to zero indicating that this conformer is nearly planar. Its effective structure was derived from a fit of the rotational constants of Table 6 by assuming a planar structure with the parameters of both formamide (see Table 3) and water[27] fixed

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(27) Harmony, M. D.; Laurie, V. W.; Kuczkowski, R. L.; Schwendeman, R. H.; Ramsey, D. A.; Lovas, F. J.; Lafferty, W. J.; Maki, A. G. *J. Phys. Chem. Ref. Data* **1979**, *8*, 619.

(28) (a) Lesarri, A.; Cocinero, E. J.; López, J. C.; Alonso, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 605. (b) Blanco, S.; Lesarri, A.; López, J. C.; Alonso, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 11675. (c) Lesarri, A.; Cocinero, E. J.; López, J. C.; Alonso, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2572.

Table 4. Rotational Parameters for Conformer Ia of the Complex Formamide···H_2O

	parent[b]	$NH_2-^{13}COH$ ···(H_2O)	$^{15}NH_2-COH$ ···(H_2O)	ND_sH_a-COH ···(H_2O)	NH_sD_a-COH ···(H_2O)	NH_2-COH ···($H_2{}^{18}O$)	NH_2-COH ···(D_bH_cO)	NH_2-COH ···(H_bD_cO)
A[a]/MHz	11 227.9330(23)[c]	11 224.4801(33)	10 925.1667(27)	10 844.4309(24)	10 419.4158(49)	11 221.9584(35)	11 191.9592(21)	11 140.3424(36)
B/MHz	4586.9623(16)	4528.4531(13)	4565.9951(10)	4588.54771(69)	4514.1426(14)	4286.04140(99)	4287.0567(14)	4520.038 65(10)
C/MHz	3258.8277(12)	3228.9331(11)	3222.31874(95)	3226.771 12(64)	3151.8641(13)	3103.508 98(94)	3105.3851(14)	3218.021 44(10)
P_c/u Å^2	0.054 070(52)	0.054 865(49)	0.052 196(40)	0.060 591(29)	0.057 643(62)	0.053 219(45)	0.148 803(60)	0.063 411(11)
Δ_J/kHz	7.844(70)	[7.844][e]	[7.844]	[7.844]	[7.844]	[7.844]	[7.844]	[7.844]
Δ_{JK}/kHz	24.24(48)	[24.24]	[24.24]	[24.24]	[24.24]	[24.24]	[24.24]	[24.24]
Δ_K/kHz	[0.0][d]	[0.0]	[0.0]	[0.0]	[0.0]	[0.0]	[0.0]	[0.0]
δ_J/kHz	2.728(58)	[2.728]	[2.728]	[2.728]	[2.728]	[2.728]	[2.728]	[2.728]
δ_K/kHz	[0.0]	[0.0]	[0.0]	[0.0]	[0.0]	[0.0]	[0.0]	[0.0]
χ_{aa}/MHz	1.3321(37)	1.3377(69)		1.3571(36)	1.3653(73)	1.3391(52)	1.3457(31)	1.3493(64)
χ_{bb}/MHz	2.0371(20)	2.0334(64)		2.0381(20)	2.0485(41)	2.0271(28)	2.0333(17)	2.0413(26)
χ_{cc}/MHz	−3.3693(96)	−3.371(26)		−3.3951(96)	−3.415(20)	−3.366(14)	−3.3791(81)	−3.391(14)
σ/kHz		4.9	2.6	3.9	8.2	5.7	6.6	6.0
N		15	5	21	21	21	21	21

[a] Parameter definition as in Table 2. [b] Rotational parameters of the parent species taken from ref 10. [c] Standard error in parentheses in units of the last digit. [d] Fixed to zero. [e] Values in square brackets were kept fixed to those given for the parent species in ref 10.

Table 5. Substitution Coordinates of Conformer Ia of Formamide···H_2O from the Rotational Data of Table 4 (Atom Labeling as in Figure 1), and Derived Substitution (r_s) and Effective (r_0) Molecular Structures

atom[a]	a	b	c
C	−1.2001(10)[b]	−0.1162(103)	[0.0][c]
N	−0.7124(17)	+1.1326(11)	[0.0]
H_s	+0.2096(57)	+1.26468(95)	+0.082(14)
H_a	−1.30190(92)	+1.90227(63)	−0.062(19)
O_w	+1.99529(60)	+0.1195(10)	[0.0]
H_b	+2.77013(43)	−0.2371(51)	+0.3200(37)
H_c	+1.27628(94)	−0.5971(20)	+0.098(12)

	r_s	r_0
r(C═O)/Å[a]	[1.23][d]	[1.230]
r(C—N)/Å	1.34(2)[e]	[1.345]
r(N—H_s)/Å	0.939(9)	[0.998]
r(N—H_a)/Å	0.971(6)	[1.025]
r(O_w—H_b)/Å	0.91(3)	[0.965]
r(O_w—H_c)/Å	1.02(1)	[0.965]
r(H_s···O_w)/Å	2.14(1)	2.061(4)
r(H_c···O)/Å	1.875(3)[f]	1.93(1)
∠(C—N—H_s)/deg	119.6(6)	[118.8]
∠(C—N—H_a)/deg	121(1)	[119.5]
∠(N—C═O)/deg	[124.8]	[124.52]
∠(H_b—O_w—H_c)/deg	107(3)	[104.8]
∠(N—H_s···O_w)/deg	136.5(8)	139.5(3)
∠(H_s···O_w—H_c)/deg	78(6)	78.2(6)
∠(O_w—H_c···O)/deg	151(2)[f]	153(1)
∠(H_c···O═C)/deg	107.0(6)[f]	110.3(3)
τ(H_b—O_w—H_c—H_s)/deg	155(6)	165(1)

[a] Atom definition as in Figure 1. [b] Errors in parentheses in units of the last digit estimated according to Costain.[25] [c] Coordinates calculated to have imaginary values were assumed to be zero. [d] Assumed structural parameters in square brackets. Values for formamide are taken from the corresponding column in Table 3. The r_0 values for water taken from ref 27. [e] Error in parentheses in units of the last digit. For the r_0 parameters these are standard errors. [f] Derived values.

to their r_0 values. The relative position of both monomers in the complex is then defined by a distance and two angles. Since only three rotational constants are available the r(H···O_w) distance and the ∠(O_w···HC) angle (see Figure 1 for notation) were fitted while ∠(H_cO_w···H) was fixed to the ab initio value. The derived effective structure is presented in Table 7.

