JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 10, 383–395 (1997)

INFLUENCE OF ISOTOPIC SUBSTITUTION ON STRENGTH OF HYDROGEN BONDS OF COMMON ORGANIC GROUPS

MARTIN ČUMA AND STEVE SCHEINER*
Department of Chemistry, Southern Illinois University, Carbondale, Illinois 62901, USA

Although the electronic contribution to the strength of a H-bond is unaffected by isotopic substitution, the heavier mass of deuterium compared with protium lowers some of the vibrational frequencies in the complex. The binding energy of the complex, which includes zero-point and thermal vibrational energies, can thus be altered by several tenths of a kcal mol^{-1} by H/D substitution. *Ab initio* calculations are used to analyze this phenomenon in a number of common organic functional groups that are prone to form H-bonds: hydroxyl, carbonyl, carboxyl and amide, both self-complexing as homodimers and with water molecules as partners. It is found that any site of D-substitution increases the complexation energy; however, the bridging sites show a stronger preference for D over H than do the non-bridging, or terminal, sites. Hence D-bonding can be considered to be stronger than H-bonding in these functional groups. Of the groups considered, the energetic preference for D over H is greatest in the hydroxyl group, so deuterium would be expected to gravitate toward solvent water molecules in isotopic scrambling experiments. The increments in H-bonding energy resulting from each site of substitution are additive in cases of multiple substitution. © 1997 by John Wiley & Sons, Ltd.

J. Phys. Org. Chem. **10**, 383–395 (1997) No. of Figures: 1 No. of Tables: 5 No. of References: 27
Keywords: hydrogen bond strength; organic groups; isotopic substitution
Received 16 July 1996; accepted 3 January 1997

INTRODUCTION

The hydrogen bond represents one of the most fundamentally important issues in chemistry.[1–4] An intramolecular H-bond can be a controlling factor in the conformational analysis of any molecule in which it is present, and intermolecular H-bonds contribute to the structural dynamics of many molecules in solution.[5] These interactions are integral ingredients in the basic structure and function of important biomolecules such as proteins, nucleic acids and carbohydrates.[6] The entire phenomenon of aqueous solvation rests upon the many H-bonds that are continuously formed and dissociated. Measurement of the pK of a given molecule takes place within an environment where protons are being rapidly transferred to and fro along H-bonds.[7]

Isotopic substitution has historically been of great utility in probing the phenomenon of H-bonding. Since the electronic structures of H and D are identical, it is sometimes assumed that a D-bond is equal in strength to an H-bond. While this may be correct from an electronic standpoint, the assumption ignores the contributions made to binding energies from other factors, most notably vibrational motions of the nuclei. The deuterium nucleus is twice as heavy as protium, so frequencies that are associated with the motion of this atomic center will tend to be lower when H is replaced by D, which will, in turn, be reflected in lesser vibrational energy. While it might appear at first sight that a D-bonded complex will be of lower energy than its H-bonded analogue, the situation is not that simple. The strength of the interaction is derived not only from the energy of the complex, but rather as the latter property in relation to the energies of the separated molecules from which the complex is constituted, and the vibrational energies of the subunits will also be lowered by substitution of H by D.

In order to obtain a fundamental understanding of this phenomenon, researchers initially restricted themselves to small systems such as the HF dimer. Consideration of the dimer in the gas phase permits a careful analysis of the vibrational modes, unobstructed by interactions with a large number of solvent molecules. Experimental and computational work has shown a greater strength for the D-bond in FD· · ·FH than the H-bond in FH· · ·FD, with the difference estimated as 0·3 kcal/mol (1 kcal = 4·184 kJ).[8, 9] Detailed analysis of the various modes identified the bending motion of the bridging hydron off of the H-bond axis to be the principal mode that leads to the observed result. The D-bonded complex is also found to be stronger than its H-bonded analogue in other systems such as $(HCl)_2$.[10] $(H_2O)_2$,[11] $(HCN)_2$[12] and complexes pairing water with formaldehyde, NH_3, formamide and various olefins.[13–16]

---

* *Correspondence to:* S. Scheiner.

Contract grant sponsor: National Institutes of Health; *Contract grant number:* GM29391.

CCC 0894–3230/97/050383–13 $17.50

Other work has extended the sizes of systems examined in the gas phase to amino acid oligomers.[17]

Recent calculations in this laboratory[18] have analyzed the situation in the water dimer and found results analogous to what was found previously in $(HF)_2$: the D-bond is stronger than the H-bond, due to the vibrational mode that displaces the bridging hydron from the H-bond axis. The work went on to demonstrate that the same principle applies to the larger water trimer. In an interesting contrast, the calculations indicated that the stronger ionic complexes, e.g. $H_2O\cdots H^+\cdots OH_2$ or $HO^-\cdots H^+\cdots OH^-$, follow a reverse trend wherein it is the H-bond that is stronger than the D-bond. All of these patterns were traced to zero-point vibrational energies and were analyzed within the framework of intramolecular and intermolecular types of modes.

We turn our attention in this paper to larger molecules containing functional groups. It was our aim to learn if the trends noted for simple molecules such as water apply also to groups commonly encountered in organic chemistry. To this end, we considered the carbonyl, carboxyl and amide groups. As in our earlier study,[18] the work is not restricted to replacement of a single H by D, but instead, all possible substitutions are considered up to and including replacement of all hydrogens.

METHODS

All computations were performed at the *ab initio* level using the Gaussian 94 set of codes.[19] Since earlier work has indicated little sensitivity of the H/D substitution trends to details of the basis set or to inclusion of electron correlation, calculations were carried out at the SCF/6–31G* level.[20] Geometries of all complexes were fully optimized. Vibrational analysis was based upon the standard harmonic approximation, with no empirical scaling factors. The electronic contribution to the binding energy of each complex was computed as the difference between energy of that complex, and the sum of the energies of the constituent monomers, also fully optimized. This quantity was then corrected for basis set superposition error by the counterpoise procedure.[21] The zero-point vibrational energy (ZPVE) of each entity is equal to half the sum of all $(3N-6)$ vibrational frequencies.

RESULTS

Formaldehyde–water

The geometry of the complex pairing formaldehyde with water is illustrated in Figure 1(a). The hydrogen bond is bent by a considerable amount, with $\theta(OH\cdots O) = 101°$. This bending may be understood on the basis of an electrostatic attraction between the oxygen atom of the water and the hydrogen of H_2CO (labeled H_{bf}), which have partial charges of opposite sign. This particular interaction would probably not be classified as a H-bond since the distance separating these two atoms is 2·725 Å. This compares with the much shorter 2·110 Å between the carbonyl oxygen and the bridging hydrogen of the water (H_{bw}). The interoxygen separation is 2·954 Å.

The three vibrational modes of the isolated water molecule retain their character largely intact in the complex with formaldehyde. The same can be said of the six modes of the larger H_2CO. The total ZPVEs of these two isolated molecules are 14·41 and 18·31 kcal/mol^{-1}, respectively. In addition to these nine intramolecular modes, formation of the complex produces six new modes, of intermolecular character. These modes are of much lower frequency, varying between 117 and 522 cm^{-1}. Together, these six new modes account for 2·06 kcal mol^{-1} of ZPVE, as indicated in the first row of Table 1. The 32·78 kcal mol^{-1} of intramolecular ZPVE in the complex is larger by 0·05 kcal mol^{-1} than the sum of the pair of isolated molecules, which is reported as the 'intra' contribution of ΔZPVE in Table 1. So together with the intermolecular ZPVE, the total change in ZPVE caused by the formation of the complex is 2·11 kcal mol^{-1}. When this quantity is subtracted from the electronic contribution to the interaction energy (3·71 kcal mol^{-1} after correction of basis set superposition error), one arrives at a theoretical estimate of 1·60 kcal mol^{-1} for D_0, as reported in the penultimate column of Table 1.

