Solvent Effects on Oxygen-17 Chemical Shifts in Amides. Quantitative Linear Solvation Shift Relationships

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A multiple-linear-regression analysis (MLRA) has been carried out using the Kamlet–Abboud–Taft (KAT) solvatochromic parameters in order to elucidate and quantify the solvent effects on the ^{17}O chemical shifts of N-methylformamide (NMF), N,N-dimethylformamide (DMF), N-methylacetamide (NMA), and N,N-dimethylacetamide (DMA). The chemical shifts of the four molecules show the same dependence (in ppm) on the solvent polarity–polarizability, i.e., $-22\pi^*$. The influence of the solvent hydrogen-bond-donor (HBD) acidities is slightly larger for the acetamides NMA and DMA, i.e., -48α, than for the formamides NMF and DMF, i.e., -42α. The influence of the solvent hydrogen-bond-acceptor (HBA) basicities is negligible for the nonprotic molecules DMF and DMA but significant for the protic molecules NMF and NMA, i.e., -9β. The effect of substituting the N–H hydrogen by a methyl group amounts to -5.9 ppm in NMF and 5.4 ppm in NMA. The effect of substituting the $O\!=\!C\!-\!H$ hydrogen amounts to 5.5 ppm in NMF and 16.8 ppm in DMF. The model of specific hydration sites of amides by I. P. Gerothanassis and C. Vakka [*J. Org. Chem.* **59**, 2341 (1994)] is settled in a more quantitative basis and the model by M. I. Burgar, T. E. St. Amour, and D. Fiat [*J. Phys. Chem.* **85**, 502 (1981)] is critically evaluated. ^{17}O hydration shifts have been calculated for formamide (FOR) by the ab initio LORG method at the 6-31G* level. For a formamide surrounded by the four in-plane molecules of water in the first hydration shell, the calculated ^{17}O shift change due to the four hydrogen bonds, -83.2 ppm, is smaller than the empirical hydration shift, -100 ppm. The ^{17}O shift change from each out-of-plane water molecule hydrogen-bonded to the amide oxygen is -18.0 ppm. These LORG results support the conclusion that no more than four water molecules are hydrogen-bonded to the amide oxygen in formamide. © 1997 Academic Press

INTRODUCTION

Simple amides have been the subject of extensive NMR investigations because of the importance of these compounds

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to study intermolecular hydrogen bonding and as model compounds for the peptide bond (*1–3*). In particular, Kamlet *et al.* (*4*) used the solvatochromic comparison method to unravel and rationalize solvent effects on the ^{15}N chemical shifts of amides. In recent years, ^{17}O chemical shifts $\delta(^{17}O)$ have received attention as a structural probe in amides and peptides (*5–15*) since these shifts are extremely sensitive, in general, to both solvation and substituent effects (*5–17*).

A simple model for separating the different contributions to the ^{17}O nuclear shieldings due to hydrogen-bonding hydration at various sites in amide molecules was suggested by Burgar, Amour, Fiat *et al.* (BAF) some years ago (*5, 9*). Recently, an improved solvation model of amides and peptides based on ^{17}O chemical shifts was presented by Gerothanassis and Vakka (*13, 15*). These authors demonstrated that both long-range dipole–dipole interactions and specific hydrogen bonds due to solvation of molecules by H_2O at the amide oxygen induce significant and specific modifications of the ^{17}O shielding which are larger than originally considered (*5, 9*). On the contrary, solvation of the N–H amide hydrogen induces a small modification of this shielding.

In this paper, the model by Gerothanassis and Vakka (*13, 15*) is reduced to a more quantitative basis by application of the Kamlet–Abboud–Taft (KAT) parameters using linear solvation-shift relationships (*18–21*). The particular equations for each amide are embodied into a general equation for the four molecules which allow us to evaluate critically the BAF model (*5, 9*) as well as to determine reliable values for the substituent effects. Ab initio calculations of ^{17}O hydration shifts have been carried out with the aim to gain information about the structure of aqueous formamide.

EMPIRICAL MODELS FOR AMIDE SOLVATION

The BAF Model (5, 9)

According to this model, the solvent effects upon the ^{17}O chemical shifts are separated into different contributions at-
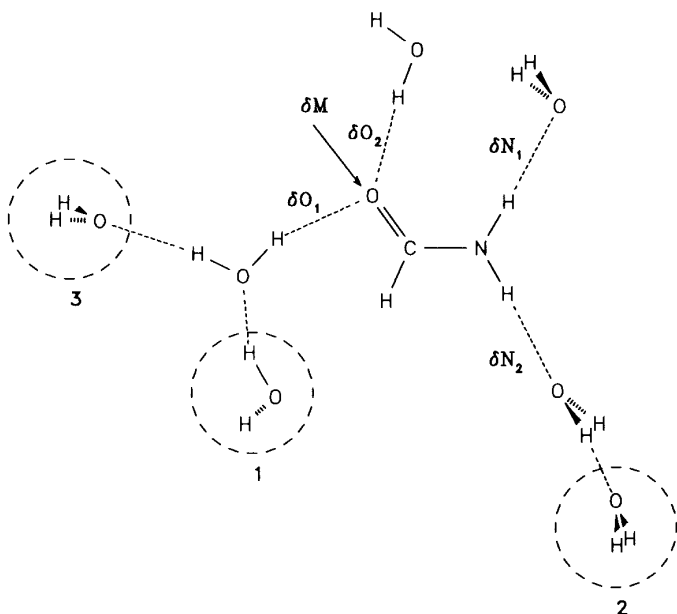
FIG. 1. Drawing of FOR + $(H_2O)_4$ system and BAF hydration model of amides based on ^{17}O chemical shifts. The three additional water molecules enclosed in circles belong to the second hydration shell.

tributed to hydrogen bonding at various sites available in the amide molecule. In formamide (FOR), these sites are the first and second oxygen lone pairs and the first and second nitrogen protons (Fig. 1). Therefore, the observed chemical shift (δ_{obs}) of FOR at infinite dilution in water is separated into five contributions

$$\delta_{obs} = \delta M + \delta O_1 + \delta O_2 + \delta N_1 + \delta N_2, \qquad [1]$$

where δM is the chemical shift of FOR in the absence of hydrogen-bonding interactions, δO_1 and δO_2 are the contributions to δ_{obs} due to the first and second oxygen lone pairs participating in a hydrogen bond, and δN_1 and δN_2 are the contributions due to the first and second nitrogen proton participating in a hydrogen bond.

The terms in Eq. [1] were determined separately for the formamides FOR, NMF, and DMF and for the acetamides ACA (acetamide), NMA, and DMA (Fig. 2). In order to evaluate these terms, two explicit assumptions were made: (i) the effects of hydrogen bonding at various sites act independently of one another, i.e., the effects are additive, and (ii) alkyl substitution at the amide nitrogen does not affect δ_{obs}, i.e., $\delta M(FOR) = \delta M(NMF) = \delta M(DMF)$ and $\delta M(ACA) = \delta M(NMA) = \delta M(DMA)$.

After solving the linear simultaneous equations that are generated from the ^{17}O chemical shifts of the six amides extrapolated to infinite dilution in water and in acetone and also of neat amides (except for ACA), the following values were obtained for formamides

$$\delta M = 323, \delta O_1 = -22, \delta O_2 = -31,$$
$$\delta N_1 = 9, \text{ and } \delta N_2 = 2 \text{ ppm}, \qquad [2]$$

and for acetamides

$$\delta M = 340, \delta O_1 = -22, \delta O_2 = -32,$$
$$\delta N_1 = 10, \text{ and } \delta N_2 = -9 \text{ ppm}. \qquad [3]$$

It was assumed that at infinite dilution in water the two oxygen lone pairs participate in CO–HOH hydrogen bonds and the existing nitrogen protons participate in NH–OH$_2$ hydrogen bonds. At infinite dilution in acetone, only the nitrogen protons participate in NH–OC(CH$_3$)$_2$ hydrogen bonds. For neat amides, the CO group of one molecule forms a CO–HN hydrogen bond with the NH of another one except for DMF and DMA. This implies a third assumption in the model: (iii) each hydrogen bond contribution in Eq. [1] does not depend upon the nature of the solvent molecule, i.e., δN_2 is the same for water, acetone, or amide and δO_1 is the same for water or amide.