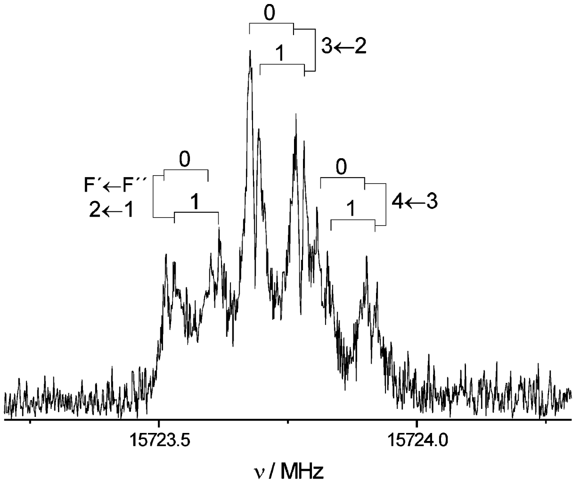

Figure 3. The $3_{1,2}-2_{1,1}$ rotational transition of conformer Ib of formamide···H_2O. The three hyperfine components due to the ^{14}N nuclear quadrupole coupling interaction (labeled with quantum numbers $F' \leftarrow F''$, $F = I + J$) present small tunneling splittings (labeled arbitrary 0 and 1) separated less than 25 kHz. Each line is observed as a doublet due to the Doppler effect.

Table 6. Rotational Parameters for Conformer Ib of the Complex Formamide···(H_2O), with Substates Labeled Arbitrarily as 0 and 1

	0	1
A/MHz [a]	26 170.8(61)[b]	
B/MHz	2682.976 53(65)	2682.978 37(68)
C/MHz	2433.849 92(64)	2433.849 00(63)
P_c/u Å^2	0.015(2)	
Δ_J/kHz	7.620(15)	
Δ_{JK}/kHz	−0.297 06(38)	
Δ_K/kHz	[0.0][c]	
δ_J/kHz	1.3691 (133)	
δ_K/kHz	[0.0]	
χ_{aa}/MHz	1.8625(22)	
χ_{bb}/MHz	1.7393(39)	
χ_{cc}/MHz	−3.6018(39)	
σ/kHz	3.3	
N	66	

[a] Parameter definition as in Table 2. [b] Standard error in parentheses in units of the last digit. [c] Parameters in square brackets were kept fixed in the fit.

The small splitting observed for some transitions of this conformer could arise from a two-fold potential well situation with an energy barrier of considerable height. Since the hydrogen atom H_b has an out of plane equilibrium position above and below the plane ab, it could give rise to a double minimum potential function. However, the near zero value of

Table 7. Effective Structure for Conformer Ib of Formamide···H_2O, Derived from the Rotational Parameters of Table 6

parameter[a]	r_0
$r(O_w\cdots H)$/Å	2.715
$\angle(O_w\cdots H-C)$/deg	104.0
$\angle(H_cO_w\cdots H)$/deg	[59.1][b]
$r(O\cdots H_c)$/Å	1.932[c]
$\angle(C{=}O\cdots H_c)$/deg	102.1[c]
$\angle(O\cdots H_cO_w)$/deg	155.4[c]

[a] Atom labeling as in Figure 1. [b] Value in square brackets taken from ab initio calculations. [c] Derived values.

the planar moment P_c indicates that if this situation is true, the barrier to planarity should be below the ground vibrational state. The ab initio computations are in agreement with this conclusion since they predict the equilibrium structure to be slightly nonplanar with a barrier to planarity below 50 cm^{-1}. A splitting of the ground vibrational state is commonly observed in molecular complexes in which water acts as a proton acceptor[29] due to the internal rotation of water about its C_2 axis. Such a periodic motion exchanges the water hydrogen atoms and thus the vibrational doublets should show a 3:1 intensity ratio due to nuclear spin statistical weight effects. The splittings observed in the present investigation (see Figure 3) show apparently different intensities, but the spacing between them is close to the limit of the resolution of our spectrometer where it is difficult to obtain clean intensities. An exploration of the ab initio potential energy surface for conformer Ib indicates that such an internal rotation is a complex motion which involves the motion of the water molecule out of the molecular plane and several changes in the angles defining the relative orientation of both monomers. Nevertheless it is possible to conceive a two-fold periodic pathway with the maxima at configurations in which the plane of water is at 90° with respect to the plane of formamide. In this configuration, predicted to be 765 cm^{-1} above the equilibrium conformation, water forms a bifurcated double bond to the carbonyl oxygen while formamide forms a weak C−H···O hydrogen bond to water. Given the order of magnitude of the calculated barrier this vibrational motion is probably at the origin of the observed splittings. However given its dynamical complexity, we have not attempted to determine the barrier from the limited set of experimental data.