The potential energy surface on which the nuclei move is determined by the electronic structure alone and so is unaffected by isotopic substitution. Therefore, the electronic contribution to the interaction energy, $-\Delta E$, remains constant at 3·71 kcal mol^{-1}. However, heavier masses generally lead to smaller vibrational energies. Since deuterium is twice as heavy as protium, replacement of the latter by the former is expected to lower the vibrational energy. This expectation is confirmed by the next rows of Table 1. Substitution of one of the four hydrogen atoms of $H_2CO\cdots HOH$ by a deuterium lowers the ZPVE from 34·84 to 32·62–32·83 kcal mol^{-1}.

The distinction between the latter values depends upon the particular site where this substitution occurs. As indicated in Figure 1(a), there are four non-equivalent sites in $H_2CO\cdots HOH$. The subscript b refers to a site in a 'bridging' location and t to a non-bridging, i.e. 'terminal' site. The second subscript introduces the notation that f refers to formaldehyde and w to water. The absence or presence of a deuterium at each site is indicated in Table 1 by a 0 or 1, respectively, under the appropriate index.

Comparison with the first row of Table 1 leads to the observation that substitution of a terminal hydrogen by deuterium increases the interaction energy by 0·06–0·09 kcal mol^{-1} for replacement on the formaldehyde and water molecule, respectively. Substitution of the bridging hydrogen of formaldehyde produces a comparable increment of 0·08 kcal mol^{-1}. By far the largest effect arises from the replacement of the bridging hydrogen of water by D, which enhances the interaction energy by 0·28 kcal mol^{-1}. These increments in the interaction strength are defined as δE and are listed in the final column of Table 1.

The deuterium substitution affects the intramolecular and intermolecular frequencies in very different ways. As may be noted by a scan of the intra ΔZPVE column of Table 1, this quantity is insensitive to D-substitution, remaining below 0·1 kcal mol^{-1} in all cases. The intermolecular ZPVE is far more sensitive to isotopic replacement. For example, substitution of the bridging water hydrogen by D lowers the intermolecular ZPVE from 2·06 to 1·79 kcal mol^{-1}, a drop of 0.27 kcal mol^{-1}. Hence it is the intermolecular modes which are essentially completely responsible for the 0·28 kcal mol^{-1} strengthening of the H-bond upon this substitution.

More detailed scrutiny of the six intermolecular modes leads to the observation that the four lowest frequencies are insensitive to the isotopic substitution, identifying modes 5 and 6 as primarily responsible for the effects noted. Mode 5 represents a wagging of the water molecule, relative to formaldehyde, and mode 6 corresponds to a displacement of the bridging hydrogen off the H-bond axis. Since the former involves motion of both hydrogens of water, and the latter only the bridging atom, it is not surprising that mode 5 drops in frequency as a result of substitution of either water hydrogen (by *ca* 40 cm^{-1}) whereas the frequency of mode

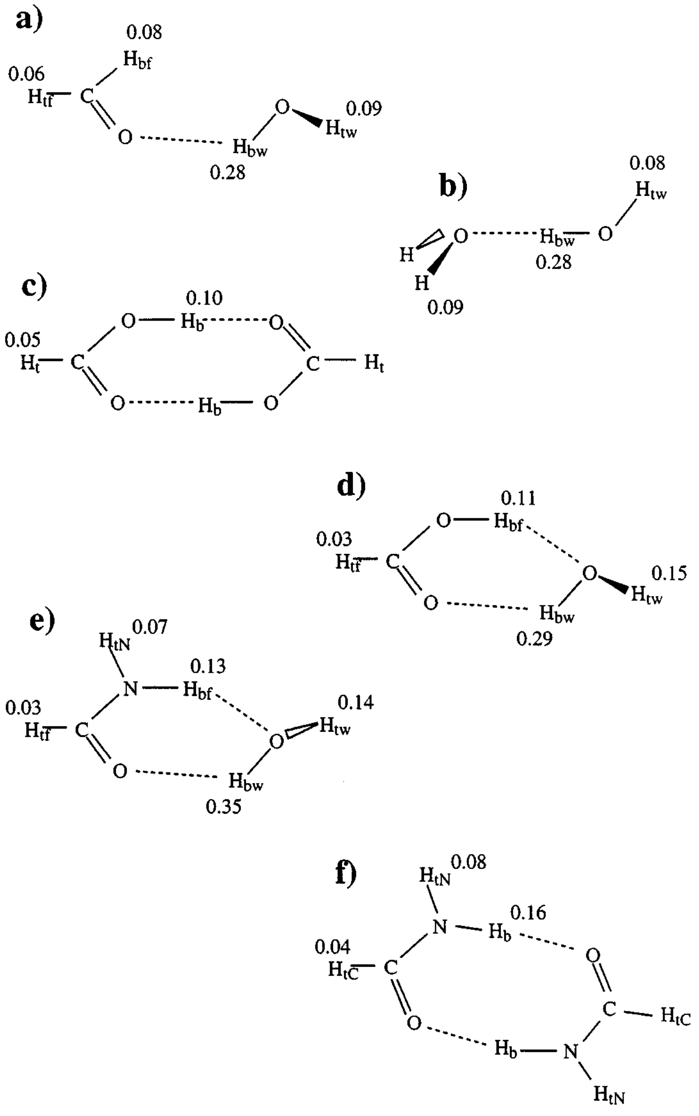

Figure 1. Schematic diagram of the systems examined· Numbers refer to approximate H-bond strengthening (in kcal mol^{-1}) caused by replacement of the indicated hydrogen atom by a deuterium

6 is lowered only by replacement of the bridging atom (by *ca* 140 cm^{-1}). It is the large magnitude of the frequency drop of the H-bond bending mode 6 which is chiefly responsible for the substantial strengthening of the interaction resulting from substitution of H_{bw}. This observation conforms to earlier findings in the water dimer.[18]

A more detailed comparison to the water dimer can be executed via Figure 1(b), which indicates the equilibrium geometry, as well as the energetic advantage of replacing each protium by deuterium. The latter data for the proton-donor water molecule is nearly identical with the values computed here for $H_2CO\cdots HOH$ in Figure 1(a), despite the loss of linearity of the H-bond in the latter complex.

The data in Table 1 that pertain to multiple replacements indicate a high degree of additivity between the energetic effects of isotopic substitutions. For example, the replacement of H_{bf} adds 0·08 kcal mol^{-1} to the H-bond energy and 0·28 kcal mol^{-1} is added by substitution of H_{bw}. Simultaneous replacement of both increments the interaction energy of the complex by the sum of these two, viz. 0·37 kcal mol^{-1}. The greatest molecular interaction thus arises from the replacement of all four hydrogens by deuterium, which increases the interaction energy from 1·60 to 2·10 kcal mol^{-1}. The increments to the interaction energy that arise from the substitution of each of the four hydrogens of $H_2CO\cdots HOH$ are indicated in Figure 1(a) by the numerical values.

Formic acid dimer

The formic acid dimer adopts a cyclic geometry with a pair of equivalent H-bonds, as illustrated in Figure 1(c). The H-bond length of each, $R(O\cdots O)$, is equal to 2·802 Å, and they are close to linear with $\theta(OH\cdots O)$ = 173·5°. Note that these bonds are shorter (and much more linear) than the single H-bond in $H_2CO\cdots H_2O$, where $R(O\cdots O)$ is 2·954 Å.

