Estimation of N−H···O=C Intramolecular Hydrogen Bond Energy in Polypeptides

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The previously proposed molecular tailoring approached (MTA) [Deshmukh, M. M.; Gadre, S. R.; Bartolotti, L. J. *J. Phys. Chem.* A **2006**, *110*, 12519] for the estimation of intramolecular O−H···O hydrogen bond energy is extended to that for the N−H···O=C bond within polypeptides. The methodology is initially tested on a tetrapeptide containing two types of N−H···O=C hydrogen bonds and is found to distinguish between them. The estimated values are in good agreement with the trends predicted by the geometrical parameters. Furthermore, this methodology is applied to partially as well as fully substituted, capped polyglycines that contain five glycine residues (acetyl-$(gly)_5$-NH_2) to check the effect of substituents on the energetics of hydrogen bonds. The estimated N−H···O=C bond energy values lie in the range of 4−6 kcal/mol. These estimated values are not only in concurrence with the geometric parameters but also able to reflect the subtle effects of substituents for the substituted polypeptides studied in the present work.

Introduction

Hydrogen bonding is an important weak interaction encountered in all of the states of the matter with significant repercussions in chemistry and biology.[1] Hydrogen bonding plays a vital role in many life processes. A significant implication of this interaction is seen in protein folding and DNA base-pairing.[2] Therefore, it is utmost important to understand the nature and estimate the strength of such interactions. Despite growing interest in protein folding and protein structures, quantitative estimates of the strength of the hydrogen bonding interactions are very rarely available, although they play a fundamental role in the determination of peptide structures.

There have been some efforts devoted especially toward understanding the nature of a hydrogen bond on the basis of quantitatively estimating its strength.[3−17] Many experimental techniques and methodologies[18] have been explored for this purpose. However, there is no direct experimental approach known for gauging the energetics of the intramolecular hydrogen bond. Theoretically, intermolecular interactions are usually investigated through a supermolecular approach,[19] wherein the interaction energy is evaluated as the difference between the energies of a supermolecular complex and its constituent monomers. However, such an approach cannot be straightforwardly extended for estimating the strength of intramolecular interactions. Some theoretical procedures are proposed for investigating the energies of intramolecular hydrogen bonds for special systems, wherein the energies of different conformers of the molecule are added/subtracted together.[20] However, the reliability of these methods is a subject of debate.[20,21] Recently, the authors have proposed the molecular tailoring approach (MTA)[22] for estimating the intramolecular hydrogen bond energies in polyhydroxy compounds on the basis of the systematic fragmentation scheme. It has been shown that this method gives quite accurate results[24] and can be easily applied to systems containing multiple O−H···O intramolecular hydrogen bonds.[23,24]

Apart from the simple supermolecular approach, the theoretical methodology[3−11] for the estimation of intramolecular N−H···O=C hydrogen bond strength in polypeptides and proteins has not been much tested. There have been some reports on evaluating the structure, stability, cooperativity, and energetics in some model peptide systems.[6−11] For instance, Gilli et al.[3] studied the intramolecular N−H···O resonance-assisted hydrogen bond in β-enaminones and related heterodienes with the help of a combination of various techniques viz. X-ray crystal-structure determination, IR, and NMR spectroscopy and quantum chemistry. Dannenberg and coworkers estimated the hydrogen bond cooperativity in various polypeptides at the B3LYP/D95(d,p) level of theory.[6] Kemp and coworkers[8] proposed a hydrogen bonding cooperativity model for understanding the helix formation in polyalanine. On the basis of this model, it was suggested that the hydrogen bonding cooperativity strongly contributes to the formation of α-helices in polyalanine. Wu and coworkers[9] gave evidence of cooperativity in 3_{10}- and α-helices based on the residue energy (energy difference between the polypeptide structure with increasing number of amino acid residues). Topol et al.[10] investigated the interconversion between α-helix and 3_{10}-helix by using HF/6-31G(d)* and B3LYP/6-31G(d) methods on a relatively large peptide system on the basis of the hydrogen bond length data. They suggested that there may be more than one possible mechanism for this interconversion. Dixon et al.[11] suggested a value of 21 kJ/mol for hydrogen bond strength between an amide proton and carboxyl oxygen of *N*-methylacetamide. This value is in the range of the values suggested (17−62 kJ/mol) by the Jeffrey for a moderate N−H···O=C hydrogen bond energy.[1] Recently, Zhang et al.[25] proposed a method for determining the intramolecular seven and ten-membered ring N−H···O=C hydrogen-bonding energies in glycine and alanine dipeptides on the basis of the difference in the conformation of peptide containing a hydrogen bond and the one with the absence of this interaction. Although the intramolecular hydrogen bond energy values reported by them for two dipeptides are in the