The above model was improved by Gerothanassis and Vakka (*13, 15*). These authors confirmed for NMF, DMF, NMA, and DMA the facts that alkyl substitution of the amide nitrogen and solvation of the amide hydrogen NH have a minor effect on $\delta(^{17}O)$ of the amide oxygen. On the contrary, the extrapolated (infinite dilution) chemical shifts of DMF, NMF, and DMF in *n*-hexane, CCl$_4$, and toluene (see Table 1) were found to be significantly different than the values of 323 and 340 ppm suggested for formamides, Eq. [2], and acetamides, Eq. [3], in the absence of hydrogen-bonding interactions. These differences were attributed to dipole–dipole solute–solvent interactions which are a function of the dielectric constant ϵ of the medium. Extrapolation to

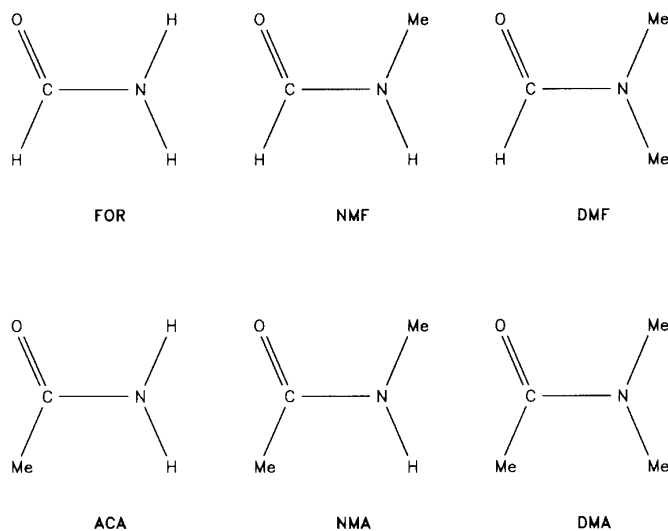**FIG. 2.** Chemical formulas of amides.

$(\epsilon - 1)/2\epsilon = 0$ in the plot of $\delta(^{17}O)$ as a function of $(\epsilon - 1)/2\epsilon$ for nonprotic solvents (which corresponds to a hypothetical case of shielding in vacuo neglecting the possible dependence of chemical shifts on the refractive index of the medium) results in the chemical shifts of 362.9, 366.7, and 372.2 ppm for DMF, NMF, and DMA, respectively. These values indicate deshielding by 40–50 ppm compared to those obtained in media of high dielectric constant. In consequence, the term δM in Eq. [1] must be substituted by the combination of the chemical shift in vacuo (isolated molecule) and the contribution from dipole–dipole interactions.

The KAT Relationships (18–21)

According to the KAT formalism, the observed chemical shift of amide X at infinite dilution in solvent Y, δ_Y^X, would be given by the relationship

$$\delta_Y^X = \delta_{CH}^X + s^X(\pi_Y^* + d^X \delta_Y) + a^X \alpha_Y + b^X \beta_Y, \quad [4]$$

where the solvent effects are described by the solvent parameters π_Y^*, δ_Y, α_Y, and β_Y. The π^* scale is an index of solvent dipolarity/polarizability, which measures the ability of the solvent to stabilize a charge or a dipole due to its dielectric effect. The α scale of solvent hydrogen-bond-donor (HBD) acidities describes the ability of the solvent to donate a proton in a solvent-to-solute hydrogen bond. The β scale of hydrogen-bond-acceptor (HBA) basicities measures the ability of the solvent to accept a proton (i.e., to donate an electron pair) in a solute-to-solvent hydrogen bond. The δ parameter is a polarizability correction term for polychlorinated ($\delta = 0.5$) and aromatic ($\delta = 1.0$) solvents. The coefficients s^X, a^X, and b^X in Eq. [4] define, respectively, the sensitivity of δ_Y^X to solvent dipolarity–polarizability, acidity, and basicity. The product of coefficients $s^X d^X$ defines the sensitivity of δ_Y^X for the polarizability correction term.

The term δ_{CH}^X in Eq. [4] is the chemical shift of amide X measured in cyclohexane since this reference solvent does not form hydrogen bonds ($\alpha_{CH} = \beta_{CH} = 0$) and was selected to define the origin of the π^* scale ($\pi_{CH}^* = 0$). The term $s^X(\pi_Y^X + d^X \delta_Y)$ accounts for the difference between the contributions to δ_Y^X in solvent Y and in cyclohexane from the solute–solvent interactions other than hydrogen bonding. The terms $a^X \alpha_Y$ and $b^X \beta_Y$ represent the contributions from hydrogen bonds of amide X with solvents HBD and HBA, respectively.

Taking into account the fact that in cyclohexane solution the hydrogen bonding interactions are absent, the chemical shift δ_0^X for the isolated molecule could be estimated as

$$\delta_0^X = \delta_{CH}^X + s^X \pi_0^*, \quad [5]$$

where π_0^* is the π^* value in vacuum (i.e., for a bulk dielectric

constant ϵ equal to 1). On the basis of vapour-phase electronic spectra of eight solvatochromic indicators, the π_g^* ($\approx \pi_0^*$) value of the gas phase was reported by Abboud et al. (22) to be -1.06 ± 0.1. Recently, a refined value of -1.23 was reported (21) for π_g^*.

Comparison of Eqs. [1] and [4] shows that the term δM in Eq. [1] would be dependent on the solvent Y and also on the particular amide X under consideration:

$$\delta M = \delta_{CH}^X + s^X(\pi_Y^* + d^X \delta_Y). \quad [6]$$

Likewise, the contributions $\delta O_1 + \delta O_2$ from the hydrogen bonds involving the oxygen lone pairs and the contributions $\delta N_1 + \delta N_2$ from the hydrogen bonds involving the nitrogen hydrogens are also dependent on the nature of solvent Y and amide X,

$$\delta O_1 + \delta O_2 = a^X \alpha_Y, \quad [7]$$

$$\delta N_1 + \delta N_2 = b^X \beta_Y, \quad [8]$$

RESULTS AND DISCUSSION

The KAT Equations

The ^{17}O chemical shifts of NMF, DMF, NMA, and DMA in various solvents, which have been previously reported (13), are listed in Table 1. These values were determined relative to external 1,4-dioxane ($+0.2$ ppm relative to H_2O at 303 K) and extrapolated to infinite dilution assuming a monomer–dimer equilibrium. The uncertainties in estimating the chemical shifts of the monomeric state were ± 1.5 ppm in apolar and low dielectric constant solvents and ± 0.7 ppm for high dielectric constant and protic solvents. The values in Table 1 are the chemical shifts corrected for the magnetic susceptibility effects.

The solvent parameters (π^*, α, β, δ) used in the present work for Eq. [4] are given in Table 2. The least-squares-fitted estimates for the solute parameters of NMF, DMF, NMA, and DMA are given in Table 3. Comparison of these values shows that the response of the oxygen chemical shifts to the solvent dipolarity–polarizability (parameter s) is important and nearly the same for the four molecules. The response to the solvent HBD acidities (parameter a) is dominant and slightly larger for the acetamides NMA and DMA (a^A) than for the formamides NMF and DMF (a^F). The response to the solvent HBA basicities (parameter b) is negligible for the nonprotic molecules DMF and DMA (b^D) but significant and nearly the same for the protic molecules NMF and NMA (b^N).