The ZPVE of a single isolated HCOOH molecule is computed to be 23·23 kcal, so that a pair of such molecules would account for 46·46 kcal mol^{-1}. As indicated in the first row of Table 2, the ZPVE of the undeuterated formic acid dimer is 48·51 kcal mol^{-1}. The difference between the

Table 1. Zero-point vibrational energies and total interaction energy computed for the complex of H_2CO with HOH (in kcal mol^{-1})

				ZPVE			ΔZPVE[b]			
n_{bf}	n_{bw}	n_{tf}	n_{tw}[a]	Inter	Intra	Total	Intra	Total	$-(\Delta E+\Delta ZPVE)$[c]	δE[d]
0	0	0	0	2·06	32·78	34·84[e]	0·05	2·11	1·60	
	$n_b+n_t=1$									
1	0	0	0	2·00	30·81	32·81	0·03	2·03	1·68	0·08
0	1	0	0	1·79	30·83	32·62	0·04	1·82	1·88	0·28
0	0	1	0	2·00	30·83	32·83	0·05	2·05	1·66	0·06
0	0	0	1	1·94	30·87	32·81	0·08	2·01	1·69	0·09
	$n_b+n_t=2$									
1	1	0	0	1·73	28·87	30·59	0·01	1·74	1·97	0·37
1	0	1	0	1·95	28·83	30·79	0·02	1·98	1·73	0·13
0	1	1	0	1·72	28·89	30·61	0·04	1·76	1·95	0·35
1	0	0	1	1·88	28·91	30·78	0·05	1·93	1·78	0·18
0	1	0	1	1·69	28·87	30·55	0·06	1·75	1·96	0·36
0	0	1	1	1·87	28·93	30·80	0·08	1·95	1·76	0·16
	$n_b+n_t=3$									
1	1	1	0	1·68	26·89	28·57	0·01	1·69	2·02	0·42
1	1	0	1	1·63	26·90	28·53	0·04	1·66	2·04	0·44
1	0	1	1	1·83	26·93	28·76	0·05	1·88	1·83	0·23
0	1	1	1	1·63	26·92	28·55	0·06	1·68	2·02	0·42
	$n_b+n_t=4$									
1	1	1	1	1·58	24·92	26·50	0·03	1·61	2·10	0·50

[a] Subscripts on indices correspond to the four hydrogens in Figure. 1(a).

[b] Difference in ZPVE between the complex and the pair of subunits to which it corresponds.

[c] D_0.

[d] Increase in binding energy resulting from indicated D substitution.

[e] Harmonic frequencies in the undeuterated complex are 117, 132, 173, 192, 305, 522, 1350, 1388, 1673, 1847, 2007, 3187, 3280, 4045 and 4167 cm^{-1}.

Table 2. Zero-point vibrational energies and total interaction energy computed for HCOOH dimer (in kcal mol^{-1})

		ZPVE			ΔZPVE			
n_b	n_t	Inter	Intra	Total	Intra	Total	$-(\Delta E+\Delta\mathrm{ZPVE})$	δE
0	0	3·65	44·86	48·51[a]	−1·60	2·06	10·84	
$n_b+n_t=1$								
0	1	3·60	42·70	46·30	−1·59	2·01	10·89	0·05
1	0	3·55	42·57	46·11	−1·59	1·96	10·94	0·10
$n_b+n_t=2$								
0	2	3·54	40·54	44·09	−1·58	1·96	10·93	0·09
1	1	3·50	40·40	43·90	−1·58	1·91	10·98	0·14
2	0	3·44	40·28	43·72	−1·59	1·85	11·04	0·20
$n_b+n_t=3$								
1	2	3·44	38·24	41·69	−1·58	1·87	11·03	0·19
2	1	3·39	38·11	41·50	−1·58	1·81	11·08	0·24
$n_b+n_t=4$								
2	2	3·34	35·95	39·29	−1·57	1·77	11·13	0·29

[a] Harmonic frequencies in the undeuterated complex are 73, 165, 167, 191, 237, 246, 733, 746, 915, 966, 1209, 1213, 1359, 1359, 1510, 1537, 1566, 1572, 1949, 2000, 3329, 3332, 3767 and 3816 cm^{-1}.

ZPVE of the complex and that of an isolated pair of HCOOH molecules is designated as ΔZPVE and is equal to 2·06 kcal mol^{-1} in this case. In other words, there is 2·06 kcal mol^{-1} more vibrational energy in the complex than in the isolated subunits from which it is derived. This larger energy is consistent with the conversion of three translational and three rotational degrees of freedom in the pair of molecules to six vibrational modes in the complex.

The electronic contribution to the binding energy of the formic acid dimer is 12·90 kcal mol^{-1}, after correction for basis set superposition error by the counterpoise procedure. In other words, the electronic energy of the complex is lower than twice that of a single HCOOH molecule by this amount. Since the complex contains more vibrational energy than the pair of isolated subunits, the total interaction energy, D_0, is computed by subtracting 2·06 kcal mol^{-1} from 12·90 kcal mol^{-1}, to arrive at the value of 10·84 kcal mol^{-1}, reported in the penultimate column of Table 2. In the general case, then, a larger ΔZPVE results in a weaker interaction.

Substitution of one of the four hydrogen atoms of $(HCOOH)_2$ by a deuterium lowers the ZPVE from 48·51 to 46·1–46·3 kcal mol^{-1}. The distinction between the latter two values depends upon whether this substitution occurs on a hydrogen atom which is or is not participating in an H-bond. The bridging hydrogens are covalently bound to oxygen and the terminal hydrogens to carbon. The numbers of such atoms are indicated in Table 2 by the designations n_b and n_t, respectively. As may be seen in the second and third rows of data in Table 2, the ZPVE is smaller by 0·2 kcal mol^{-1} when the substitution occurs on one of the bridging, as compared with terminal, sites.

This smaller ZPVE translates into a larger value of total interaction energy in the penultimate column of the table. Comparison with the first row of Table 2 leads to the observation that substitution of a terminal hydrogen (i.e. CH) by deuterium increases the interaction energy by 0·05 kcal mol^{-1} whereas replacement of a bridging (OH) atom by D enhances this quantity by 0·10 kcal mol^{-1}. This rule appears to be general enough as to apply also to multiple substitutions. That is, the 0·05 and 0·10 kcal mol^{-1} increments in the H-bond energy appear to be additive. One may therefore write a simple expression for the total interaction energy for the formic acid dimer as

$$D_0\ (\mathrm{kcal\ mol^{-1}}) = 10{\cdot}84 + 0{\cdot}05\,n_t + 0{\cdot}10\,n_b \qquad (1)$$

Having established the effect of D-substitution on either the bridging or terminal position, it is possible to carry the analysis one step further by distinguishing the intramolecular vibrational modes of the complex from the intermolecular modes. The distinction in the case of the formic acid dimer is not as obvious as in formaldehyde plus water. In the present case, analysis of the various modes shows that the eight of lowest frequency represent primarily the motion of one subunit relative to the other, and are consequently categorized as intermolecular. In contrast, the intramolecular modes, which are of higher frequency, refer to motions that are localized largely within the subunits themselves, and resemble the modes of the isolated monomers.