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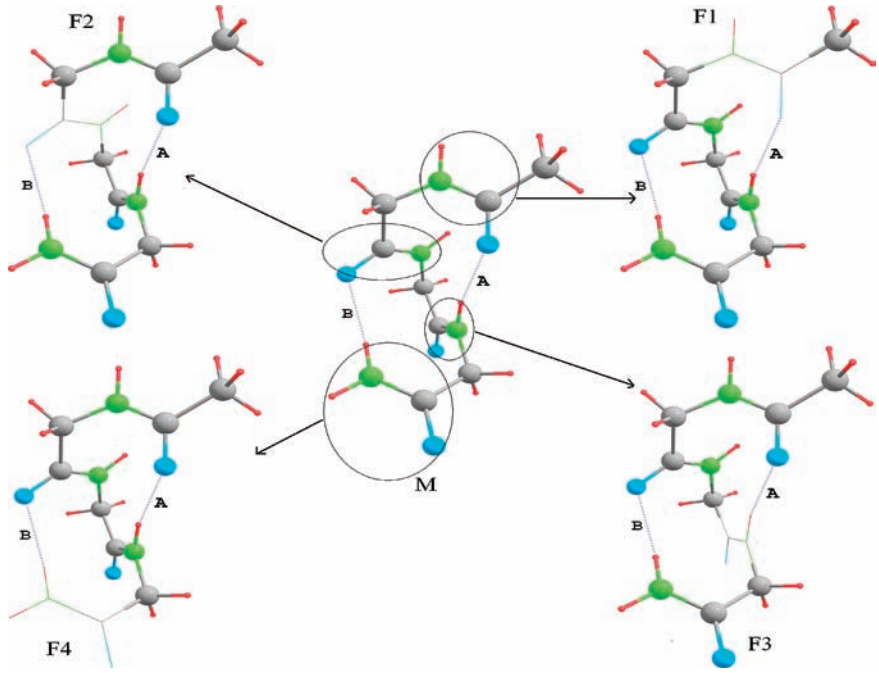
SCHEME 1: Primary Fragmentation of Tetrapeptide, Shown as M[a]



[a] See the text for details.

range of expected values,[1] the methodology involved is not clear because of a variety of approximations made. Moreover, the application of this methodology to a real polypeptide containing multiple hydrogen bonds does not seem to be straightforward. Therefore, although there exist some methodologies for estimating N−H···O═C intramolecular hydrogen bond energy reported in the literature, these are either applied to limited model systems or are difficult to apply to more intricate real-life molecules, necessitating the search of a new approach.

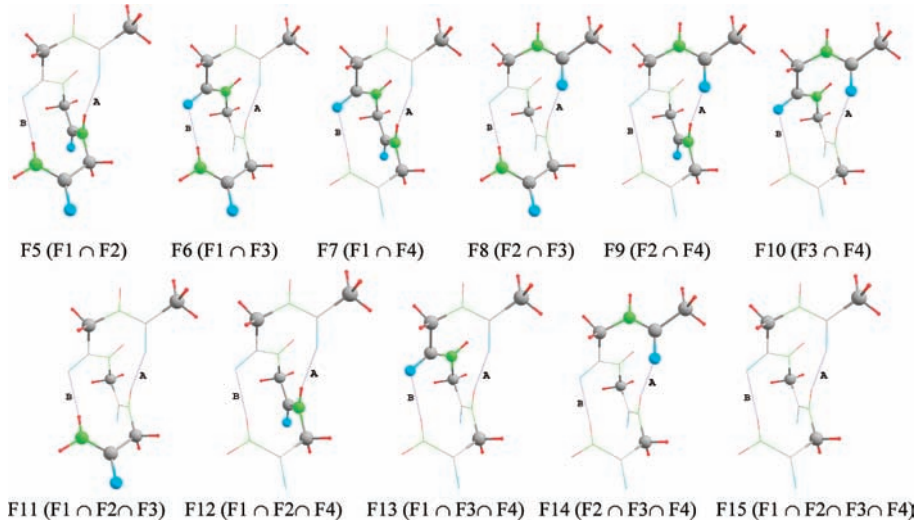
The MTA proposed by Deshmukh et al.[21−23] is found to be quite successful for O−H···O intramolecular hydrogen bond energy estimation. However, a simple extension of it looks apparently difficult for estimating energetics of N−H···O═C intramolecular hydrogen bonds in polypeptides because of the difference in the functional group involved (−N−H and O═C rather than O−H in the polyhydroxy case). One may consider fragmenting the polypeptide molecule by replacing NH and C═O groups by H atoms, as was done in the case of polyhydroxy systems.[21−23] Upon doing so, it is found that although this fragmentation scheme works quite well in the sense of estimating both molecular and N−H···O═C intramolecular hydrogen bond energy, there are some unphysical interactions present in such fragments. For example, upon replacing NH and C═O groups by H atoms in any of the NHCO groups, the binary overlapping fragments (Methodology Section) have the replaced hydrogen atoms too close to each other (within the bond distance of standard H_2 bond length, that is, less than 0.74 Å). Authors believe that the reason for good energy estimates, if any, with this scheme is due to fortuitous cancellation of these unphysical interactions while estimating the energetics.[21] This has prompted us to look for the new fragmentation scheme.