Taking into account the results obtained from the fits to Eq. [4] for each amide separately, a joint fit was carried out including the complete set of chemical shifts for the four amides. The estimates for parameters appear in the last col-

TABLE 1
Solvent Effects on the ¹⁷O Chemical Shifts δ_Y^X (ppm) of Amides X and Differences d^X between Calculated[a] and Experimental Values

Solvent Y	δ_Y^{NMF}	d^{NMF}	δ_Y^{DMF}	d^{DMF}	δ_Y^{NMA}	d^{NMA}	δ_Y^{DMA}	d^{DMA}
n-Hexane	—	—	347.1	−1.2	—	—	—	—
CCl₄	343.7	2.3	337.8	2.3	—	—	353.7	3.2
Toluene	340.0	0.1	335.3	−0.1	—	—	—	—
CH₂Cl₂	323.6	−1.6	316.8	−0.7	326.8	−1.0	332.5	−1.3
CHCl₃	319.8	−2.8	310.5	0.6	320.5	−0.4	325.9	−0.4
Acetone	328.7	−0.8	327.1	−0.6	333.5	−0.5	343.6	−0.7
CH₃CN	323.0	1.0	320.1	0.9	327.5	1.0	336.1	0.7
DMSO[b]	320.9	−0.6	320.4	1.1	326.5	−0.7	338.3	0.0
EtOH	295.9	−0.5	299.2	−2.5	297.0	−0.6	311.3	−2.3
MeOH	290.6	0.7	292.3	−1.1	290.3	1.4	302.9	0.1
H₂O	272.4	2.2	268.9	1.5	272.8	0.9	280.1	0.7

[a] Values calculated using Eq. [4] with parameters in the last column of Table 3.
[b] Chemical shifts not corrected for the magnetic susceptibility effects.

umn of Table 3. A different parameter δ_{CH}^X was used for each amide which corresponds to the estimated chemical shift in cyclohexane solution. A single value was used for parameter s, and the small parameter d (that corrects for polarizability of polychlorinated and aromatic solvents) was determined. Two values were used for parameter a: the a^F for the formamides NMF and DMF and the a^A for the acetamides NMA and DMA. A single value was used for parameter b: the b^N for the N-methyl derivatives NMF and NMA. For the N,N-dimethyl derivatives DMF and DMA, the value of b^D was set equal to zero. The deviations d between calculated and experimental chemical shifts are given in Table 1. Although the fit may be considered very satisfactory, some systematic deviations, which also appear for the individual fits, reveal that Eq. [4] with the parameter values in the last

column of Table 3 does not account for all the solvent effects. In particular, the sign of the deviations is the same, independently of the amide considered, for the solvents CCl₄ (−2.3 to −3.2), CH₂Cl₂ (0.7 to 1.6), CH₃CN (−0.7 to −1.0), CH₃CH₂OH (0.5 to 2.5), and H₂O (−0.7 to −2.8 ppm).

The Model for Amide Solvation

The joint fit to Eq. [4] of the chemical shifts of NMF, DMF, NMA, and DMA provides a nearly quantitative model for the description of the ¹⁷O chemical shifts of amides which allows us to reduce the model of specific hydration sites of amides by Gerothanassis and Vakka (*13, 15*) to a more quantitative basis.

TABLE 2
Solvent Parameters (π^*, α, β, δ) Used for Eq. [4] and Contributions (in ppm) to the ¹⁷O Chemical Shifts ($s\pi^*$, $sd\delta$, $a^F\alpha$, $a^A\alpha$, $b^N\beta$) from Terms in Eqs. [9] to [12]

Solvent	π^*	α	β	δ	$s\pi^*$	$sd\delta$	$a^F \alpha$	$a^A \alpha$	$b^N \beta$	$(a^A - a^F)\alpha$
n-Hexane	−0.11	0.00	0.00	0.0	2.4	0.0	0.0	0.0	0.0	0.0
CCl₄	0.21	0.00	0.00	0.5	−4.6	1.2	0.0	0.0	0.0	0.0
Toluene	0.49	0.00	0.11	1.0	−10.7	2.5	0.0	0.0	−1.0	0.0
CH₂Cl₂	0.73	0.30	0.00	0.5	−16.0	1.2	−12.6	−14.2	0.0	−1.6
CHCl₃	0.69	0.44	0.00	0.5	−15.1	1.2	−18.5	−20.9	0.0	−2.4
Acetone	0.62	0.08	0.48	0.0	−13.6	0.0	−3.4	−3.8	−4.5	−0.4
CH₃CN	0.66	0.19	0.31	0.0	−14.4	0.0	−8.0	−9.0	−2.9	−1.0
DMSO	1.00	0.00	0.76	0.0	−21.5	0.0	0.0	0.0	−7.1	0.0
EtOH	0.54	0.83	0.77	0.0	−11.8	0.0	−34.9	−39.4	−7.2	−4.5
MeOH	0.60	0.93	0.62	0.0	−13.1	0.0	−39.1	−44.2	−5.8	−5.1
H₂O	1.09	1.17	0.18	0.0	−23.9	0.0	−49.2	−55.6	−1.7	−6.4
Formamide	0.97	0.71	0.60	0.0	−21.2	0.0	−29.8	−33.6	−5.6	−3.8
DMF	0.88	0.00	0.69	0.0	−19.3	0.0	0.0	0.0	−6.5	0.0
DMA	0.85	0.00	0.76	0.0	−18.6	0.0	0.0	0.0	−7.1	0.0

TABLE 3
Least-Squares-Fitted Solute Parameters for Eq. [4]

	NMF	DMF	NMA	DMA	JOINT
δ_{CH}^{NMF}	350.6 ± 2.0	—	—	—	349.4 ± 1.1
δ_{CH}^{DMF}	—	344.9 ± 1.1	—	—	343.5 ± 0.9
δ_{CH}^{NMA}	—	—	356.9 ± 2.3	—	354.9 ± 1.3
δ_{CH}^{DMA}	—	—	—	360.1 ± 1.9	360.3 ± 1.0
s	−21.2 ± 3.2	−24.1 ± 1.8	−22.6 ± 2.7	−21.5 ± 2.7	−21.9 ± 1.1
sd	—	—	—	—	2.5 ± 1.1
a^F	−43.3 ± 1.8	−41.4 ± 1.4	—	—	−42.0 ± 0.9
a^A	—	—	−48.9 ± 1.2	−47.1 ± 1.6	−47.5 ± 0.9
b^N	−11.0 ± 2.4	—	−10.9 ± 1.7	—	−9.4 ± 1.4
b^D	—	0.6 ± 1.8	—	0.4 ± 2.1	0.0
σ^a	1.9	1.4	1.1	1.6	1.4
ρ^a	0.997	0.998	0.999	0.998	0.995
n^a	10	11	8	9	38

[a] Statistics for a least-squares straight line regression analysis of calculated vs experimental chemical shifts: root-mean-squared deviation (σ), correlation coefficient (ρ), and number of data points (n).