The first two columns of data in Table 2 illustrate that the ZPVE of the eight intermolecular modes of unsubstituted $(HCOOH)_2$ is 3·65 kcal mol^{-1}, in comparison with the 44·86 kcal mol^{-1} associated with modes 9–24. The latter quantity is 1·60 kcal mol^{-1} lower than the total vibrational energy of the two isolated HCOOH monomers, as reported in the ZPVE column in Table 2. The total value of ΔZPVE, equal to 2·06 kcal mol^{-1}, is thus constituted of two parts: the 1·60 kcal mol^{-1} decrement in the intramolecular modes cancels in part the 3·65 kcal mol^{-1} contribution from the intermolecular modes (which have no counterpart in the isolated monomers).

Turning now to the 0·05 kcal mol^{-1} decrease in ΔZPVE that arises when one terminal H is replaced by D, comparison of the first two rows of Table 2 shows this decrement to originate in the intermolecular modes; the intra ΔZPVE shows no change. The same is true when the replacement occurs on a bridging site, except that the decrement in inter ZPVE is larger, around 0·10 kcal mol^{-1}. (In the case where one or two bridging hydrogens are replaced by D, modes 7 and 8 become nearly equal in frequency, within about 40 cm^{-1}, and reverse their order.) Again, the patterns noted here for single substitutions persist as additive effects in the multiple replacements characterized by the following rows of Table 2. Each substitution of H by D has little effect on intra ΔZPVE but lowers inter ZPVE by 0·05 kcal mol^{-1} for a terminal site and by 0·10 kcal mol^{-1} for a bridging substitution.

One can carry the analysis a step further so as to identify the specific intermolecular modes that are responsible for this pattern. The replacement of a protium by deuterium produces little change in the six lowest frequencies of the dimer. It is the pair of modes 7 and 8, with frequencies 733 and 747 cm^{-1} in the unsubstituted dimer, that undergo significant changes upon replacement by D. In particular, substitution at the bridging site lowers these frequencies by *ca* 60 cm^{-1} for each such replacement, which translates into a 0·09 kcal mol^{-1} drop in ZPVE. This reduction is sensible as modes 7 and 8 represent bends of the H-bond that displace the bridging hydron off the H-bond axis. The higher mass of the deuterium might therefore be expected to lower the associated frequency. The replacement of the terminal protium by the heavier D also lowers the ZPVE, albeit by not as much. The frequency drops occur in some of the lower frequency modes, in particular those that contain significant contributions from motion of the terminal CH hydrogen.

The greater decrease in intermolecular vibrational energy associated with substitution of a bridging as compared to a terminal hydrogen is consistent with findings in smaller systems such as $H_2CO\cdot\cdot\cdot HOH$ in the previous section, and $(H_2O)_2$ or the HF dimer.[8, 9, 18] In those simpler cases, too, the largest contributor to the observed effect is the bending motion of the H-bond.

It may be noted that eight modes have been categorized here as intermolecular, two more than the customary six. It should be stressed, however, that we are concerned in this paper not so much with the total ZPVE of either the inter- or intramolecular modes, but rather with the *changes* observed in these quantities upon isotopic substitution, and in identifying the particular modes which are most sensitive, regardless of whether they are classified is inter or intramolecular. For that reason, the classification into either of these two categories, which is admittedly arbitrary to some degree, becomes less important than the effects of substitution upon the total ZPVE.

Formic acid–water

The optimal geometry of the complex pairing formic acid with water also contains two distinct H-bonds. As illustrated in Figure 1(d), the terminal hydrogen of the water molecule, designated H_{tw}, is positioned out of the plane of the remainder of the system. The two H-bonds in this complex are different from a geometric perspective. The bond in which formic acid acts as proton donor to the water oxygen acceptor would appear to be the stronger of the two. The $O\cdot\cdot\cdot O$ distance is 2·80 Å compared with 2·89 Å for the other bond in which the water acts as donor to the carbonyl oxygen of the formic acid. The former H-bond is also the more linear of the two with a $\theta(OH\cdot\cdot\cdot O)$ angle of 157°, compared with 130° for the latter bond. These bonds are probably weaker than those in the formic acid dimer, both of which are 2·80 Å long and within 7° of linear.

Table 3 lists the vibrational energy data arising from the substitution of all combinations of the four hydrogen atoms by deuterium. As indicated in the first row, the total ZPVE of the unsubstituted complex is 40·31 kcal mol^{-1}, about 8 kcal mol^{-1} less than in the formic acid dimer. This smaller energy can be easily attributed to the smaller number of vibrational modes in $HCOOH\cdot\cdot\cdot HOH$. Of the 18 modes, the seven of lowest frequency can be classified as intermolecular in nature. The cumulative ZPVE of these seven modes is computed to be 3·55 kcal mol^{-1}. The total of 40·31 kcal mol^{-1} is 2·67 kcal mol^{-1} higher than the sum of the ZPVE of the two constituent molecules, prior to the formation of the complex, as indicated by the entry for the total ΔZPVE in Table 3. When the latter quantity is subtracted from the electronic contribution to the interaction energy (8·64 kcal mol^{-1}), D_0 is computed to be 5·97 kcal mol^{-1}, somewhat weaker than that of the formic acid dimer. This weaker character is consistent with the geometrical aspects mentioned above.

Inspection of the next four rows of Table 3 indicates that the replacement of each H of the complex by D leads to a strengthening of the interaction, with the amount depending upon the specific atom substituted. The largest increment arises from the two atoms on the water: the bridging atom H_{bw} is associated with an increase of 0·29 kcal mol^{-1}, while that of the terminal hydrogen H_{tw} is 0·15 kcal mol^{-1}. These increases are indicated in Figure 1(d), which shows the increments arising from replacement of the two hydrogens on formic acid, H_{bf} and H_{tf}, to be 0·11 and 0·03 kcal mol^{-1}, respectively.

Comparison with Figure 1(c) indicates that the increments associated with the two hydrogens of formic acid are not changed dramatically when the partner molecule is changed from formic acid to water. Comparison of the data for the water molecule with what was noted previously for the water dimer[18] is complicated by the different equilibrium geometry of the latter species which contains only a single, linear H-bond. Nonetheless, it is interesting that the increment of 0·29 kcal mol^{-1} computed here for the bridging water hydrogen in HCOOH· · ·HOH matches closely the increment of 0·28 in $(H_2O)_2$, as indicated in Figure 1(b).

The succeeding rows of Table 3 indicate that the increments arising from monosubstitution are very nearly additive when more than one H is replaced by D. For example, substitution of both bridging atoms in HCOOH· · ·HOH enhances the binding energy by 0·29 + 0·11 = 0·40 kcal mol^{-1}, to 6·37 kcal mol^{-1}. Consistent with this additivity, the strongest interaction arises when all four protiums are changed to deuterium, stronger than the unsubstituted case by 0·57 kcal mol^{-1}.

The partitioning of the ZPVE into intra and intermolecular modes provides a certain consistency with the data for the formic acid dimer in Table 2. In both cases, the intramolecular contributions to ΔZPVE are very little affected by isotopic substitution. One may hence trace the effect on the energy to the intermolecular modes. Also as in the formic acid dimer case, one can further focus on the two intermolecular modes of highest frequency which contain the largest segment of the isotopic sensitivity. Mode 7 corresponds approximately to an H-bond bend, involving chiefly the displacement of the bridging hydrogen of formic acid. It is therefore not surprising that this mode drops in frequency by 49 cm^{-1} upon replacement of H_{bf} by the heavier deuterium; the bending frequency of the water, mode 6, is reduced by 144 cm^{-1} when H_{bw} is substituted by D.