In this article, we propose a new scheme for the fragmentation of a polypeptide via MTA for accessing the N−H···O═C intramolecular hydrogen bond. This scheme is applied to a test tetrapeptide molecule that contains two intramolecular N−H···O═C hydrogen bonds and can be generalized for any number of hydrogen bonds. Furthermore, the methodology is also applied to five different polypeptides viz. polyglycine with five amino acid residues abbreviated as GGGGG apart from capped acetyl and NH_2 groups (acetyl-$(gly)_5$-NH_2) and polyglycines in which the second amino acid residue is replaced by alanine (A), valine (V), leucine (L), and isoleucine (I), abbreviated as GAGGG, GVGGG, GLGGG, and GIGGG, respectively. Apart from these partially substituted polyglycines, the corresponding completely substituted polypeptides (i.e., AAAAA, VVVVV, LLLLL, and IIIII) are also employed as a test case for estimating the N−H···O═C intramolecular hydrogen bond with a view to address the effect of substituents on the strength of an individual hydrogen bond. Such substituent effects were recently noticed by Dannenberg and coworkers[6b] in the partially substituted polyglycines studied in the present work. However, these effects were analyzed purely on N−H···O bond distances and bond angle results and need to be quantified. We hope that the present approach will bring out these subtle effects of substituents in a quantitative manner.

Methodology

In the present work, the B3LYP/D95(d,p) optimized geometries of polyglycine and the partially substituted polyglycines are taken from the recent work of Dannenberg and coworkers[6] and further optimized at the B3LYP/6-311++G(d,p) level of theory employing the Gaussian suite of programs.[26] We have restricted our calculations to the 3_{10}-type helix, although the methodology can be extended to other types of helices and strands. Moreover, the geometries of fully substituted polyglycines (polyalanine, polyvaline, polyleucine, and ployisoleucine) are generated from the respective B3LYP/D95(d,p) optimized geometries by the addition of the respective substituents. These generated geometries are further optimized at the B3LYP/D95(d,p) level of theory. For estimating the N−H···O═C hydrogen bond energy, a systematic fragmentation of a polypeptide molecule is carried out with the help of a cross-platform, programmable integrated development environment (IDE) viz. MeTA Studio.[27] For visualizing the fragments, the other package developed in our laboratory viz. UNIVIS-2000 was also used.[29]

SCHEME 2: Fragmentation Scheme Applied to Tetrapeptide Molecule M As Shown in Scheme 1[a]



[a] Here the binary, ternary, and quaternary fragments are shown as overlaps of primary ones. See the text for details.