The observed chemical shift of amide X in solvent Y, δ_Y^X, is separated into four contributions,

$$\delta_Y^X = \delta_0^X + S_Y^X + A_Y^X + B_Y^X, \qquad [9]$$

where δ_0^X is the chemical shift for the isolated molecule. S_Y^X is the contribution due to the solvent dielectric effect,

$$S_Y^X = -s\pi_0^* + s\pi_Y^* + sd\delta_Y. \qquad [10]$$

A_Y^X is the contribution due to hydrogen bonding of the amide oxygen lone pairs with a HBD solvent,

$$A_Y^X = a^X\alpha_Y, \qquad [11]$$

with $a^X = a^F$ for formamides and $a^X = a^A$ for acetamides. B_Y^X is the contribution due to hydrogen bonding of the N–H proton of NMF or NMA with a HBA solvent,

$$B_Y^X = b^N\beta_Y. \qquad [12]$$

The contributions to the ^{17}O chemical shifts of amides from the different terms in Eqs. [9] to [12] are listed in Table 2 for a set of solvents. The effects upon the chemical shifts of the long-range dipole–dipole interactions described by Gerothanassis and Vakka are accounted for by the contribution S_Y^X, Eq. [10]. The term $-s\pi_0^*$ represents the contribution from the dielectric effects of cyclohexane. The term $s\pi_Y^*$ corresponds to the difference between the contributions from the dielectric effects of solvent Y and of cyclohexane. The term $sd\delta_Y$ corrects polarizabilities of polychlorinated and aromatic solvents. The coefficient s in Eq. [10] is independent of the amide X under consideration. Therefore, in a given solvent Y, the contribution S_X^Y is the same for the four amides and cannot be assigned, in principle, to specific solvation sites of amides.

If π_0^* is taken equal to −1.06, the dielectric contribution of cyclohexane $-s\pi_0^*$ amounts to −20.8 ppm. The gas-phase chemical shifts provided by Eq. [5] are then 370.2 for NMF, 364.3 for DMF, 375.7 for NMA, and 381.1 ppm for DMA. On the other hand, extrapolation at $(\epsilon - 1)/2\epsilon = 0$ of plots for δ_Y^X, which correspond to a hypothetical case of chemical shifts in vacuo, provides (13) values of 366.7 for NMF and 362.9 ppm for DMF which do not differ too much from those given by Eq. [5]. For DMA, the extrapolated value of 372.2 ppm is 9 ppm smaller than that calculated by means of Eq. [5]. In any case, the reliability of the δ_0^X chemical shifts provided by Eq. [5] could be improved, in principle, using an appropriate set of solvents (21).

When the δ_0^X value cannot be determined with precision, the combination of terms $\delta_0^X + S_Y^X$ in Eq. [9] may be substituted by $\delta_{CH}^X + \Delta S_Y^X$,

$$\delta_0^X + S_Y^X = \delta_{CH}^X + \Delta S_Y^X, \qquad [13]$$

where ΔS_Y^X is the contribution from the dielectric effect of solvent Y relative to cyclohexane,

$$\Delta S_Y^X = s\pi_Y^* + sd\delta_Y. \qquad [14]$$

The contribution to the ^{17}O chemical shift of amides from the dielectric effect of water with respect to that of cyclohexane amounts to −23.9 ppm (Table 2) which is about half of the contribution from the hydrogen bonding at the amide oxygen lone pairs of −49.2 for formamides and of −55.6 ppm for acetamides. However, the total contribution from

TABLE 4
Contributions to the ^{17}O Chemical Shifts of Amides between Infinite Dilution in Water (subscript w) and Acetone (subscript a)

Amide	$S_w - S_a$	$A_w - A_a$	$B_w - B_a$	$(\delta_w - \delta_a)_{calc}$	$(\delta_w - \delta_a)_{obs}$ [a]	$(\delta_w - \delta_a)_{obs}$ [b]
NMF	−10.3	−45.8	2.8	−53.3	−56.3	−53
DMF	−10.3	−45.8	0.0	−56.1	−58.2	−52
NMA	−10.3	−51.8	2.8	−59.3	−60.7	−55
DMA	−10.3	−51.8	0.0	−62.1	−63.5	−53

[a] Reference (13).
[b] Reference (5).

dielectric effects, with respect to gas phase, amounts to −44.7 ppm (−23.9 ppm for the term $s\pi^*_{water}$ and −20.8 ppm for the term $s\pi^*_0$) being of comparable importance to that from hydrogen bonding of oxygen. The contribution from hydrogen bonding of the amide hydrogen N–H is small for water (15), −1.7 ppm, but reaches −7.2 ppm for ethanol.

Analysis of the BAF Model (5)

The 10 parameters in the BAF model, Eqs. [2] and [3], were obtained by solving the 17 linear equations generated from the ^{17}O chemical shift measured for FOR, NMF, DMF, ACA, NMA, and DMA given in Table II of Ref. (5). This system of equations, with coefficients equal to one or zero, can be solved easily by the successive elimination method. Subtraction of selected pairs of equations, which is equivalent to subtraction of the corresponding chemical shifts, provides directly the values of the parameters δO_1, δO_2, δN_1, and δN_2. Application of Eqs. [9] to [12] to these chemical-shift differences reveals the limitations of the BAF model. Through this section, the chemical shifts measured by Fiat *et al.* (5) will be utilized instead of the more accurate chemical shifts measured recently (13) except when the contrary is indicated.

Contributions of $\delta O_1 + \delta O_2$. Fiat *et al.* (5) found that the ^{17}O chemical shifts for amides between infinite dilution in water and acetone were close to −53 ppm. According to the BAF model (5), Eq. [1], this value corresponds to the contribution $\delta O_1 + \delta O_2$ due to hydrogen bonding of amide oxygen, see Eqs. [2] and [3]. When Eqs. [9] to [12] are applied to the corresponding chemical shifts, the explanation becomes more complicated, see Table 4. There is always a contribution $S_w - S_a$ of −10.3 ppm from the different dielectric effects of water and acetone, i.e., −21.9 (1.09 − 0.62) = −23.0 − (−13.6). The contribution $A_w - A_a$ from hydrogen bonding of amide oxygen is dominant, amounting to −45.8 ppm for formamides, i.e., −42.0 (1.17 − 0.08) = −49.2 − (−3.4), and −51.8 ppm for acetamides, i.e., −47.5 (1.17 − 0.08) = −55.6 − (−3.8). In the case of NMF and NMA, there is a small contribution $B_w - B_a$ of 2.8 ppm from hydrogen bonding of amide hydrogen N–H, i.e., 9.4 (0.18 − 0.48) = −1.7 − (−4.5). The order of the differences $(\delta_w - \delta_a)_{obs}$

measured by Gerothanassis and Vakka is well reproduced, see Table 4. These differences are larger than those measured by Fiat *et al.* (5) (up to 10 ppm in the case of DMA, see Table 4) reflecting the smaller precision of the older chemical shifts of amides extrapolated at infinite dilution by Fiat *et al.* (5) which should be used with caution.

The terms δM. Fiat *et al.* (5) found that the ^{17}O chemical shifts for neat DMF and at dilution in acetone are equal to 323 ppm. According to the BAF model, this value corresponds to the δM term for formamides in Eq. [1]. When Eqs. [9] to [12] are applied, the difference $\delta^{DMF}_{neat} - \delta^{DMF}_{acetone}$ is calculated as −2.3 ppm, i.e., −21.9 (0.88 − 0.62) − 42.0 (−0.08) = −19.3 − (−13.6) − (−3.4).

The $\delta(^{17}O)$ shifts for neat DMA and at dilution in acetone were found to be 341 and 339 ppm, respectively (5). According to the BAF model, the average of these values, i.e., 340 ppm, corresponds to the δM term for acetamides in Eq. [1]. The difference $\delta^{DMA}_{neat} - \delta^{DMA}_{acetone}$ is calculated as −1.2 ppm with Eqs. [9] to [12], i.e., −21.9 (0.85 − 0.62) − 47.5 (−0.08) = −18.6 − (−13.6) − (−3.8).