Formamide–water

We now turn our attention to the formamide molecule and its complex with water. As illustrated in Figure 1(e), the geometry is much like that in the case of formic acid + water. There are two H-bonds present. R(O· · ·O) is equal to 2·895 Å, similar to the length of the equivalent H-bond in HCOOH· · ·HOH. The other H-bond is somewhat longer with R(N· · ·O) = 2·988 Å. The former H-bond is also slightly more linear, with θ(OH· · ·O) = 148°, compared with

Table 3. Zero-point vibrational energies and total interaction energy computed for the complex of HCOOH with HOH (in kcal mol^{-1})

				ZPVE			ΔZPVE			
n_{bf}	n_{bw}	n_{tf}	n_{tw}[a]	Inter	Intra	Total	Intra	Total	$-(\Delta E+\Delta\text{ZPVE})$	δE
0	0	0	0	3·55	36·76	40·31[b]	−0·88	2·67	5·97	
$n_b+n_t=1$										
1	0	0	0	3·44	34·46	37·91	−0·88	2·56	6·08	0·11
0	1	0	0	3·26	34·82	38·08	−0·88	2·38	6·26	0·29
0	0	1	0	3·50	34·61	38·11	−0·86	2·64	6·00	0·03
0	0	0	1	3·37	34·85	38·22	−0·86	2·52	6·12	0·15
$n_b+n_t=2$										
1	1	0	0	3·15	32·53	35·68	−0·89	2·27	6·37	0·40
1	0	1	0	3·40	32·31	35·71	−0·86	2·54	6·10	0·13
0	1	1	0	3·21	32·68	35·88	−0·87	2·34	6·30	0·33
1	0	0	1	3·27	32·55	35·82	−0·86	2·41	6·23	0·26
0	1	0	1	3.11	32.85	35.96	−0.87	2.24	6.40	0.43
0	0	1	1	3·32	32·70	36·03	−0·84	2·48	6·16	0·19
$n_b+n_t=3$										
1	1	1	0	3·10	30·37	33·48	−0·87	2·24	6·40	0·43
1	1	0	1	3·00	30·55	33·55	−0·87	2·13	6·51	0·54
1	0	1	1	3·22	30·40	33·62	−0·84	2·38	6·26	0·29
0	1	1	1	3·06	30·71	33·76	−0·85	2·21	6·43	0·46
$n_b+n_t=4$										
1	1	1	1	2·95	28·40	31·35	−0·85	2·10	6·54	0·57

[a] Subscripts on indices correspond to the four hydrogens in Figure 1(d).

[b] Harmonic frequencies in the undeuterated complex are 166, 179, 218, 247, 352, 578, 748, 937, 1204, 1342, 1526, 1574, 1831, 1997, 3315, 3825, 4024 and 4157 cm^{-1}

θ(NH$\cdot\cdot\cdot$O) = 139° in the second H-bond. In agreement with the inference one might draw from the bond lengths, comparison of Table 4 with Table 3 indicates that the interaction energy in the HCONH$_2\cdot\cdot\cdot$HOH complex is smaller than that for formic acid. This weaker interaction can be attributed to the weaker proton-donating ability of the amide group compared with carboxyl.

The first rows of Tables 3 and 4 point out further similarities. The intermolecular ZPVEs of the two systems are nearly identical, at 3·55 and 3·56 kcal mol^{-1}, respectively. Of course, the intramolecular ZPVE is larger for the formamide complex, owing to its greater number of vibrational modes. More importantly for our purposes, the change in ZPVE due to formation of the complex from a pair of isolated subunits is similar in both complexes, slightly less than 3 kcal mol^{-1}. In fact, ΔZPVE is a bit

Table 4. Zero-point vibrational energies and total interaction energy computed for the complex of HCONH$_2$ with HOH (in kcal mol^{-1})

					ZPVE			ΔZPVE			
n_{bf}	n_{bw}	n_{tC}	n_{tN}	n_{tw}[a]	Inter	Intra	Total	Intra	Total	$-(\Delta E+\Delta$ZPVE)	δE
0	0	0	0	0	3·56	44·51	48·07[b]	−0·61	2·95	4·52	
$n_b+n_t=1$											
1	0	0	0	0	3·32	42·45	45·77	−0·50	2·82	4·65	0·13
0	1	0	0	0	3·22	42·58	45·80	−0·62	2·61	4·87	0·35
0	0	1	0	0	3·52	42·38	45·91	−0·61	2·92	4·55	0·03
0	0	0	1	0	3·48	42·38	45·85	−0·59	2·89	4·59	0·07
0	0	0	0	1	3·40	42·60	46·00	−0·59	2·81	4·66	0·14
$n_b+n_t=2$											
1	1	0	0	0	2·99	40·50	43·49	−0·51	2·48	4·99	0·47
1	0	1	0	0	3·20	40·40	43·60	−0·41	2·79	4·68	0·16
1	0	0	1	0	3·15	40·38	43·54	−0·39	2·76	4·71	0·19
1	0	0	0	1	3·10	40·60	43·70	−0·42	2·68	4·79	0·27
0	1	1	0	0	3·19	40·44	43·63	−0·62	2·57	4·90	0·38
0	1	0	1	0	3·16	40·41	43·58	−0·62	2·54	4·93	0·41
0	1	0	0	1	3·09	40·61	43·70	−0·59	2·49	4·98	0·46
0	0	1	1	0	3·37	40·32	43·68	−0·52	2·85	4·62	0·10
0	0	1	0	1	3·34	40·50	43·84	−0·56	2·78	4·69	0·17
0	0	0	1	1	3·29	40·49	43·78	−0·54	2·75	4·72	0·20
$n_b+n_t=3$											
1	1	1	0	0	2·94	38·37	41·32	−0·50	2·45	5·02	0·50
1	1	0	1	0	2·91	38·35	41·26	−0·49	2·42	5·05	0·53
1	1	0	0	1	2·86	38·53	41·39	−0·50	2·36	5·11	0·59
1	0	1	1	0	3·11	38·25	41·36	−0·38	2·74	4·74	0·22
1	0	1	0	1	3·06	38·47	41·53	−0·41	2·65	4·82	0·30
1	0	0	1	1	3·04	38·43	41·47	−0·41	2·63	4·85	0·33
0	1	1	1	0	3·13	38·28	41·41	−0·62	2·51	4·97	0·45
0	1	1	0	1	3·05	38·48	41·53	−0·59	2·46	5·01	0·49
0	1	0	1	1	3·03	38·44	41·48	−0·61	2·43	5·04	0·52
0	0	1	1	1	3·25	38·37	41·61	−0·53	2·71	4·76	0·24
$n_b+n_t=4$											
1	1	1	1	0	2·86	36·22	39·08	−0·48	2·39	5·08	0·56
1	1	1	0	1	2·81	36·40	39·22	−0·48	2·33	5·14	0·62
1	1	0	1	1	2·78	36·37	39·16	−0·48	2·30	5·17	0·65
1	0	1	1	1	3·00	36·29	39·29	−0·41	2·60	4·87	0·35
0	1	1	1	1	3·00	36·30	39·30	−0·61	2·39	5·08	0·56
$n_b+n_t=5$											
1	1	1	1	1	2·74	34·24	36·98	−0·47	2·27	5·20	0·68

[a] Subscripts on indices correspond to the five hydrogens in Figure 1(e).