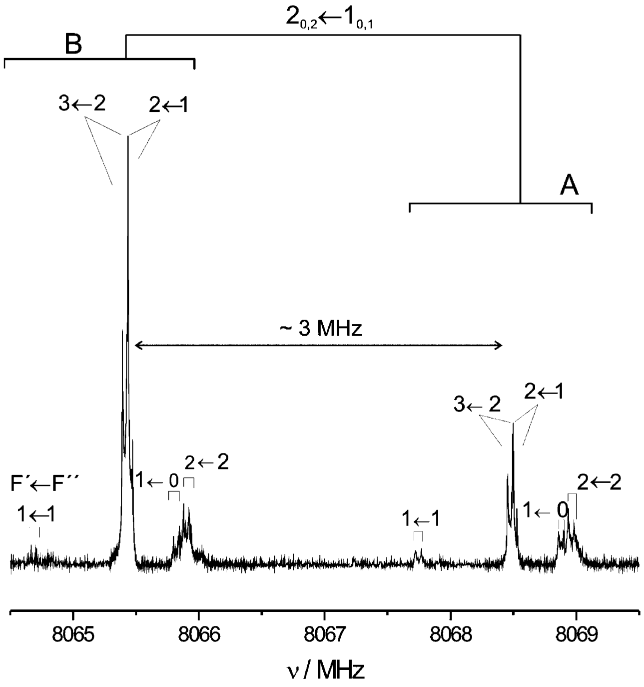

Figure 4. The $2_{0,2}-1_{0,1}$ rotational transition of conformer Ic of formamide···H_2O. The water molecule internal rotation doubling (A and B states) is larger than the ^{14}N nuclear quadrupole coupling hyperfine splittings ($F' \leftarrow F''$, $F = I + J$). The nuclear spin statistical effects due to the exchange of two protons are apparent from the 3:1 intensity ratio. Each component appears as a doublet due to the Doppler effect.

Table 8. Rotational Parameters for Conformer Ic of the Complex Formamide···(H_2O), with Torsional Substates Labeled as A and B

	state A	state B
A/MHz[a]	[35 288][b]	
B/MHz	2084.6937(141)	2083.6092(141)[c]
C/MHz	1949.7643(136)	1949.3169(136)
χ_{aa}/MHz	1.5073(78)	
χ_{bb}/MHz	[2.01]	
χ_{cc}/MHz	[−3.62]	
σ/kHz[c]	2.5	
N	26	

[a] Parameter definition as in Table 2. [b] The A rotational constant and the χ_{bb} and χ_{cc} nuclear quadrupole coupling constants were kept fixed in the fit to the ab initio values. [c] Standard error in parentheses in units of the last digit.

4. Formamide···H_2O: Conformer Ic. New searches were conducted at this point to locate the Ic amino-bonded conformer of formamide···H_2O which is expected to have a large value of the μ_a electric dipole moment component (see Table 1). A prediction for the most intense μ_a-type R-branch transitions with $K_{-1} = 0$ led to the discovery of the $2_{0,2} \leftarrow 1_{0,1}$, $3_{0,3} \leftarrow 2_{0,2}$, and $4_{0,4} \leftarrow 3_{0,3}$ transitions of a new conformer. The assignment was confirmed with the observation of the $5_{0,5} \leftarrow 4_{0,4}$ transition. The observed transitions are weaker than those corresponding to conformer Ib and exhibited the characteristic hyperfine pattern due to ^{14}N nuclear quadrupole coupling. However, the most significant feature of the spectrum was the observation of an additional doubling which produced two identical nuclear quadrupole patterns separated ca. 3−8 MHz as shown in Figure 4 for the $2_{0,2} \leftarrow 1_{0,1}$ transition. The members of the doublet show relative intensities with a ratio of approximately 3:1 which corresponds to the nuclear spin statistical weight effects of a motion which exchanges two protons, plausibly attributable to an internal rotation of water in the cluster. According to this model the observed vibrational states have been labeled as A and B. Unfortunately no transitions with $K_{-1} > 0$ could be observed in the jet-cooled spectrum for this conformer. As occurs for conformer Ib the lines with $K_{-1} = 1$ are expected to be much less intense than those with $K_{-1} = 0$ and might be affected by larger internal rotation splittings. The observed transitions were analyzed in two independent sets corresponding to the two members of the internal rotation splitting with a rigid rotor Hamiltonian supplemented by a ^{14}N nuclear quadrupole coupling term. The results are given in Table 8. From the limited set of observed transitions, the A rotational constant is not determinable and the B and C rotational constants are highly correlated. In fact, only the sum $B + C$ can be determined without ambiguity. In the fit, the rotational constant A and the

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(29) Berden, G.; Meerts, W. L.; Schmitt, M.; Kleinermanns, K. *J. Chem. Phys.* **1996**, *104*, 972. Blanco, S.; Lopez, J. C.; Alonso, J. L.; Ottaviani, P.; Caminati, W. *J. Chem. Phys*, **2003**, *119*, 880.

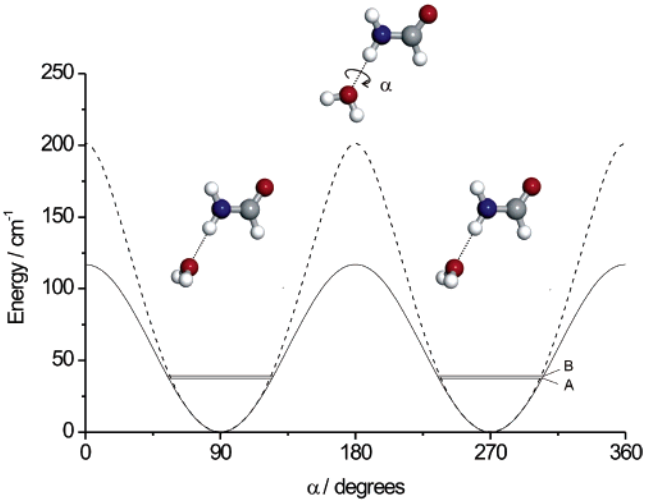

Figure 5. Potential energy function for the internal rotation of water molecule in conformer Ic of formamide···H_2O. Solid line: Function that reproduces the observed shift of (B + C) in going from state A to state B from flexible model computations. Dotted line: Ab initio (MP2-FC/6-311++G(d,p)) computed function.

quadrupole coupling constants were constrained to have the same values in both states and the values of A, χ_{bb}, and χ_{cc} were fixed to those predicted theoretically. A comparison of the determined spectroscopic parameters with the predicted values (Table 1) supports the identification of this new conformer as Ic.