In Schemes 1 and 2, the systematic fragmentation of a test tetrapeptide (M) containing two N−H···O═C intramolecular hydrogen bonds (A and B) is shown. In Scheme 1, the parent molecule, M, is fragmented into four primary fragments, F1, F2, F3, and F4, wherein the first, second, third, and fourth HNCO groups are, respectively, removed as depicted by the circled region in the parent molecule, M. The removed HNCO groups are shown by a thin line in the respective fragments. The valencies of the cut regions (atoms) are satisfied by the addition of the hydrogen atoms at appropriate distances and directions. The details of the addition of hydrogen atoms are similar to those discussed in our previous studies.[21−23] In Scheme 2, the binary, ternary, and quaternary overlaps (intersection) of the primary fragments are shown. Here the binary overlap means the common structure part of the two primary fragments apart from the added dummy atoms (H atoms). For example, fragment F5 is the intersection (F1 ∩ F2) of the fragments F1 and F2. Similarly, the ternary and quaternary fragments are generated from the common overlap of the three and four primary fragments, respectively, as shown in Scheme 2. To validate the present fragmentation scheme, we have estimated the total molecular energy (E_e) with the single-point energy of all 15 fragments to be: $E_e = E_{F1} + E_{F2} + E_{F3} + E_{F4} - E_{F5} - E_{F6} - E_{F7} - E_{F8} - E_{F9} - E_{F10} + E_{F11} + E_{F12} + E_{F13} + E_{F14} - E_{F15}$; that is, the energies of primary fragments are added, the energies of secondary fragments are subtracted, the energies of tertiary fragments are added, and the energy of the quaternary fragment is subtracted. Such energy estimation has also recently been independently proposed and tested for a set of overlapping fragments in our laboratory.[28] The results of estimates of intramolecular N−H···O═C hydrogen bond energy for the chosen set of polypeptide molecules is presented in the subsequent section.

Results and Discussion

We first present the result of intramolecular hydrogen bond energy estimates in test tetrapeptide shown in Schemes 1 and 2. The approximate estimated energy, as discussed in the previous section of this test tetrapeptide molecule, M, is $E_e = -833.52037$ au at the B3LYP/6-311++G(d,p) level of theory. The actual energy of this molecule is $E_M = -833.52019$ au, indicating that the error in the estimating the molecular energy is indeed rather small (∼0.11 kcal/mol), validating the present fragmentation scheme. The hydrogen bond energy, E_{HA}, is calculated using fragments F1, F3, and F6. The reason for using these fragments is that the hydrogen bond **A** (Scheme 1) is present between the first and third NHCO residues. Fragment F6 is the intersection of F1 and F3, that is, F6 = F1 ∩ F3. (See Scheme 2.) Therefore, the estimated hydrogen bond energy is $E_{HA} = (E_{F1} + E_{F3} - E_{F6}) - E_e = 0.00793$ au = 4.98 kcal/mol. Similarly, the hydrogen bond energy E_{HB} is estimated using the fragments F2, F4, and the corresponding intersecting fragment, F9. The hydrogen bond energy in this case is $E_{HB} = (E_{F2} + E_{F4} - E_{F9}) - E_e = 0.00660$ au = 4.14 kcal/mol. The calculated hydrogen bond energies are in accordance with the NH···O bond distances (angles) of 2.150 (167.58°) and 2.294 Å (165.03°), respectively. Therefore, the present methodology is able to not only distinguish between relatively strong and weak bonds but also to yield reasonably correct energy estimates.[1a] The present methodology is also tested on more extended polypeptide systems.

Figure 1 shows the hydrogen bonding patterns in the polypeptide studied in the present work. Here **X** represents the substituents viz. alanine (A), valine (V), leucine (L), and isoleucine (I). There are two types of hydrogen bonds, as shown in chains 1 and 2. In Chain 1, the two hydrogen bonds viz. **A** and **C** are shown with the corresponding amino acid residue in a ball−stick model. Similarly, in chain 2, the hydrogen bonds viz. **B** and **D** are depicted. Here the notation of Dannenberg and coworkers[6] is followed. Table 1 shows the various geometrical parameters viz. N−H···O bond lengths, bond angles along the respective hydrogen bond energies viz. E_{HA}, E_{HB}, E_{HC}, and E_{HD} obtained by the application of the above fragmentation Schemes for various partially substituted polyglycines studied. Here all of the parameters are obtained at density functional methods employing the B3LYP functional with both D95(d,p) and 6-311++G(d,p) basis sets. It may be seen from Table 1 that the first hydrogen bond, **A**, is expected on the basis of the geometrical parameters being the strongest as compared with the other hydrogen bonds (**B**, **C**, and **D**) in all of the partially substituted polyglycines. However, as one goes from one peptide to another in Table 1, the overall strength of hydrogen bond as expected from the geometrical parameters is not altered much in partially substituted polyglycines. Although, the hydrogen