Contributions of δN_2. The differences between the ^{17}O chemical shifts of NMF and DMF measured by Fiat *et al.* (5) at dilution in acetone, ∼2 ppm, or water, ∼1 ppm, correspond in the BAF model to the contribution $\delta N_2 = 2$ of Eq. [2] due to hydrogen bonding of NMF hydrogen N–H. According to Eqs. [9] to [12], this contribution corresponds to a difference of chemical shifts $\delta^{NMF}_{CH} - \delta^{DMF}_{CH}$ of 5.9 ppm plus a hydrogen bonding effect $b^F\beta$ of −4.5 ppm for acetone and of −1.7 ppm for water. The calculated values of 1.4 and 4.2 are in good agreement with those measured with more precision (13) of 1.6 and 3.5 ppm, respectively.

Contributions of δO_2. The difference between ^{17}O chemical shifts of NMF in water and neat sample (5) corresponds in the BAF model to the contribution $\delta O_2 = -31$ ppm of Eq. [2] due to the second oxygen lone pair participating in a hydrogen bond. This difference is calculated as −33.5 ppm with Eqs. [9] to [12] and taking for the NMF solvent parameters the values $\pi^* = 0.93$, $\alpha = 0.35$, and $\beta = 0.65$, which are averages of the corresponding values for formamide and DMF in Table 2. The difference of contributions from dielectric effects of solvents is −3.5 ppm, i.e., −21.9

$(1.09 - 0.93)$. The difference of contributions from hydrogen bonding to the NMF hydrogen N–H is 4.4 ppm, i.e., -9.4 $(0.18 - 0.65)$. The difference of contributions from the hydrogen bond to the NMF oxygen amounts to -34.4 ppm, i.e., -42.0 $(1.17 - 0.35)$. Therefore, as long as the differences of contributions from dielectric effects of solvents and from hydrogen bonding to the NMF hydrogen N–H near cancel out each other, the measured difference $\delta_{\text{water}}^{\text{NMF}} - \delta_{\text{NMF}}^{\text{NMF}}$ becomes close to the difference of contributions from the hydrogen bond to the NMF oxygen in water and the neat sample. This is in agreement with the BAF model hypothesis.

The difference between $\delta(^{17}\text{O})$ shifts of NMA in water and neat sample (5) corresponds in the BAF model to the contribution $\delta O_2 = -32$ ppm of Eq. [3]. This difference is calculated as -38.4 ppm with Eqs. [9] to [12] and the values $\pi^* = 0.91$, $\alpha = 0.35$, and $\beta = 0.68$ for the parameters of the NMA solvent, which are averages of the corresponding values for acetamide and DMA in Table 2. The calculated differences of contributions from dielectric effects of solvents, hydrogen bonding of the NMA hydrogen N–H, and hydrogen bonding of the NMA oxygen amount to -4.0, 4.6, and -39.0 ppm, respectively.

Contributions of δO_1. The difference between ^{17}O chemical shifts of neat NMF and at dilution in acetone (5) corresponds in the BAF model to the contribution $\delta O_1 = -22$ ppm of Eq. [2] due to the first oxygen lone pair participating in a hydrogen bond. This difference is calculated as -19.7 ppm with Eqs. [9] to [12]. The difference of contributions from dielectric effects of solvents is -6.8 ppm, i.e., -21.9 $(0.93 - 0.62)$. The difference of contributions from hydrogen bonding to the NMF hydrogen N–H is -1.6 ppm, i.e., -9.4 $(0.65 - 0.48)$. The difference of contributions from the hydrogen bond to the NMF oxygen amounts only to -11.3 ppm, i.e., -42.0 $(0.35 - 0.08)$, unlike the BAF model.

The difference between $\delta(^{17}\text{O})$ shifts of neat NMA and at dilution in acetone (5) corresponds in the BAF model to the contribution $\delta O_1 = -22$ ppm of Eq. [3]. This difference is calculated as -20.9 ppm with Eqs. [9] to [12]. The difference of contributions from dielectric effects, hydrogen bonding of the NMA hydrogen N–H, and hydrogen bonding of the NMA oxygen are calculated as -6.3, -1.8, and -12.8 ppm, respectively.

Contributions of δN_1. The difference between ^{17}O chemical shifts of FOR and NMF in water or in acetone (5), 9 ppm, corresponds in the BAF model to the contribution δN_1 $= 9$ ppm of Eq. [2] due to the hydrogen bonding of the amide hydrogen N–H in cis position with respect to the carbonyl oxygen. Likewise, the differences between the $\delta(^{17}\text{O})$ shifts for ACA and NMA in water, 10 ppm, and that in acetone, 7 ppm, correspond to the contribution $\delta N_1 = 10$ ppm of Eq. [3]. The parameters in Eq. [4] for FOR and

ACA have still not been determined, which precludes the possibility of testing adequately the reliability of the δN_1 values of the BAF model. Under the assumption that the parameters for Eq. [4] in the last column of Table 3 are also valid for FOR and ACA and that the effects of hydrogen bonding at the two hydrogen N–H are additive, the only new parameters to be determined would be the chemical shifts in cyclohexane of FOR, $\delta_{\text{CH}}^{\text{FOR}}$, and ACA, $\delta_{\text{CH}}^{\text{ACA}}$, and the coefficient b^C of the β solvent basicity in Eq. [4] which corresponds to hydrogen bonding of amide hydrogen N–H in cis position with respect to the carbonyl oxygen. The determination of these parameters from the $\delta(^{17}\text{O})$ shifts measured by Fiat *et al.* (5) does not provide satisfactory results. From the data for FOR and NMF in water and in acetone the following equations are derived:

$$\delta_{\text{CH}}^{\text{FOR}} + 0.18b^C = 358.4, \qquad [15]$$

$$\delta_{\text{CH}}^{\text{FOR}} + 0.48b^C = 358.4. \qquad [16]$$

These equations provide the values $\delta_{\text{CH}}^{\text{FOR}} = 358.4$ and $b^C = 0.0$. The equations obtained from the data for FOR and DMF,

$$\delta_{\text{CH}}^{\text{FOR}} + 0.18b^C = 355.2, \qquad [17]$$

$$\delta_{\text{CH}}^{\text{FOR}} + 0.48b^C = 359.0, \qquad [18]$$

provide different values: $\delta_{\text{CH}}^{\text{FOR}} = 352.9$ and $b^C = 12.7$. The equations derived from the data for ACA and NMA,

$$\delta_{\text{CH}}^{\text{ACA}} + 0.18b^C = 364.9, \qquad [19]$$

$$\delta_{\text{CH}}^{\text{ACA}} + 0.48b^C = 361.9, \qquad [20]$$

give $\delta_{\text{CH}}^{\text{ACA}} = 366.7$ and $b^C = -10.0$. On the other hand, the equations from data of ACA and DMA,

$$\delta_{\text{CH}}^{\text{ACA}} + 0.18b^C = 362.0, \qquad [21]$$

$$\delta_{\text{CH}}^{\text{ACA}} + 0.48b^C = 363.8, \qquad [22]$$

provide the values $\delta_{\text{CH}}^{\text{ACA}} = 360.9$ and $b^C = 6.0$.

The differences between ^{17}O chemical shifts which are taken in the BAF model as the contributions $\delta N_1 = 9$ ppm of Eq. [2] and $\delta N_1 = 10$ ppm of Eq. [3] correspond in part to the chemical-shift differences $\delta_{\text{CH}}^{\text{FOR}} - \delta_{\text{CH}}^{\text{NMF}}$ and $\delta_{\text{CH}}^{\text{ACA}} - \delta_{\text{CH}}^{\text{NMA}}$, respectively. These differences are assumed to be equal to zero in the BAF model. The former difference is calculated as 9.0 ppm from $\delta_{\text{CH}}^{\text{FOR}} = 358.4$ ppm, Eqs. [15] and [16], and as 3.5 ppm from $\delta_{\text{CH}}^{\text{FOR}} = 352.9$ ppm, Eqs. [17] and [18]. The latter difference is calculated as 11.8 ppm from $\delta_{\text{CH}}^{\text{ACA}} = 366.7$ ppm, Eqs. [19], and [20] and as 6.0 ppm from $\delta_{\text{CH}}^{\text{ACA}} = 360.9$ ppm, Eqs. [21], and [22].