No minor isotopomers could be measured for conformer Ic. The B and C rotational constants for this conformer are reasonably reproduced using the ab initio values of the intermolecular parameters, $r(H_a{\cdots}O_w) = 2.005$ Å, $\angle NH_aO_w = 175°$, $\angle CNH_aO_w = 0°$ with the planes of water and formamide mutually perpendicular (see Figure 1).

The splitting observed in the rotational lines of conformer Ic of formamide−water is typical of molecular complexes in which water acts as a proton acceptor.[29] It arises from the internal rotation of the water molecule around its symmetry axis. Ab initio calculations predict a periodic two-fold potential energy function with a barrier $V_2 = 200$ cm^{-1}. The minima correspond to the configuration of the water molecule perpendicular to the plane of the formamide molecule and the barrier to approximately coplanar configurations, as shown in Figure 5. The minimum energy pathway for this potential energy function can be essentially described as an internal rotation of water accompanied by a small distortion of the $r(N-H{\cdots}O)$ distance.

We have used the flexible model of Meyer[30] to estimate the value of the C_2 barrier from our experimental data. This model allows the numerical calculation of the rotational constants, energies, and the wave functions for the overall momentum quantum numbers $J = 0, 1$ in the ground and vibrational excited states. From the observed rotational transitions only the value of $(B + C)$ is unambiguously determined so we have chosen the observed shift of $(B + C)$ in going from state A to state B, $\Delta(B + C)$ as the experimental parameter to be fitted. We adopted the simplest form of a two-fold potential:

$$V(\alpha) = {}^{1}/_{2}V_2[1 + \cos(2\alpha)] \qquad (1)$$

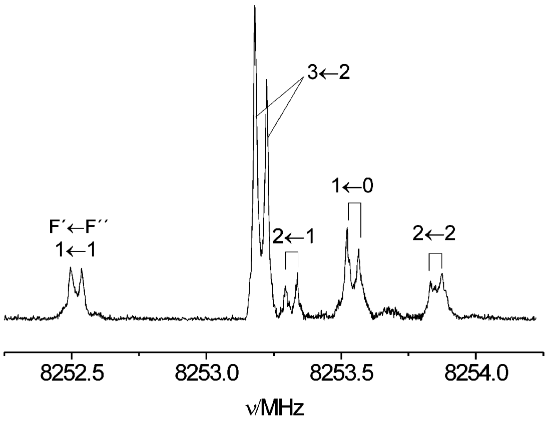

Figure 6. The $2_{0,2}-1_{0,1}$ rotational transition of conformer IIa of formamide···$(H_2O)_2$, showing five hyperfine components due to ^{14}N nuclear quadrupole coupling interaction ($F' \leftarrow F''$, $F = I + J$). Each component is observed as a doublet due to the Doppler effect.

where α is the internal rotation angle, and V_2, the barrier height to be determined from the fit of $\Delta(B + C)$. The potential function takes the values $V = V_2$ for $\alpha = 0°$ or 180° and $V = 0$ for $\alpha = 90°$ or 270°. The r_0 structures of formamide (see Table 3) and water[27] have been assumed. A dynamical model in which a coaxial arrangement of the N−H bond and the C_2 axis of water is preserved has been considered with the $r(N-H{\cdots}O)$ distance varying as described by ab initio computations according to $r(\alpha) = 2.045 - 0.0198[1 - \cos(2\alpha)] - 0.0033[1 - \cos(4\alpha)]$ Å.

The value $V_2 = 117$ cm^{-1} reproduced the experimental value $\Delta(B + C) = 1.53$ MHz for this model. The calculated energy spacing between the observed A and B states is 2.13 cm^{-1}. The corresponding potential energy function is shown in Figure 5. However, given the reduced set of experimental data available it should be considered only as an estimate.

5. Formamide···$(H_2O)_2$: Conformer IIa. The rotational spectrum of the formamide···$(H_2O)_2$ complex was searched on the basis of the ab initio spectroscopic parameters of Table 1. A set of eight μ_a- and one μ_b-type R-branch transitions attributable to this species were found close to the predicted frequencies. The observed transitions exhibited the expected hyperfine structure due to a ^{14}N nuclear quadrupole coupling interaction (Figure 6), but no tunneling splittings were observed. The rotational spectrum could be analyzed with the same Hamiltonian described for formamide. The rotational constants and the diagonal elements of the nuclear quadrupole coupling tensor were determined along with four quartic centrifugal distortion constants. These measurements were later extended to nine monosubstituted isotopomers of the cluster, namely $^{15}NH_2-COH{\cdots}(H_2O)_2$, $NH_2-{}^{13}COH{\cdots}(H_2O)_2$, $ND_sH_a-COH{\cdots}(H_2O)_2$, $NH_2-COH{\cdots}(H_2{}^{18}O_w)(H_2O)$, $NH_2-COH{\cdots}(D_bH_cO)(H_2O)$, $NH_2-COH{\cdots}(H_bD_cO)(H_2O)$, $NH_2-COH{\cdots}(H_2O)(H_2{}^{18}O_v)$, $NH_2-COH{\cdots}(H_2O)(D_dH_eO)$, and $NH_2-COH{\cdots}(H_2O)(H_dD_eO)$ (see notation of Figure 2), which confirmed the observation of conformer IIa. The spectroscopic parameters of the parent and the three isotopomers corresponding to substituted positions of formamide are given in Table 9, while those corresponding to monosubstituted species of the two water molecules are listed in Table 10.