[b] Harmonic frequencies in the undeuterated complex are 137, 161, 182, 211, 335, 423, 651, 667, 801, 1187, 1195, 1425, 1561, 1800, 1854, 1964, 3232, 3779, 3950, 3988 and 4150 cm^{-1}.

larger in the formamide complex, 2·95 versus 2·67 kcal mol^{-1} for HCOOH· · ·HOH. This difference can be traced to the intramolecular modes which undergo a lowering of ZPVE in $HCONH_2$· · ·HOH by 0·61 kcal mol^{-1} compared with 0·88 kcal mol^{-1} in the formic acid analogue. The smaller changes in the formamide can also be traced to the weaker interaction, which has less of a perturbing influence upon the internal modes of each subunit.

The effects of substitution of each hydrogen of $HCONH_2$ · · ·HOH by a deuterium are reported in the next section of Table 4. It might be observed from the last column that each replacement has a strengthening effect upon D_0, although the magnitude of this enhancement is variable. The greatest increase is associated with the bridging hydrogen of the water molecule, which increases D_0 by 0·35 kcal mol^{-1}. The terminal hydrogen of the water produces a much smaller change, only 0·14 kcal mol^{-1}. Substitution at the bridging site of the formamide molecule enhances D_0 by 0·13 kcal mol^{-1}. These changes, along with the smaller changes induced by substitution of the two terminal sites of the formamide, are indicated by the numerical values reported in Figure 1(e). As in the earlier cases, these increments are approximately additive when there are multiple isotopic substitutions present. By replacing all protium nuclei of $NCOHN_2$· · ·HOH by deuterium, the strength of the interaction is enhanced by 0·68 kcal mol^{-1}, an increase of 15%.

Analysis of the vibrational frequency data supports the earlier conclusion that the bulk of the important changes occur in the intermolecular modes. The change in ZPVE undergone by the intramolecular modes, as a result of formation of the complex, may be seen from the fourth to last column of Table 4 to be within the range between −0·4 and −0·6 kcal mol^{-1} for all 32 of the possible isotopic combinations considered. (The distinction between intra- and intermolecular modes in the formamide complexes is clouded by the presence of low-frequency vibrations even in the monomer.)

Formamide dimer

Like the dimer of HCOOH, the formamide dimer also forms a cyclic structure with a pair of equivalent H-bonds, as illustrated in Figure 1(f). Owing to the lower acidity of formamide, its dimer is less strongly bound than is $(HCOOH)_2$, with values of 8·32 and 10·84 kcal mol^{-1}, respectively, for D_0. The weaker H-bonds are reflected also in the H-bond geometries. The H-bond lengths R(N· · ·O) are 2·898 Å in $(HCONH_2)_2$, which compares with R(O· · ·O) = 2·802 Å in the dimer of formic acid; the H-bonds in $(HCONH_2)_2$ are also 5° less linear.

The effects of deuterium substitution in the various sites of the formamide dimer are exhibited in Table 5. As in the previous cases, each substitution leads to an increase in the interaction energy. The magnitudes of these increments are reported as the numerical values in Figure 1(f) and the last column of Table 5. Again, as for the earlier cases, the effects of multiple substitution are additive.

Classification of the various modes as intra- or intermolecular is not straightforward in the formamide dimer. It appears that modes 1–6 are indeed intermolecular, but modes 7 and 8 are of intramolecular type despite their low frequencies of less than 500 cm^{-1}. The last two modes are largely symmetric and antisymmetric combinations of the puckering modes of the nitrogen atoms. Modes 9 and 10 are in the range 650–670 cm^{-1} and are classified here as intermolecular since they contain a large contribution involving bending of the H-bonds. Upon deuterium substitution, the frequencies diminish. The results in Table 5 indicate that the bond strengthening that arises from deuterium substitution is associated with changes in both the intra- and intermolecular vibrational frequencies, although the latter appears in most cases to be the larger contributor.

DISCUSSION

Examination of the various numerical values in Figure 1 provides a provocative set of comparisons. Figure 1(a), (b) and (d) indicate that the energetic preference for deuterium over protium in the bridging site of the water molecule is about 0.28 kcal mol^{-1} in a number of situations. The H-bond is very nearly linear in the water dimer, but is significantly bent in the complex with formaldehyde or formic acid. This value remains about the same even when a second H-bond is present in the complex, as when the acidic hydrogen of formic acid interacts with the oxygen of the water. Figure 1(e) shows a slight increase, to 0.35 kcal mol^{-1}, in this energetic preference for deuterium in the complex with formamide. The primary distinction of this complex is that the oxygen of the water accepts a proton from an NH group, but the geometry is otherwise very much like that between water and formic acid. Turning now to the bridging sites of the other molecules, the energetic preference for D is much smaller, 0·10–0·11 kcal mol^{-1} for the formic acid hydrogen and 0·13–0·16 kcal mol^{-1} for the acidic hydrogen of formamide. It might be noted that in all of these cases, the complex contains a second H-bond.

The terminal hydrogens, i.e. those not engaged in an H-bond, also show an energetic preference for D over H, albeit a smaller one. With reference first to the water molecule, comparison of Figure 1(a) and (b) with Figure 1(d) and (e) reveals that this preference is 0·08–0·09 kcal mol^{-1} when the water acts only as a proton donor, but this quantity increases to 0·14–0·15 kcal mol^{-1} when the water oxygen acts as proton acceptor. The terminal hydrogens of the proton-acceptor molecule generally show a small preference for D over H. The magnitude of this quantity lies in the range 0·06–0·09 kcal mol^{-1} when only a single H-bond is present, as in Figure 1(a) and (b), but is even smaller when the acceptor molecule is HCOOH or $HCONH_2$. The exception is the terminal site on the nitrogen of formamide (the proton-donor atom), for which the preference is slightly larger at 0·07–0·08 kcal mol^{-1}. Another way to generalize this behavior is that the energetic preference lies in the 0·07–0·09 kcal mol^{-1} ranger when this hydrogen is directly bonded to a proton donor atom as in Figure 1(a), (b), (e) and (f). When further removed from the donor atom, and bonded to a carbon, as in Figure 1(c), (d), (e) and (f), the preference lessens to 0·03–0·05 kcal mol^{-1}.

One can discuss what might be expected if various partially deuterated molecules are mixed together. As already described for the water dimer, an HOD molecule would tend to act as the proton donor molecule, with the deuterium acting as the bridge. The same is true when HOD is mixed with H_2CO. The continued preference for deuterium to occupy bridging sites in functional groups would lead HCOOD to form a slightly stronger H-bond than would DCOOH. HCONHD would more likely use its deuterium as the bridging center than the protium.

Table 5. Zero-point vibrational energies and total interaction energy computed for the dimer of $HCONH_2$ (in kcal mol^{-1})