On the other hand, recent measurements (23) of the ^{17}O chemical-shift differences Δ_Y of trans and cis NMF (t- and

c-NMF) indicate that the sensitivity b^C to solvent basicity of hydrogen N–H in cis position with respect to the carbonyl oxygen is close to the sensitivity b^N of an hydrogen in trans position, i.e., −9.4 ppm. In fact, the Δ_Y measured in seven solvents range from about 0 to 2.6 ppm only with an average value of 1.7 ppm. Therefore, the sensitivity of the [17]O chemical shift to the solvent effects is near equal for c-NMF, with the methyl group in trans position to the carbonyl oxygen, and for t-NMF, with the methyl group in cis position (the acronym NMF in this paper means t-NMF). This implies that $b^N = b^C$ and $\delta_{CH}^{t\text{-}NMF} - \delta_{CH}^{c\text{-}NMF} \approx 1.7$ ppm. Equations [19] and [20], derived from the data for ACA and NMA in water and acetone (5), are in good agreement with the former relationships, i.e., $b^C = -10.0$ is close to $b^N = -9.4$. This result supports the reliability of the value of about 367 ppm provided by Eqs. [19] and [20] for δ_{CH}^{ACA}. The difference $\delta_{CH}^{ACA} - \delta_{CH}^{NMA}$ amounts then to about 12 ppm. A chemical shift of about 362 ppm is estimated for δ_{CH}^{FOR} from Eqs. [15] and [16] by assuming that $b^C = -10$. The difference $\delta_{CH}^{FOR} - \delta_{CH}^{NMF}$ of about 13 ppm is close then to the difference $\delta_{CH}^{ACA} - \delta_{CH}^{NMA}$, indicating that the effect upon the [17]O chemical shifts of substituting an hydrogen N–H in cis position with respect to the carbonyl oxygen is near equal for ACA compared to that for FOR as one might expect.

The Substituent Effects

Reliable values for the substituent effects can be determined by using Eqs. [9] to [14] with the parameter set in the last column of Table 3. A molecule of DMF can be set up from a molecule of NMF after substitution of the N–H hydrogen in position trans to the carbonyl oxygen by a methyl group. The difference Z_T^{NMF} between the chemical shifts of the isolated molecules of DMF, δ_0^{DMF}, and NMF, δ_0^{NMF}, represents, therefore, the effect upon the [17]O chemical shifts of substituting the hydrogen N–H in NMF by a methyl group,

$$Z_T^{NMF} = \delta_0^{DMF} - \delta_0^{NMF}. \qquad [23]$$

Likewise, the difference

$$Z_T^{NMA} = \delta_0^{DMA} - \delta_0^{NMA} \qquad [24]$$

represents the effect of substituting the N–H hydrogen in NMA by a methyl group. On the other hand, the differences

$$Z_G^{NMF} = \delta_0^{NMA} - \delta_0^{NMF}, \qquad [25]$$

$$Z_G^{NMA} = \delta_0^{DMA} - \delta_0^{DMF}, \qquad [26]$$

represent the effects of substituting the O=C—H hydrogen in NMF and DMF, respectively, by a methyl group.

According to the results given in Table 3 for the fits to

Eq. [4] of the chemical shifts of NMF, DMF, NMA, and DMA, the response of δ_Y^X to the solvent polarity–polarizability, i.e., the value of parameter s^X, is the same for the four molecules. Therefore, after substitution of Eq. [5] in Eqs. [23] to [26], the substituent effects Z are expressed as differences between chemical shifts measured in cyclohexane:

$$Z_T^{NMF} = \delta_{CH}^{DMF} - \delta_{CH}^{NMF}, \qquad [27]$$

$$Z_T^{NMA} = \delta_{CH}^{DMA} - \delta_{CH}^{NMA}, \qquad [28]$$

$$Z_G^{NMF} = \delta_{CH}^{NMA} - \delta_{CH}^{NMF}, \qquad [29]$$

$$Z_G^{NMA} = \delta_{CH}^{DMA} - \delta_{CH}^{DMF}. \qquad [30]$$

From these equations and from Eq. [4], with the parameter set in last column of Table 3 provided by the joint fit of chemical shifts, the following relationships are obtained:

$$Z_T^{NMF} = (\delta_Y^{DMF} - \delta_Y^{NMF}) + b^N\beta_Y, \qquad [31]$$

$$Z_T^{NMA} = (\delta_Y^{DMA} - \delta_Y^{NMA}) + b^N\beta_Y, \qquad [32]$$

$$Z_G^{NMF} = (\delta_Y^{NMA} - \delta_Y^{NMF}) - (a^A - a^F)\alpha_Y, \qquad [33]$$

$$Z_G^{NMA} = (\delta_Y^{DMA} - \delta_Y^{DMF}) - (a^A - a^F)\alpha_Y. \qquad [34]$$

The measured differences $(\delta_Y^M - \delta_Y^N)$ between the chemical shifts of each pair of molecules M and N are listed in Table 5 together with the corresponding substituent effects Z calculated by means of Eqs. [31] to [34]. In accordance with these equations, the differences $(\delta_Y^M - \delta_Y^N)$ show a rather larger variation with the nature of solvent Y than the effects Z.

For formamides NMF and DMF, as well as for acetamides NMA and DMA, the contributions to the chemical shifts from a given solvent Y are equal for each pair of molecules except for the term $b^X\beta_Y$ from solvent basicity. Therefore, the effects Z_T^{NMF} and Z_T^{NMA} of substituting the N–H hydrogen of NMF and NMA, respectively, with a methyl group are calculated by adding to the corresponding differences $(\delta_Y^{DMF} - \delta_Y^{NMF})$ and $(\delta_Y^{DMA} - \delta_Y^{NMA})$ the values $b^N\beta_Y$ in Table 2, see Eqs. [31] and [32].

On the other hand, for N-methyl derivatives NMF and NMA, as well as for the N,N-dimethyl derivatives DMF and DMA, the only contribution to the chemical shifts which differs for each pair of molecules is the term $a^X\alpha_Y$ from solvent acidity. Therefore, the effects Z_G^{NMF} and Z_G^{NMA} of substituting the O=C—H hydrogen of NMF and NMA with a methyl group are calculated by subtracting from the corresponding differences $(\delta_Y^{NMA} - \delta_Y^{NMF})$ and $(\delta_Y^{DMA} - \delta_Y^{DMF})$ the values $(a^A - a^F)\alpha_Y$ in Table 2, see Eqs. [33] and [34].