The formamide···$(H_2O)_2$ spectrum has roughly half the intensity of that ot formamide···H_2O, conformer Ia, but it is

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(30) Meyer, R. *J. Mol. Spectrosc.* **1976**, *76*, 266.

Table 9. Rotational Parameters for Conformer IIa of the Complex Formamide$\cdots(H_2O)_2$ for the Parent Species and Isotopomers with Substitutions Located on the Formamide Subunit

	parent	$NH_2{-}^{13}COH\cdots(H_2O)_2$	$^{15}NH_2{-}COH\cdots(H_2O)_2$	$ND_sH_a{-}COH\cdots(H_2O)_2$
A/MHz [a]	4384.3559(50)[b]	4384.3493(25)	4334.6691(20)	4321.9095(33)
B/MHz	2630.4957(16)	2590.069 90(52)	2611.206 93(44)	2630.4276(31)
C/MHz	1651.1140(13)	1635.098 80(34)	1636.470 57(26)	1642.262 44(72)
P_c/u Å^2	0.654 08(24)	0.654 503(85)	0.654 872(68)	0.664 44(22)
Δ_J/kHz	2.08(68)	[2.08]	[2.08]	[2.08]
Δ_{JK}/kHz	16.3(3.8)	[16.3]	[16.3]	[16.3]
Δ_K/kHz	[0.0][c]	[0.0]	[0.0]	[0.0]
δ_J/kHz	0.565(152)	[0.565]	[0.565]	[0.565]
δ_K/kHz	18.1(5.7)	[18.1]	[18.1]	[18.1]
χ_{aa}/MHz	1.0739(34)	1.0608(69)		1.0467(168)
χ_{bb}/MHz	2.0063(45)	2.0220(101)		2.0141(208)
χ_{cc}/MHz	−3.0802(45)	−3.0828(101)		−3.0607(208)
σ/kHz	3.9	4.0	2.0	5.1
N	37	20	8	13

[a] Parameter definition as in Table 2. [b] Standard error in parentheses in units of the last digit. [c] Values in square brackets were kept fixed in the fit.

Table 10. Rotational Parameters for Conformer IIa of the Complex Formamide$\cdots(H_2O)_2$ for Isotopomers with Substitutions Located on the Water Subunits

	$NH_2{-}COH\cdots(H_2{}^{18}O)(H_2O)$	$NH_2{-}COH\cdots(D_bH_cO)(H_2O)$	$NH_2{-}COH\cdots(H_bD_cO)(H_2O)$	$NH_2{-}COH\cdots(H_2O)(H_2{}^{18}O_v)$	$NH_2{-}COH\cdots(H_2O)(D_dH_eO)$	$NH_2{-}COH\cdots(H_2O)(H_dD_eO)$
A/MHz[a]	4257.8773(40)[b]	4267.0569(37)	4380.5341(46)	4258.4216(31)	4313.5588(35)	4230.0411(31)
B/MHz	2550.8117(12)	2554.0717(29)	2582.1595(36)	2558.178 03(94)	2625.2749(24)	2575.6094(23)
C/MHz	1601.768 73(42)	1609.035 94(50)	1631.645 17(66)	1604.741 85(33)	1639.015 99(51)	1611.427 73(41)
P_c/u Å^2	0.652 20(14)	1.110 59(26)	0.656 47(25)	0.651 64(11)	0.661 40(18)	1.034 57(17)
Δ_J/kHz	[2.08][c]	[2.08]	[2.08]	[2.08]	[2.08]	[2.08]
Δ_{JK}/kHz	[16.3]	[16.3]	[16.3]	[16.3]	[16.3]	[16.3]
Δ_K/kHz	[0.0]	[0.0]	[0.0]	[0.0]	[0.0]	[0.0]
δ_J/kHz	[0.565]	[0.565]	[0.565]	[0.565]	[0.565]	[0.565]
δ_K/kHz	[18.1]	[18.1]	[18.1]	[18.1]	[18.1]	[18.1]
χ_{aa}/MHz	1.0493(91)	0.9975(193)	1.0447(234)	1.0754(75)	1.0717(181)	1.0575(123)
χ_{bb}/MHz	2.0142(147)	2.0295(238)	2.0334(290)	2.0009(121)	2.0286(225)	2.0108(177)
χ_{cc}/MHz	−3.0634(147)	−3.0269(238)	−3.0782(290)	−3.0763(121)	−3.1002(225)	−3.0684(177)
σ/kHz	6.4	5.9	7.2	5.2	5.5	5.0
N	21	17	16	21	16	18

[a] Parameter definition as in Table 2. [b] Standard error in parentheses in units of the last digit. [c] Values in square brackets were kept fixed in the fit.

more intense than those of conformers Ib and Ic. Taking into account the predicted values of the electric dipole moment components for all these species (see Table 1), the observed intensities indicate that formamide$\cdots(H_2O)_2$ is the second most abundant formamide−water complex in the postexpansion. It is difficult in this case to establish a relation between populations in the jet and relative stability since the formation of the 1:2 complex is kinetically less probable than any of the 1:1 complexes. If we admit that complexes are formed after three-body collisions in the initial stages of the supersonic expansion, it is highly probable that the formation of the 1:2 observed complex requires a formamide−water Ia complex and a second water molecule as collision partners. In any case the experimental intensities indicate that formamide$\cdots(H_2O)_2$ should be very stable. The calculated dissociation energies predict this complex to be more stable than any of the 1:1 adducts (see Table 1).