			ZPVE			ΔZPVE			
n_b	n_{tC}	n_{tN}	Inter	Intra	Total	Intra	Total	$-(\Delta E+\Delta\mathrm{ZPVE})$	δE
0	0	0	3·11	61·11	64·22[a]	−0·32	2·79	8·32	
$n_b+n_t=1$									
1	0	0	3·02	58·86	61·88	−0·39	2·63	8·48	0·16
0	1	0	3·07	58·97	62·05	−0·32	2·76	8·36	0·04
0	0	1	3·05	58·93	61·98	−0·34	2·71	8·40	0·08
$n_b+n_t=2$									
2	0	0	2·92	56·62	59·54	−0·46	2·47	8·65	0·33
1	1	0	2·97	56·73	59·70	−0·38	2·59	8·52	0·20
1	0	1	2·94	56·70	59·64	−0·40	2·55	8·56	0·24
0	2	0	3·03	56·84	59·87	−0·31	2·72	8·40	0·08
0	1	1	3·01	56·80	59·80	−0·34	2·67	8·44	0·12
0	0	2	2·98	57·76	59·74	−0·36	2·63	8·49	0·17
$n_b+n_t=3$									
2	1	0	2·88	54·48	57·36	−0·45	2·43	8·68	0·36
2	0	1	2·87	54·42	57·29	−0·48	2·39	8·73	0·41
1	2	0	2·94	54·59	57·53	−0·38	2·56	8·56	0·24
1	1	1[b]	2·88	54·57	57·45	−0·36	2·52	8·59	0·27
1	1	1	2·91	54·55	57·46	−0·40	2·51	8·61	0·29
1	0	2	2·90	54·49	57·39	−0·43	2·47	8·65	0·33
0	2	1	2·97	54·66	57·63	−0·34	2·63	8·48	0·16
0	1	2	2·94	54·62	57·56	−0·36	2·59	8·53	0·21
$n_b+n_t=4$									
2	2	0	2·85	52·33	55·18	−0·45	2·40	8·72	0·40
2	1	1	2·84	52·27	55·11	−0·48	2·36	8·76	0·44
2	0	2	2·82	52·22	55·04	−0·51	2·31	8·80	0·48
1	2	1[b]	2·85	52·42	55·28	−0·37	2·48	8·63	0·31
1	2	1	2·88	52·41	55·29	−0·40	2·47	8·64	0·31
1	1	2	2·86	52·35	55·21	−0·43	2·44	8·68	0·36
0	2	2	2·91	52·48	55·39	−0·36	2·55	8·57	0·25
$n_b+n_t=5$									
2	2	1	2·80	50·13	52·93	−0·48	2·32	8·79	0·47
2	1	2	2·79	50·07	52·86	−0·51	2·28	8·83	0·51
1	2	2	2·83	50·20	53·03	−0·43	2·40	8·72	0·40
$n_b+n_t=6$									
2	2	2	2·75	47·93	50·68	−0·51	2·25	8·87	0·55

[a] Harmonic frequencies in the undeuterated complex are 60, 127, 137, 162, 170, 197, 477, 484, 656, 670, 827, 881, 1194, 1197, 1197, 1203, 1432, 1445, 1565, 1566, 1818, 1824, 1939, 1976, 3226, 3229, 3699, 3725, 3936 and 3936 cm^{-1}.

[b] Three D on same subunit·

There is some experimental evidence that our calculated energy differences are essentially correct. Némethy and Scheraga[22] found a 0·24 kcal mol^{-1} higher H-bond energy for liquid D_2O than H_2O. This energy difference agrees very well with our calculated difference of 0·3 kcal mol^{-1}.[18] More recent gas-phase measurements of the complex pairing 1-naphthol with ammonia[23] indicate that interaction is strengthened by 0·41 kcal mol^{-1} when the bridging proton is changed to a deuteron. *Ab initio* computations yielded a difference of 0·35 kcal mol^{-1}, in remarkable coincidence with the experimental value. This agreement adds confidence that *ab initio* computations of the vibrational frequencies, using a harmonic approximation throughout, are capable of accurate reproduction of experiment. One last point concerns our finding that the effects of deutero substitution at multiple sites are additive. This notion has been confirmed by measurements of the solvation dynamics of methanol and its deuterated derivatives.[24]

The data in Figure 1 provide some clues as to what might happen when various chemical groups are placed in aqueous solution. Of course it is understood that a liquid environment offers the possibility of changes in various vibrational modes, especially the intermolecular ones, but the results presented here provide a useful starting point for discussion nonetheless. The fractionation factor concept serves as an experimentally accessible measure of the preference for D over H. The preferences for the bridging and terminal sites of the water dimer are obvously different, so it would probably be best to consider the fractionation factor of liquid water as some sort of weighted average between these two types of site. If one imagines liquid water as consisting of networks of H-bonded chains, then most of the hydrogens can be considered as bridging. In such a scenario, then, the fractionation factor would reflect an energetic preference for D over H of between 0.08 and 0.28 kcal mol^{-1}, but closer to the larger number.

Formaldehyde contains no hydrogens that can be donated in an H-bond. Consequently, deuterium would favor solvent water over any hydrogen sites on an aldehyde. The same is true of the carboxylic group; the preference for D over H on the acidic hydrogen is only 0·11 kcal mol^{-1} in the complex between formic acid and water, considerably smaller than the preference of 0·29 kcal mol^{-1} for the water hydrogen. One arrives at a similar conclusion for a solvated amide group. Hence for the various functional groups considered here, deuterium would favor occupation of water sites over any sites on the functional groups.

The data in Figure 1 offer some insights into what might occur when the concentration of the functional group rises to the point where self-association begins to occur. Comparison of Figure 1(c) with (d) or (e) with (f) suggests that the dimerization of carboxylic or amide groups produces little perturbation of the energetic preference for D over H of any of the sites relative to that seen in the interaction with water. One might therefore conclude that the tendency for a deuterium to gravitate to the solvent will be unchanged by any self-association that might occur.

The calculations reported up to this point pertain to the very cold regime near 0 K. As the systems approach room temperature, another effect that becomes important is the occupation of excited vibrational states. Whereas the vibrational levels are far enough apart in isolated molecules that there is little excitation even at 298 K, the situation is different in complexes. The strength of an H-bond is many times weaker than that of a normal covalent bond, so the intermolecular vibrational levels are much closer together. This closer spacing permits significant excitation at relatively low temperatures, and leads to a certain amount of ‘thermal’ vibrational energy. It is possible to compute the amount of this quantity by using standard partition functions[25] based on the harmonic vibrational frequencies computed here.

In the case of the complex between water and formaldehyde, for example, this thermal energy amounts to slightly more than 2 kcal mol^{-1} at 298 K. The exact amount depends upon the degree of substitution. Since deuterium is heaver than protium, vibrational frequencies tend to be slightly smaller, so the levels are closer together, leading to higher excitation and more thermal energy. The latter quantity varies from 2·01 kcal mol^{-1} for $H_2CO\cdot\cdot\cdot HOH$ to 2·31 kcal mol^{-1} when all four protiums are replaced by D. Since the interaction energy corresponds to the energy lowering of the complex, relative to a pair of isolated monomers, a larger thermal vibrational energy in the complex is reflected by a weaker interaction. The 0·3 kcal mol^{-1} greater thermal energy in $D_2CO\cdot\cdot\cdot DOD$ washes out some of the 0·5 kcal mol^{-1} larger interaction energy reported above, when the temperature is raised from 0 to 298 K.

Of some importance to our discussion here is the difference in thermal energy that is connected with the particular site of substitution. This distinction appears to have a relatively minor effect upon the thermal energy. Taking the monosubstituted complex between water and formaldehyde as an example again, the thermal energy is computed to be 2·06 kcal mol^{-1} when the replacement occurs in either of the sites on H_2CO. This quantity is equal to 2·09 kcal mol^{-1} for the terminal site on water and 2·13 kcal mol^{-1} for its bridging site. The net result is that the slightly larger thermal energy for bridge substitution lowers the preference for D to occupy this site, based only on electronic and zero-point vibrational effects. In quantitative terms, the 0·19 kcal mol^{-1} preference of the D of HDO to occupy a bridging vs a terminal position in the complex of 0 K [see Figure 1(a)] would be reduced to 0·15 kcal mol^{-1} when the temperature is raised to 298 K. These effects are noted also when multiple substitutions occur; inclusion of thermal vibrational energy tends to diminish slightly the quantitative aspects of the preferences noted above, based only on zero-point vibrational considerations.