In the next to last row of Table 5, the substituent effects Z are presented, obtained by averaging the corresponding values calculated with Eqs. [31] to [34]. The numbers differ

TABLE 5
Differences $\delta_Y^M - \delta_Y^N$ between Chemical Shifts and Substituent Effects Z^N Provided by Eqs. [31] to [34] (in ppm)

Solvent Y	$\delta_Y^{DMF} - \delta_Y^{NMF}$	Z_T^{NMF}	$\delta_Y^{DMA} - \delta_Y^{NMA}$	Z_T^{NMA}	$\delta_Y^{NMA} - \delta_Y^{NMF}$	Z_G^{NMF}	$\delta_Y^{DMA} - \delta_Y^{DMF}$	Z_G^{DMF}
CCl$_4$	−5.9	−5.9	—		—		15.9	15.9
Toluene	−4.7	−5.7	—		—		—	—
CH$_2$Cl$_2$	−6.8	−6.8	5.7	5.7	3.2	4.8	15.7	17.3
CHCl$_3$	−9.3	−9.3	5.4	5.4	0.7	3.1	15.4	17.8
Acetone	−1.6	−6.1	10.1	5.6	4.8	5.2	16.5	16.9
CH$_3$CN	−2.9	−5.8	8.7	5.8	4.4	5.4	16.0	17.0
DMSO	−0.5	−7.6	11.9	4.8	5.5	5.5	17.9	17.9
EtOH	3.3	−3.9	14.7	7.5	1.1	5.6	12.1	16.6
MeOH	1.7	−4.1	12.6	6.8	−0.3	4.8	10.6	15.7
H$_2$O	−3.5	−5.2	8.3	6.6	0.4	6.8	11.2	17.6
Average		−6.0		6.0		5.2		17.0
Cyclohexane[a]		−5.9		5.4		5.5		16.8

[a] From δ_{CH}^M values in last column of Table 3.

less than 1 ppm from those in the last row of Table 5 calculated from the δ_{CH}^M values in the last column of Table 3 provided by the joint fit of all chemical shifts to Eq. [4].

Calculations of ^{17}O Shielding Constants

Reliable calculations of ^{17}O shielding constants may contribute to the elucidation of the structure of aqueous formamide and of the challenging question about the number of water molecules hydrogen-bonded to the carbonyl oxygen in amides (*23, 24*).

Hydration of amides has been the subject of a large number of theoretical studies dealing with the characterization of the energetics of amide–water complexes via ab initio molecular calculations (*24*) or with the modeling of the complete solvation of amide moiety via statistical mechanical methods (*23*).

The four principal hydration sites of FOR depicted in Fig. 1 were located by Alagona *et al.* using a minimal basis set (*25*). Full gradient optimization of the corresponding four FOR + H$_2$O complexes were performed by Jasien and Stevens for basis sets of double zeta plus polarity quality (*26*).

A statistical-thermodynamic Monte-Carlo computer simulation of a dilute aqueous solution of FOR has been carried out by Marchese *et al.* (*27*). The essential structural feature from the results of this simulation is a first hydration shell consisting of 11.2 water molecules, of which 2.4 are associated with the NH$_2$ groups, 4.6 with the carbonyl group, and 5.0 with the CH fragment. A structure indicating the nature of the first hydration shell of the carbonyl oxygen includes four solvent water molecules, and is shown in Fig. 24 in (*27*). There are clearly two in-plane and two out-of-plane solvent–oxygen interactions. The in-plane solute–water distances are shorter than the out-of-plane solute–water distances. The latter involve hydrogen bonding with the π

cloud. On the other hand, another Monte-Carlo simulation performed by Jorgensen and Swenson (*28*), using different FOR–water potential functions, yielded only two water molecules hydrogen-bonded to the carbonyl oxygen. Accordingly, the peak heights for the hydrogen-bonding interactions in the radial distribution functions were 50–100% higher in the work by Marchese *et al.* (*27*) than in the work by Jorgensen and Swenson. This is consistent, according to the opinion of the latter authors, with an overestimation of the strengths of FOR–water hydrogen bonding in the simulation by Marchese *et al.* (*27*).

The ^{17}O magnetic-shielding constants of FOR and hydrated FOR have been calculated previously by Ribas Prado *et al.* (*29*) using self-consistent perturbation methods at the ab initio level with a minimal basis set. The method of computation utilized was developed by Ditchfield (*30*) using

TABLE 6
Hydration Shifts (ppm) for FOR

Hydrate	Shift	Ab initio		Empirical models	
		m.b.s[a]	6-31G$^-$	BAF	KAT
FOR + H$_2$O	δO_1	−47.2	−33.1	−22	—
FOR + H$_2$O	δO_2	−46.6	−28.5	−31	—
	$\delta O_1 + \delta O_2$	−93.8	−61.6	−53	−49.2
FOR + H$_2$O	δN_1	−20.8	−15.3	9	−1.7
FOR + H$_2$O	δN_2	−14.8	−4.9	2	−1.7
	$\delta O_1 + \delta O_2 + \delta N_1$				
	$+ \delta N_2$	−129.4	−81.8	−42	−52.6
FOR + (H$_2$O)$_4$		−128.0	−83.2	—	—
Additivity deviation		1.4	−1.4		

[a] Calculated with a minimal basis set (*29*).

gauge-invariant atomic orbitals. The calculated ^{17}O hydration shifts are given in Table 6. The calculated ^{17}O shift change due to the four hydrogen bonds, -128.0 ppm, is larger than the empirical hydration shift estimated for FOR, about -100 ppm ($\delta_{water}^{NMF} - \delta_0^{NMF} + b^N\beta_{water} = 272.4 - 349.4 - 20.9 - 1.7$). The calculated ^{17}O shift changes due to each particular hydrogen bond, i.e., δO_1, δO_2, δN_1, and δN_2, are significantly larger in magnitude than those predicted by the BAF model, as shown in Table 6.

Ribas Prado *et al.* (*29*) also studied the variation of the ^{17}O magnetic-shielding constants of NMF with the conformation of the methyl group. A deshielding effect of 22.0 ppm with a minimal basis and of 23.7 ppm with a split basis was predicted going from a conformation with an *N*-methyl C–H bond eclipsing the C–N bond to a conformation with a C–H bond eclipsing the N–H bond. Smaller deshielding effects of 13.9 ppm with a 6-31G* basis and of 15.0 ppm with a 6-311G** basis have been calculated recently by Contreras *et al.* (*31*) using the LORG method (*32*). These differences prompted us to recalculate the ^{17}O hydration shifts with the LORG method at the 6-31G* level using a geometry calculated after full gradient optimization of the FOR + $(H_2O)_4$ system (Fig. 1) with basis sets of double zeta plus polarity quality (*26*). The calculated hydration shifts appear in Table 6. Details about these calculations are given in the Appendix.

The ^{17}O hydration shifts calculated at the 6-31G* level are smaller in magnitude than those calculated with a minimal basis set. The 6-31G* ^{17}O shift change due to the four hydrogen bonds, -83.2 ppm, becomes smaller than the empirical hydration shift, -100 ppm. The calculated ^{17}O shift change $\delta O_1 + \delta O_2$ due to the two hydrogen bonds at the amide oxygen, -61.6 ppm, is in reasonable agreement with the empirical value, -49.2 ppm, provide by the KAT relationships. Likewise, the calculated δN_1 shift, -4.7 ppm, does not differ very much from the empirical value, -1.7 ppm. This agreement is remarkable, keeping in mind the fact that the KAT hydrogen bond contributions are defined from the shift difference between the actual macroscopic system (where there are water molecules hydrogen-bonded to FOR) and an hypothetical system (where the hydration shifts come only from the solvent dielectric effects, see Eq. [4]). On the other hand, the ab initio calculated hydrogen bond contributions are here defined simply as the shift differences between the FOR + H_2O complexes and the isolated FOR molecule.