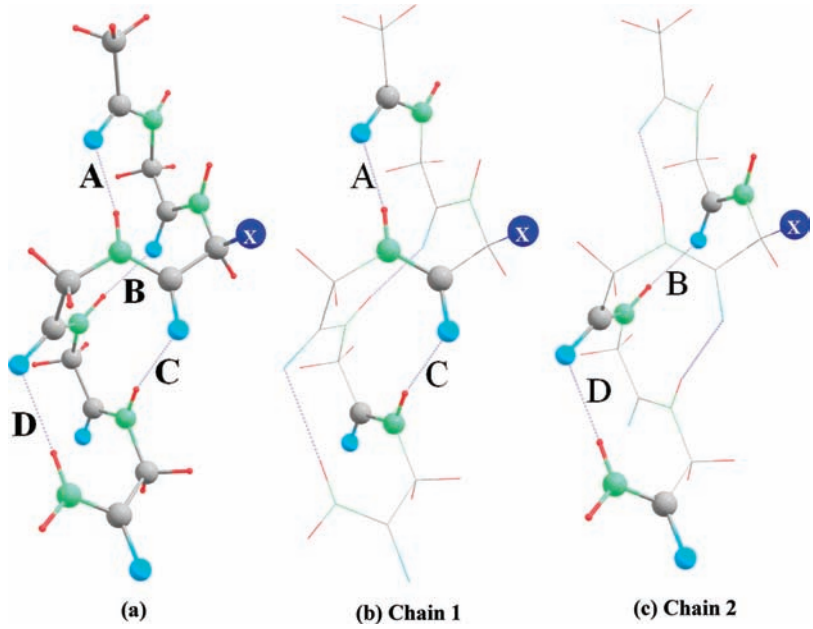


Figure 1. Hydrogen bonding chains in the helical peptide structures. "X" represents the substituent at the second position. See the text for details.

TABLE 1: Geometrical Parameters viz. NH···O Bond Lengths (in angstroms), Bond Angles (in degrees), and Bond Energies (kilocalories per mole) in Various Polypeptides Optimized at the B3LYP Level of Theory[a,b]

	B3LYP/D95(d,p)					B3LYP/6-311++G(d,p)				
polypeptides	GGGGG	GAGGG	GVGGG	GLGGG	GIGGG	GGGGG	GAGGG	GVGGG	GLGGG	GIGGG
R(O···H)	2.029	2.028	2.037	2.034	2.036	2.083	2.079	2.089	2.086	2.089
A(N−H···O)	169.6	169.5	169.5	169.7	169.8	169.4	168.9	168.6	168.7	168.8
E_{HA}	5.92	5.97	5.91	5.93	5.85	5.41	5.43	5.38	5.38	5.31
R(O···H)	2.141	2.120	2.074	2.070	2.068	2.189	2.180	2.135	2.123	2.217
A(N−H···O)	168.7	168.8	168.2	168.2	168.2	169.3	169.6	169.0	168.7	168.9
E_{HB}	4.94	5.10	5.35	5.34	5.35	4.60	4.67	4.91	4.90	4.81
R(O···H)	2.165	2.172	2.162	2.140	2.149	2.218	2.22	2.207	2.191	2.199
A(N−H···O)	166.7	167.5	167.5	167.9	167.5	168.0	168.4	168.3	168.6	168.3
E_{HC}	4.84	4.92	4.92	5.03	4.90	4.49	4.53	4.56	4.62	4.47
R(O···H)	2.178	2.158	2.152	2.145	2.149	2.218	2.210	2.201	2.198	2.202
A(N−H···O)	164.3	164.3	164.2	164.0	164.2	165.7	165.9	166.0	165.7	165.9
E_{HD}	5.05	5.14	5.26	5.24	5.22	4.65	4.65	4.75	4.72	4.65

[a] B3LYP/D95(d,p) optimized geometries are taken from ref 6b and are further optimized at B3LYP/6-311++G(d,p) level. [b] Energies of four types of hydrogen bonds are indicated as E_{HA}, E_{HB}, E_{Hc}, and E_{HD}. See the text for details.