Similar patterns are observed in the other complexes studied here. Addition of thermal energies is found in general to reduce the overall greater stability of complexes containing D vs H by ca 50%. However, thermal energies have a much smaller effect on the results noted above that relate to the preference of D for one site over another.

Other factors that contribute to the thermodynamic energy arise from the translational and rotational motions of the complexes and their constituent subunits. While these terms will indeed contribute to the total interaction energy, their contribution will not vary appreciably with the number of isotopic substitutions, or with the particular sites of replacement. The translational and rotational modes will have the net effect of increasing interaction energies by 1·8 kcal mol^{-1} at 298 K; conversion of ΔE to ΔH will add a further 0·6 kcal mol^{-1}. The combined increment of 2·44 kcal mol^{-1} is not very different from the decrements that arise from thermal vibrational energy mentioned above. As a consequence, the values of $-(\Delta E + \mathrm{ZPVE})$ reported in the tables will be similar to final values of the full thermodynamic $-\Delta H$ at 298 K.

The property of interest in equilibrium situations is not the enthalpy or energy, but rather the free energy, ΔG. This quantity can be evaluated from ΔH with the aid of entropic factors. Since the formation reaction involves the merging together of two free molecules into a single complex, the consequent loss of entropy is reflected in a negative value of ΔS. This property varies in the range -26 to -39 cal $\mathrm{K}^{-1}\,\mathrm{mol}^{-1}$, depending on the particular system. Within a given complex, e.g. $H_2CO\cdots HOH$, there is a much smaller variation upon isotopic substitution. In general, the replacement of a bridging protium by deuterium is associated with *ca* 0·2 cal $\mathrm{K}^{-1}\,\mathrm{mol}^{-1}$ larger increase in magnitude of $-\Delta S$ compared with a non-bridging position. When this distinction is converted to its free energy correlate at 298 K, entropic factors are responsible for a small decrement in the purely energetic preference of D over H for a bridging site by perhaps 0·06 kcal mol^{-1}. At temperatures higher than 298 K, this preference will diminish further and eventually vanish entirely.

In any set of quantum calculations, it is always valid to wonder how the results might be changed were another level of theory to be applied. As discussed earlier,[18] application of a larger basis set or inclusion of explicit correlation would certainly be expected to influence the magnitude of binding energies or the vibrational frequencies. However, the thrust of this work is concerned not with the absolute magnitudes of these quantities, but rather with the *changes* that they undergo upon replacement of various protium nuclei by deuterium. These changes are not expected to vary substantially with higher levels of theory, a supposition which is supported by previous work.[18,26] Another primary source of concern is the use of the harmonic approximation in extracting the various vibrational frequencies. Again, there is reason to believe that any changes in these frequencies that would arise from applying anharmonic correction factors would largely cancel in the comparison between protium and deuterium,[18,27] the major focus of this paper.

The above results apply directly to the systems in isolation from other molecules. It is no simple matter to convert rigorously these gas-phase results to a situation wherein the systems of interest are immersed in solvent. In the first place, the translational and rotational modes of the isolated systems will be changed into vibrations involving surrounding molecules. The presence of solvent is also likely to affect the internal vibrational modes of the complexes. Nevertheless, the major conclusions of this work should offer a starting point to consider what might occur in solution. In particular, it is likely that the principal conclusion of a preference of deuterium to occupy a bridging versus a terminal site will survive, although the quantitative aspects of this preference will be changed.[18]

A number of functional groups have been considered here, including hydroxyl, carbonyl, carboxyl and amide. While the particular systems chosen for study place these groups on small model molecules such as water, formaldehyde, formic acid and formamide, there is no reason to believe that the conclusions would be altered in any meaningful way by the use of much larger prototype molecules. As an example, our earlier set of computations[18] compared the protonated methanol and water dimers. The elongation of the water by the methyl group had no significant impact on the qualitative aspects of the H/D competition. Nor were the conclusions arrived at for the water dimer altered when the chain was elongated by a third water molecule.

ACKNOWLEDGMENT

This work was supported by the National Institutes of Health (GM29391).

REFERENCES

1. P. Schuster, G. Zundel and C. Sandorfy (Eds), *The Hydrogen Bond. Recent Developments in Theory and Experiments.* North-Holland, Amsterdam (1976).
2. D. A. Smith (Ed), *Modeling the Hydrogen Bond,* Vol. 569. American Chemical Society, Washington, DC (1994).
3. S. Scheiner, in *Reviews in Computational Chemistry,* edited by D. Boyd and K. Lipkowitz, Vol. 2, pp. 165–218. VCH, New York (1991).
4. S. Scheiner, *Hydrogen Bonding. A Theoretical Perspective.* Oxford University Press, New York (1997).
5. E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis.* American Chemical Society, Washington DC (1981).
6. G. A. Jeffrey and W. Saenger, *Hydrogen Bonding in Biological Structures.* Springer, Berlin (1991).
7. R. Stewart, *The Proton: Applications to Organic Chemistry.* (*Organic Chemistry* edited by H. H. Wasserman, Vol. 46). Academic Press, Orlando, FL (1985).
8. S. A. C. McDowell and A. D. Buckingham, *Chem. Phys. Lett.* **182**, 551–555 (1991).
9. L. A. Curtiss and J. A. Pople, *J. Mol. Spectrosc.* **61**, 1–10 (1976).
10. M. D. Schuder and D. J. Nesbitt, *J. Chem. Phys.* **100**,

7250–7267 (1994).
11. A. Engdahl and B. Nelander, *J. Chem. Phys.* **86**, 1819–1823 (1987).
12. A. J. Fillery-Travis, A. C. Legon, L. C. Willoughby and A. D. Buckingham, *Chem. Phys. Lett.* **102**, 126–131 (1983).
13. B. Nelander and L. Nord, *J. Phys. Chem.* **86**, 4375–4379 (1982).
14. A. Engdahl and B. Nelander, *J. Chem. Phys.* **91**, 6604–6612 (1989).
15. B. Nelander, *J. Chem. Phys.* **72**, 77–84 (1980).
16. A. Angdahl and B. Nelander, *J. Phys. Chem.* **90**, 4982–4987 (1986).
17. S. Campbell, M. T. Rodgers, E. M. Marzluff and J. L. Beauchamp, *J. Am. Chem. Soc.* **117**, 12840–12854 (1995).
18. S. Scheiner and M. Çuma, *J. Am. Chem. Soc.* **118**, 1511–1521 (1996).
19. M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. A. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. J. P. Stetwart, M. Head-Gordon, G. Gonzalez and J. A. Pople. *Gaussian 94*, Gaussian, Pittsburgh, PA (1995).
20. P. C. Hariharan and J. A. Pople, *Theor. Chim. Acta.* **28**, 213–222 (1973).
21. S. F. Boys and F. Bernardi, *Mol. Phys.* **19**, 553–556 (1970).
22. G. Némethy and H. A. Scheraga, *J. Chem. Phys.* **41**, 680–689 (1964).
23. T. Bürgi, T. Droz and S. Leutwyler, *Chem. Phys. Lett.* **246**, 291–299 (1995).
24. H. Shirota, H. Pal, K. Tominaga and K. Yoshihara, *J. Phys. Chem.* **100**, 14575–14577 (1996).
25. I. N. Levine, *Physical Chemistry.* McGraw-Hill, New York (1988).
26. N. J. Harris, *J. Phys. Chem.* **99**, 14689–14699 (1995).
27. P.-O. Åstrand, G. Karlström, A. Engdahl and B. Nelander, *J. Chem. Phys.* **102**, 3534–3554 (1995).