The ab initio calculated chemical-shift variations produced by each of the four molecules of water in Fig. 1 are near additive. Deviations from simple additivity are smaller than 2 ppm for the FOR + $(H_2O)_4$ complex, see Table 6. Nonadditivity solvation phenomena in amides have been studied by Johansson *et al.* (*33*) using ab initio methods. The three complexes of type FOR–water–water indicated in Fig. 1 were considered. The central water molecule in
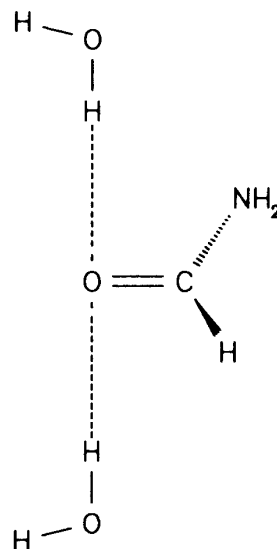

FIG. 3. Drawing of the FOR + $(H_2O)_2$ system with two out-of-plane water molecules.

each complex was that which in Fig. 1 gives rise to the contribution δO_1 (complex **1**), δN_2 (complex **2**), or δO_1 (complex **3**). The second water molecules (those not hydrogen-bonded to FOR) are enclosed on circles. In complexes **1** and **2,** the central water is functioning as a proton donor and acceptor and the nonadditivity is negative (-1.7 and -1.6 Kcal/mol). In complex **3,** the central water is functioning as a double-proton donor and the nonadditivity is positive (1.6 Kcal/mol). Analogously, the nonadditivity of the ^{17}O chemical shifts calculated at the 6-31G* level is positive for complexes **1** (2.5 ppm) and **2** (1.5 ppm) but negative for complex **3** (-0.4 ppm). The corresponding shift changes from the second water molecules amount to -11.5, -1.8, and 2.5 ppm for complexes **1, 2,** and **3,** respectively. These results indicate the convenience of including the second hydration shell of FOR in the calculation of ^{17}O chemical shifts or, at least, the second water of complex **1.** The significant shift change from this water is due to the fact that its oxygen lies close to the $O{=}C{-}H$ hydrogen, see Fig. 1. The remaining in-plane water molecules of the second hydration shell are far from FOR giving much smaller shift changes.

The ^{17}O shift change calculated for a FOR + $(H_2O)_5$ hydrate with the four waters in the first hydration shell plus the second water of complex **1,** -94.7 ppm, is close to the empirical hydration shift, -100 ppm.

Until now, only the in-plane water molecules have been considered. On the other hand, the possible hydrogen bonds of the amide oxygen with two out-of-plane water molecules could give rise to important ^{17}O shift changes (see Fig. 3). The hydration shift calculated at the 6-31G* level for a complex FOR + $(H_2O)_4$ with two in-plane and two out-of-plane water molecules hydrogen-bonded to the amide oxygen amounts to -94.2 ppm, close to the empirical hydration

shift of FOR, -100 ppm. As the chemical-shift variations produced by each water molecule are near additive, and the shift change from each out-of-plane water is equal to -18.0 ppm, the calculated hydration shifts for complexes with more than four water molecules hydrogen-bonded to the amide oxygen would be probably too large.

The above results show that reliable ab initio calculations of ^{17}O chemical shifts for the FOR + $(H_2O)_n$ complexes may be of considerable assistance in determining the most probable location of the water molecules around FOR. Additional calculations are being undertaken with this aim which cover three topics: (i) improved ^{17}O chemical-shift calculations including correlation for FOR + H_2O dimers, (ii) study of FOR + $(H_2O)_n$ complexes incorporating the first and second hydration shells, and (iii) calculations of ^{17}O chemical shifts changing the distance and relative orientation of the FOR and H_2O molecules. Recently, Hansen *et al.* (*34*) have calculated by the ab initio LORG method the shieldings of ACA and NMA in the presence of point charges and hydrogen fluoride simulating dipolar perturbations. The results were analyzed in terms of electric field effects and contributions along the bond directions, assuming a cos θ angular dependence between the charge and the bond that is polarized, and a $1/r^2$ distance dependence. Expressions were parameterized which can form a basis for a protocol for analyzing changes in amide and peptide shieldings caused by charged perturbers or, conversely, for inferring the locations of an atom or group changing charge from the chemical-shift response of nuclei in its vicinity. Likewise, from our ab initio calculations (topic iii), we project to parameterize expressions for describing the dependence of the ^{17}O chemical shifts of FOR with the orientation and distance of a H_2O molecule. These expressions would be useful for estimating the hydration shifts of amides and peptides from statistical mechanical computer simulations of diluted aqueous solutions.

CONCLUSION

The BAF model (*5*) for separating the different contributions to the ^{17}O chemical shifts due to hydrogen bonding at various sites in the amide molecule provided, as long ago as in 1981, a coherent basis for the quantitative description and physical interpretation of the solvent effects upon the ^{17}O chemical shifts of amides and peptides.

The main limitation of the BAF model is that it does not take into account the significant contribution of the solvent dielectric effect on the ^{17}O chemical shifts. This fact was recently demonstrated by Gerothanassis and Vakka (*13*) after careful extrapolation to infinite dilution of the ^{17}O chemical shifts of NMF, DMF, NMA, and DMA in a series of solvents. A multiple-linear-regression analysis of these data using the KAT solvatochromic parameters provides a very satisfactory model for the quantitative description of

the ^{17}O chemical shifts in amides and peptides. The observed chemical shift is separated into four contributions:

(i) The chemical shift for the isolated (or dissolved in cyclohexane) molecule.

(ii) A contribution due to the solvent dielectric effect which only depends on the solvent, i.e., for a given solvent this contribution is the same for the four amides.

(iii) A contribution due to hydrogen bonding of the amide oxygen lone pairs with a HBD solvent. The response to the solvent acidity is slightly larger for acetamides than formamides.

(iv) A contribution due to hydrogen bonding of the N–H proton of NMF or NMA with a HBA solvent.

The quantitative linear solvation shift relationships which embody the model allowed us to determine reliable values for the effects of methyl substituents upon the ^{17}O chemical shifts of amides.

The ^{17}O chemical shifts of DMF and DMA are highly sensitive to solvent HBD acidity and show excellent correlations with π^* and α. Therefore, these shifts might in the future prove to be quite useful for the determination of new α values.

The results provided by ab initio LORG calculations at the 6-31G* level of ^{17}O hydration shifts of FOR support the conclusion that no more than four water molecules are hydrogen-bonded to the amide oxygen.

APPENDIX

The ^{17}O hydration shifts have been calculated using full gradient optimized structures for the complex FOR + $(H_2O)_4$, with the four in-plane water molecules in the first hydration shell, as well as for the complexes **1, 2,** and **3** of type FOR–water–water indicated in Fig. 1. For the complex FOR + $(H_2O)_4$, with four water molecules hydrogen-bonded to the amide oxygen, only the position of the two out-of-plane water molecules was optimized as shown in Fig. 3. The two in-plane water molecules were constrained to have the same position as those in the FOR + $(H_2O)_4$ planar complex.

The ab initio optimizations have been performed at the SCF level for basis sets of double zeta plus polarization quality (*26*). These basis sets were constructed as 3, 1 contractions of the shared-exponent valence basis sets of Stevens *et al.* (*35*). The H basis was the scaled Dunning DZ basis (*36*). The exponents used with polarization functions were $\alpha_p(H) = 1.0$, $\alpha_d(O) = 0.80$, $\alpha_d(N) = 0.77$, and $\alpha_p(C) = 0.75$. In all calculations, the 1s core electrons of carbon, nitrogen, and oxygen were replaced by compact effective potentials CEP (*35*) which results in a decrease in the basis set superposition error relative to comparable all electron calculations (*26, 37*). The structures were restricted to C_s symmetry during the optimization. All calculations were

done with the Gaussian 92 (*38*) and the GAMESS programs (*39*). Geometries and stabilities for the formamide–water complexes studied in this paper have been discussed by other authors in Refs. (*26, 33, 40*).

The ab initio calculations of ^{17}O hydration shifts have been performed at the 6-31G* level with the RPAC program (*41*) interfaced to the GAMESS program. The Local Origin (LORG) method was used with localization of both occupied and virtual orbitals and including all ''core'' orbitals.

ACKNOWLEDGMENTS

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