bonds **B** and **D** are slightly more affected relative to the hydrogen bonds **A** and **C** because of substitution at the second residue in polyglycines. These geometrical parameter-based observations are in agreement with the one reported by Dannenberg and coworkes.[6] The estimated hydrogen bond energies are also reported in Table 1. The hydrogen bond energy values are in the range of 4−6 kcal/mol. These estimated hydrogen bond energy values are in agreement with those reported in the literature.[1,11] As expected from the geometrical parameters, the strongest hydrogen bonds (the hydrogen bonds of type **A**) are endowed with the higher values of hydrogen bond energy (∼6 kcal/mol). Moreover, the subtle effects are well reflected in the hydrogen bond energies. As one can notice, the strengths of the hydrogen bonds **B** and **D** are affected to a greater extent[6] (energy difference between the hydrogen bonds in different polypeptides is in the range of 0.1 to 0.3 kcal/mol) as compared with the hydrogen bonds of type **A** and **C** (energy difference between the hydrogen bonds in different polypeptides is in the range of 0.01 to 0.1 kcal/mol). It can be seen from Table 1 that the trends in both the geometrical parameters as well as the estimated hydrogen bond energies are similar at both the basis sets, and only the numerical values are different. Considering this fact, the calculations of fully substituted polyglycines (polypeptides) are carried out at only the B3LYP/D95(d,p) level of theory.

Table 2 displays the geometrical parameters as well as the corresponding hydrogen bond energies of the fully substituted polypeptides. All of the optimized geometries of both partially as well as fully substituted polypeptides are available as Supporting Information. As seen from the geometrical parameters in Table 2, there is an overall decrease in the bond strength for fully substituted polypeptides as compared with those in polyglycine, except the hydrogen bond of type **D**. (See Figure 1.) The hydrogen bond strengths of type **D** have increased in all of the polypeptides as compared with those in polyglycine. This geometrical-based parameter observation is in agreement with the estimated hydrogen bond energy values. As clearly seen, the estimated hydrogen bond energy values of types **A**, **B**, and **C** are smaller, and that of **D** is higher in fully substituted polypeptides as compared with those in polyglycine. Upon comparing the respective hydrogen bond energies in fully substituted polypeptides with the respective partially substituted polyglycines, similar trends are observed. Here the hydrogen bond strengths of types **A**, **B**, and **C** have also decreased in all

TABLE 2: Geometrical Parameters viz. NH···O Bond Lengths (in angstroms), Bond Angles (in degrees), and Bond Energies (kilocalories per mole) in Various Polypeptides Optimized at the B3LYP/D95(d,p) Level of Theory[a]

	B3LYP/D95(d,p)				
polypeptides	GGGGG	AAAAA	VVVVV	LLLLL	IIIII
R(O···H)	2.029	2.085	2.115	2.080	2.109
A(N−H···O)	169.6	171.3	173.1	170.2	173.0
E_{HA}	5.92	5.34	5.46	5.34	5.36
R(O···H)	2.141	2.169	2.223	2.140	2.232
A(N−H···O)	168.7	169.7	172.7	169.2	172.9
E_{HB}	4.94	4.56	4.73	4.60	4.44
R(O···H)	2.165	2.172	2.283	2.137	2.273
A(N−H···O)	166.7	167.1	173.3	168.2	172.4
E_{HC}	4.84	4.49	4.50	4.57	4.34
R(O···H)	2.178	2.127	2.051	2.058	2.067
A(N−H···O)	164.3	164.2	164.8	167.4	164.4
E_{HD}	5.05	5.22	5.91	5.64	5.72

[a] Energies of four types of hydrogen bonds are indicated as E_{HA}, E_{HB}, E_{Hc}, and E_{HD}. See the text for details.

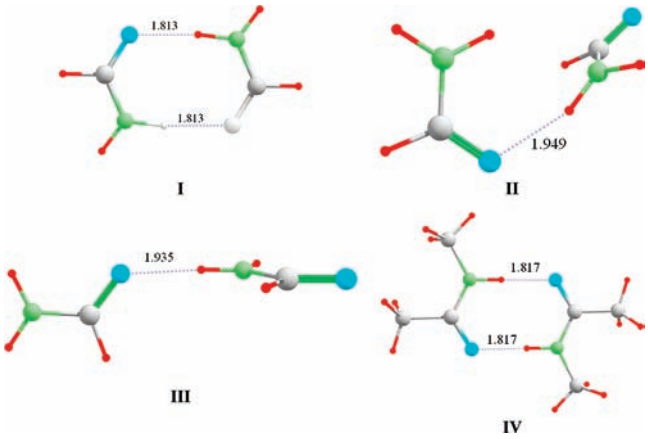


Figure 2. Geometries of formamide dimers I, II, and III and *N*-methyl acetamide dimer, IV optimized at the B3LYP/D95(d,p) level of theory. The respective interaction energies (ΔE) of these dimers are −16.04, −8.04, −7.35, and −15.80 kcal/mol. See the text for details.