The structure of conformer IIa of formamide$\cdots(H_2O)_2$ was derived from the set of 30 rotational constants given in Tables 9 and 10. Initial inspection of the P_c planar moments, using the same arguments raised with conformer Ia, revealed that all atoms of conformer IIa of formamide$\cdots(H_2O)_2$ are essentially on the same plane with the exception of the two hydrogen atoms of water not participating in the intermolecular hydrogen bonds (H_b and H_e in Figure 2), for which deuteration produces a noticeable P_c increment. In consequence conformer IIa of formamide$\cdots(H_2O)_2$ exhibits C_1 symmetry. The structure was determined following the same steps as those for formamide$\cdots H_2O$, conformer Ia. According to ab initio predictions, an up−down configuration of the complex, with the hydrogen atoms of water molecules not participating in the intermolecular bonds lying out of the formamide plane in opposite sides, has been assumed. The r_s nuclear coordinates and the derived substitution (r_s) structure are shown in Table 11, where they can be compared with the alternative effective (r_0) structure. The latter has been determined under the assumption that the monomers do not change upon formation of the complex, and so the geometries of formamide (see Table 3) and water[27] were fixed to their r_0 values. As for conformer Ia the errors introduced into the r_0 structural parameters by assuming unchanged monomer geometries in the complex were estimated from the ab initio predicted structural changes to be roughly one order of magnitude larger than the quoted standard errors.

Discussion

The conformational preferences of monohydrated formamide$\cdots H_2O$ are dominated by the bridged structure of conformer Ia, predicted to be the global minimum. In this conformer, the water molecule spans the peptide group of formamide with two intermolecular hydrogen bonds ($N{-}H\cdots O_w(H){-}H\cdots O{=}C$), linking the donor and acceptor hydrogen-bond sites. A similar water solvent bridge has been observed using

Table 11. Substitution Coordinates of Conformer IIa of Formamide⋯$(H_2O)_2$ from the Rotational Data of Tables 9 and 10, and Derived Substitution (r_s) and Effective (r_0) Structures

atom[a]	*a*	*b*	*c*
C	−1.739 31(69)[b]	[0.0][c]	0.021(57)
N	−1.1897(10)	+1.1685(10)	[0.0][c]
H_s	−0.072(16)	+1.290 34(93)	−0.103(12)
O_w	+1.712 51(70)	+1.374 21(87)	[0.0][c]
H_b	+2.263 71(53)	+1.704 38(70)	−0.6952(17)
H_c	+1.895 19(63)	+0.2869(42)	+0.1515(79)
O_v	+1.629 36(74)	−1.366 55(88)	[0.0][c]
H_d	+0.6064(20)	−1.380 28(87)	−0.087(14)
H_e	+1.882 36(64)	−2.005 09(60)	+0.6351(19)

parameter[a]	r_s	r_0
$r(C{=}O)$/Å	[1.23][d]	[1.231]
$r(C{-}N)$/Å	1.29(7)[e]	[1.344]
$r(N{-}H_s)$/Å	1.13(2)	[0.998]
$r(O_w{-}H_b)$/Å	0.95(3)	[0.965]
$r(O_w{-}H_c)$/Å	1.11(1)	[0.965]
$r(O_v{-}H_d)$/Å	1.027(5)	[0.965]
$r(O_v{-}H_e)$/Å	0.94(3)	[0.965]
$r(H_s \cdots O_w)$/Å	1.79(2)	1.936(5)
$r(H_c \cdots O_v)$/Å	1.681(6)	1.829(4)
$r(H_d \cdots O)$/Å	1.764(4)[f]	1.797(8)
$r(O_v \cdots O_w)$/Å	2.742(2)	2.755(3)
$\angle(C{-}N{-}H_s)$/deg	121.3(2)	[118.8]
$\angle(N{-}C{=}O)$/deg	[124.8]	[124.52]
$\angle(H_b{-}O_w{-}H_c)$/deg	110(2)	[104.8]
$\angle(H_d{-}O_v{-}H_e)$/deg	109(2)	[104.8]
$\angle(N{-}H_s \cdots O_w)$/deg	171(4)	178.9(3)
$\angle(H_s \cdots O_w{-}H_c)$/deg	97.2(3)	97.6(7)
$\angle(O_w{-}H_c \cdots O_v)$/deg	157(2)	160(1)
$\angle(H_c \cdots O_v{-}H_d)$/deg	100.2(4)	99(1)
$\angle(O_v{-}H_d \cdots O)$/deg	168(2)[g]	171(2)
$\angle(H_d \cdots O{=}C)$/deg	130(2)[g]	130.2(8)
$\tau(H_b{-}O_w{-}H_c \cdots H_s)$/deg	−127(3)	−130.8(7)
$\tau(H_e{-}O_v{-}H_d \cdots H_c)$/deg	128(1)	136(2)

[a] Atom definition as in Figure 2. [b] Errors estimated according to Costain.[25] [c] Coordinates calculated to have imaginary values are assumed to be zero. [d] Assumed structural parameters in square brackets. Values for formamide are taken from the corresponding column in Table 3. r_0 values for water taken from ref 27. [e] Error in parentheses in units of the last digit. For the r_0 parameters these are standard errors. [f] Derived values.