of the fully substituted polypeptides as compared with the respective values in partially substituted polyglycines. Again, the strengths of type **D** hydrogen bonds are enhanced in fully substituted polyglycines as compared with the respective hydrogen bond strengths in partially substituted polyglycines. The differential trends seen between the partially substituted polyglycine (wherein clear distinction of hydrogen bonds of types **A**, **C** and **B**, **D**) and the fully substituted polypeptides (wherein types **A**, **B**, and **C** fall into one category and type **D** forms another one) may be attributed to the larger number of C−H···O═C weak interactions in fully substituted ones.

To validate the present approach, a quantitative comparison of the intramolecular hydrogen bond energies with their intermolecular counterparts obtained via a supermolecular approach is felt worthwhile. Although a full quantitative comparison of these two may not be possible, it would give some further confidence in our MTA approach. To compare the prototype N−H···O═C interactions in polypeptides, a few conformers of formamide and *N*-methyl acetamide dimers are chosen. These dimers were previously studied by Dixon and coworkers.[11] Figure 2 shows the B3LYP/D95(d,p) optimized geometries of these dimers along with the respective interaction energy as a measure of the H-bond strength. As can be seen, the hydrogen bond energies (interaction energy per hydrogen bond) in the formamide dimers I, II, and III are −8.02, −8.04, and −7.35 kcal/mol respectively, and that for the *N*-methyl acetamide is −7.90 kcal/mol. (Here the values are reported as negative numbers considering them to be interaction energies.) The average interaction energy per hydrogen bond of these dimers is thus −7.8 kcal/mol. This value is in close agreement with the one estimated by Dixon and coworkers[11b] for these systems (−7.1 kcal/mol for formamide dimer and −8.6 kcal/mol both at MP2/aug-cc-p-VTZ level). Although the substrates in the present study are not strictly comparable with these model systems, a qualitative comparison with intramolecular hydrogen bond energies can be made. The higher value (by about 2 to 3 kcal/mol) in these model systems as compared with hydrogen bond energy estimated (*cf.* Tables 1 and 2) via MTA is attributed to the shorter distances and the linearity due to the proper directionality of the interactions in the intermolecular dimers. On the contrary, these intramolecular interactions are more rigid and less directional in the polypeptides studied in the present work and are hence expected to be lower in energy as compared with the intermolecular ones.

With the present MTA and appropriate fragmentation schemes, one can estimate the energetics of weak C−H···O═C interaction as well. However, considering the scope of the present work, we have restricted ourselves to the energetics of the N−H···O═C intramolecular hydrogen bond, keeping in mind the applications to large polypeptide molecules.

Concluding Remarks

A simple extension of the previously proposed fragmentation scheme due to Deshmukh et al.[21−23] for estimating intramolecular O−H···O hydrogen bond energy to the polypeptide molecules apparently is not obvious because of the different functional groups involved. Therefore, a new fragmentation procedure is proposed in the present work. This new fragmentation procedure is initially tested on a tetrapeptide that has two hydrogen bonds. The estimated hydrogen bond energy values are in good agreement with those indicated by the geometrical parameters viz. the N−H···O bond distances and angles. Furthermore, to validate the new fragmentation scheme, more intricate polypeptides are tested. These test molecules involve partially as well as fully substituted capped polyglycines that contain five glycine residues (acetyl-$(gly)_5$-NH_2). The estimated hydrogen bond energy values lie in the range of 4−6 kcal/mol in both the partially as well as the fully substituted polypeptides. The trends in the hydrogen bond strengths in these partially and fully substituted polypeptides are in good agreement with those anticipated from the corresponding geometrical parameters.[6]

It is thus hoped that the general methodology proposed in this article will enable wide applications to more intricate and biologically interesting systems that contain intramolecular N−H···O═C interactions. For example, estimating the contribution of the intramolecular N−H···O═C interactions during the folding and unfolding of polypeptides would be of great help in understanding why a particular polypeptide folds in a particular manner. Currently, we wish to automate the whole process right from the detection of the weak interactions, fragmentation of the molecule, and evaluation of the energetics of the hydrogen bond. These studies are underway in our laboratory.

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Supporting Information Available: All optimized geometries of both fully and partially substituted polyglycines. This material is available free of charge via the Internet at http://pubs.acs.org.

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