rotational spectroscopy for glycine⋯H_2O,[31] where water closes a cycle with the carboxylic group of glycine. The investigation of seven new isotopomers in the present work has provided accurate rotational parameters, allowing the determination of the structure of the intermolecular hydrogen bonds in conformer Ia of formamide⋯H_2O and the most detailed description of the solvation of the *cis*-amide group available. The comparison of the intermolecular hydrogen bond parameters given in Table 5 confirms that the $O_w{-}H_c \cdots O{=}C$ hydrogen bond distance (r_0 = 1.93(1) Å) is shorter than that of the $N{-}H_s \cdots O_w$ link (r_0 = 2.061(4) Å). In the same way, the $O_w{-}H_c \cdots O{=}C$ bond ($\angle(O_w{-}H_c \cdots O)$ = 153(1)°) is closer to a linear arrangement than $N{-}H_s \cdots O_w$ ($\angle(N{-}H_s \cdots O_w)$ = 139.5(3)°). If the bond distances and the nonlinearity angles are related to the hydrogen bond strength, the structural data of this work indicate that the intermolecular hydrogen bond $O_w{-}H_c \cdots O{=}C$ is the dominant interaction. The same structural arguments have been used in the complex glycine−water[31] to show that the $O{-}H \cdots O_w$ interaction, where water acts as a proton acceptor, is dominant over the $O_wH \cdots O{=}C$ interaction. It is also interesting to note that the $\angle(H_c \cdots O{=}C)$ angle of 110° (see Table 5) is smaller than the angle of 120° at which the axes of the sp^2 lone pairs of the carbonyl group are expected to occur. This distortion can be attributed to the existence of the second $N{-}H_s \cdots O_w$ hydrogen bond and reflects the well-known angular flexibility at C═O acceptor oxygen atoms.[9]

The two new higher energy conformers Ib and Ic of formamide⋯H_2O, observed for the first time in gas phase, can be thought to model the two types of peptide−water interactions that may coexist in *trans*-peptide groups. Conformer Ib is characterized by a carbonyl−water bonded interaction $O_wH_c \cdots O{=}C$ ($r(C{=}O \cdots H_c)$= 1.932 Å) reinforced by a longer weak $C{-}H \cdots O_w$ hydrogen bond (ab initio $r(C{-}H \cdots O_w)$= 2.715 Å). The distortion of the $\angle(H_c \cdots O{=}C)$ angle (102.1°, see Table 7) from the expected sp^2 lone-pair configuration is also noticeable and could be taken as proof of the existence of a secondary weak $C{-}H \cdots O$ hydrogen bond. In conformer Ic, water acts only as a base and formamide acts only as an acid to form a $N{-}H_a \cdots O_w$ hydrogen bond.

The splittings observed in the spectra of confomers Ib and Ic of formamide−(H_2O) (see Figures 3 and 4) are attributable to a motion of water which exchanges its hydrogen atoms. In conformer Ic the internal motion can be described in a rather simple way using a two-fold periodic energy function and a simple dynamical model that can be described as the rotation of water around its C_2 axis. Using this model a two-fold barrier of 117 cm^{-1} has been estimated from the experimentally observed data (see Figure 5). This low barrier is proof of the lack of noncovalent interactions, other than the $N{-}H_a \cdots O_w$ hydrogen bond, in this conformer. For conformer Ib this internal motion is dynamically more complex and hindered by a larger two-fold barrier predicted from ab initio calculations to be 765 cm^{-1}. This result is consistent with the fact that conformer Ib is stabilized by a weak $C{-}H \cdots O$ and a $O{-}H \cdots O{=}C$ hydrogen bond. In passing to conformer Ia, where the strength of the $N{-}H \cdots O$ is increased with respect to the $C{-}H \cdots O$ hydrogen bond, the barrier to internal rotation of water should increase consistently with the fact that no splittings are observed in the rotational spectrum of this form.

On the basis of the relative intensities of the observed transitions, and taking into account the calculated electric dipole moment components (see Table 1), it can be concluded that conformer Ib, dominated by a $O_w{-}H \cdots O{=}C$ interaction, is more stable than conformer Ic formed through a $N{-}H \cdots O_w$ hydrogen bond. This result is in good agreement with the conclusions on the relative strength of these types of hydrogen bond in conformer Ia and with the observation that bound water molecules establish preferentially hydrogen bonds to the peptide carbonyl groups in globular proteins.[9] The results presented here suggest the following: (i) the basicity of the C═O group should play an important role in driving the different amide−water interactions; (ii) the angular flexibility at the C═O acceptor oxygen atoms allows satisfaction of the multiple acceptor capacity of water that can form other hydrogen bonds that reinforce the $O{-}H \cdots O{=}C$ bond. In this way water will prefer to accept the hydrogen bond from a moderate acid like the NH donor, but if these are not available, it will resort to forming weak $C{-}H \cdots O$ hydrogen bonds. This is not in conflict with the observations that in the gas phase water is known to be a

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(31) Alonso, J. L.; Cocinero, E. J.; Lesarri, A.; Sanz, M. E.; López, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 3471.

better proton acceptor than donor,[7b] as it has been recently confirmed in the glycine−water complex.[31] In fact water exhibits its acceptor capacity in all observed complexes. In conformers Ia and Ib water is playing a double donor/acceptor role, while in conformer Ic it seems to act only as an acceptor.

The observed conformer of dihydrated formamide$\cdots(H_2O)_2$ is a larger solvent-bridged structure with two water molecules spanning the cis-amide group with three intermolecular hydrogen bonds ($N{-}H\cdots O_w(H){-}H\cdots O_v(H){-}H\cdots O{=}C$). Its structure corresponds to what has been called a "chemically substituted water trimer"[32] with the nonbonded hydrogen atoms of water adopting an up−down configuration similar to that found in related complexes.[5,14] The hydrogen bonds appear to be stronger than those observed in the 1:1 adducts, since they are characterized by shorter bond distances and almost linear angular structures. This stability, also reflected in the relative intensities of the observed spectra, can be seen as a consequence of hydrogen bond cooperativity. σ-Bond cooperativity[8] occurs for continuous chains or cycles of hydrogen bonded functional groups possessing both donor and acceptor properties. The adducts of formamide$\cdots H_2O$ Ia and formamide$\cdots(H_2O)_2$ can be considered as cyclic sequential[13] complexes since in both of them water and formamide act as proton donors and proton acceptors and close a cycle in a sequential way. These cycles are particularly stable and are characterized by a shortening of the hydrogen bond distances and an increase of hydrogen bond energy with respect to typical values (see Chart 1). The experimental information reported in the present work reflects vividly the reinforcement of the hydrogen bonds in passing from conformer Ia to formamide$\cdots(H_2O)_2$. The $r_0(N{-}H\cdots O)$ hydrogen bond distance reduces from 2.061(4) Å to 1.936 (5) Å, and the $r_0(O{-}H\cdot\cdot O{=}C)$ distance, from 1.93(1) Å to 1.797(8) Å. On the other hand the hydrogen bonds in formamide$\cdots H_2O$ are markedly nonlinear ($\angle(N{-}H_s\cdots O_w) = 139.5(3)°$, $\angle(O_w{-}H_c\cdots O) = 153(1)°$), while in formamide$\cdots(H_2O)_2$ these are close to a linear arrangement ($\angle(N{-}H_s\cdots O_w) = 178.9(3)°$, $\angle(O_v{-}H_d\cdots O) = 171(2)°$). This reinforcement of the hydrogen bonds is also strongly evident from the comparison of the distance $r_0(O_v{-}O_w) = 2.755(3)$ Å in formamide$\cdots(H_2O)_2$ with that reported for the water dimer $r_0(O{-}O) = 2.98$ Å.[33] In fact, formamide$\cdots(H_2O)_2$ has more similarities with the water trimer, and its $r_0(O_v{-}O_w)$ distance is comparable but still shorter than the $r(O{-}O)$ distance of 2.84 Å established for the water trimer in the gas phase.[32] This shortening of the $r(O{-}O)$ distances in passing from the water trimer to formamide$\cdots(H_2O)_2$ may also reflect the enhanced proton donor/acceptor capabilities of formamide with respect to water. To see if the ab initio energies also reflect the reinforcement of the hydrogen bonds we have compared the dissociation energy $D_e = 75$ kJ mol^{-1} of the formamide$\cdots(H_2O)_2$ complex with the energies of its hydrogen bonds. The dissociation energies of complexes Ib and Ic of formamide$\cdots H_2O$ have been taken as reasonable approximations to the energies of the isolated $O_v{-}H_d\cdots O$ and $N{-}H_s\cdots O_w$ hydrogen bonds, respectively, and the dissociation energy of the water dimer calculated at the same level (19.3 kJ mol^{-1}) as the energy of the isolated $O_w{-}H_c\cdots O_v$. The sum of these three energies, 64.3 kJ mol^{-1}, is smaller than that calculated for the formamide$\cdots(H_2O)_2$ complex of 75.6 kJ mol^{-1}. The difference in energy could be in fact greater than 10.3 kJ mol^{-1} since the energy of the conformer Ib of formamide$\cdots H_2O$ includes the contribution of a weak $C{-}H\cdots O$ hydrogen bond. This increment of the energy of the cyclic sequential set of three hydrogen bonds with respect to the sum of the energies of three isolated hydrogen bonds should be attributed to σ-bond cooperativity.

Resonance-enhanced or π-cooperativity should cause a polarization of the amide group π-electron distribution, promoting the ionic resonant form $H_2N^+{=}CO^-H$ of formamide and enhancing its donor/acceptor capabilities. Manifestations of π-bond cooperativity should include reinforcement of the $N{-}H\cdots O$ and $OH\cdots O{=}C$ bonds and small changes in the C−N and C═O bond lengths that would tend to increase the C═O bond and to shorten the C−N bond distance (see Chart 1). Our ab initio computations predict $r_e(C{-}N) = 1.369$, 1.354, and 1.348 Å and $r_e(C{=}O) = 1.219$, 1.226, and 1.229 Å, respectively, in formamide, formamide$\cdots H_2O$ Ia, and formamide$\cdots(H_2O)_2$ IIa. Though the lack of isotopic substitution on the carbonyl oxygen precludes an accurate comparison of the C═O distances, valid conclusions can be obtained from a comparison of the C−N bond lengths in formamide on formation of the water bridges. The r_s structural data from Tables 3, 5, and 11 do not reveal detectable changes within our error limits ($r_s(C{-}N) = 1.34(2)$, 1.34(2) and 1.29(7) Å, respectively, in formamide, formamide$\cdots H_2O$ Ia, and formamide$\cdots(H_2O)_2$ IIa). In any case, the possible bond length distortions (if they take place as predicted from ab initio computations) should be limited to changes below these experimental errors.

In conclusion, this study has proved that the microsolvated clusters of formamide constitute excellent models to explain the observed preferences of bound water in proteins and to investigate the effects of hydrogen bond cooperativity. This work will be extended soon to other molecules carrying the peptide group in order to get more insight on these interesting problems.

Acknowledgment. We would like to thank the Dirección General de Investigación − Ministerio de Ciencia y Tecnología (Grant BQU2003-03275) and the Junta de Castilla y León (Grant VA012-C05) for financial support.

Supporting Information Available: Complete ref 19 and tables of experimental rotational frequencies of all the observed isotopic species of formamide, formamide$\cdots H_2O$, and formamide$\cdots(H_2O)_2$ (25 tables, 21 pages, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0618393

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