

# Density Functional Theory Study of the Cooperativity of Hydrogen Bonds in Finite and Infinite $\alpha$ -Helices

Joel Ireta,<sup>\*,†</sup> Jörg Neugebauer,<sup>†</sup> Matthias Scheffler,<sup>†</sup> Arturo Rojo,<sup>‡</sup> and Marcelo Galván<sup>‡,§</sup>

Fritz-Haber-Institut der Max-Planck-Gesellschaft, Faradayweg 4-6, D-14195 Berlin-Dahlem, Germany, Departamento de Química, División de Ciencias Básicas e Ingeniería, Universidad Autónoma Metropolitana-Iztapalapa, A.P. 55-534, México D. F. 09340, and Programa de Simulación Molecular, Instituto Mexicano del Petróleo, Eje Central Lázaro Cárdenas No. 152 México D. F.

Received: August 27, 2002; In Final Form: November 13, 2002

We studied the energetics of finite and infinite polyaniline chains in the  $\alpha$ -helical and extended structure by employing density-functional theory. On the basis of these results we extracted the energy of hydrogen bonds (hb's) and their interactions by taking the full peptide–peptide connectivity (backbone) of proteins into account. We focus on two limiting cases: an isolated hb and one within an infinite  $\alpha$ -helical chain. In the infinite chain the cooperativity within an infinite network of hb's strengthens each individual bond by more than a factor of 2. This effect has important consequences for the stability of  $\alpha$ -helices.

## 1. Introduction

The interaction of the form  $AH\cdots B$ , where A and B are commonly oxygen, nitrogen, or fluorine atoms, is called a “hydrogen bond” (hb) between the donor atom A and the acceptor atom B.<sup>1</sup> Although the strength of a hb is around 1 order of magnitude smaller than that of covalent bonds, they play a key role in many biological processes, e.g., stabilization of the structure of proteins and nucleic acids, molecular recognition, or influence in the mechanism of enzymatic reactions.<sup>2–4</sup> Therefore, a large number of experimental and theoretical studies have been performed to estimate the energy of hb's in biomolecules.<sup>1,3–9</sup> A crucial aspect emerged from these investigations is that due to its polar electrostatic nature hb's may strongly interact with each other.<sup>10</sup> Thus, embedding an isolated hb into an array of hb's modifies its bond strength, local vibrational modes, dipole moment, and atomic geometry,<sup>1</sup> making the interaction of hb's strongly nonlinear (cooperative). This cooperativity of hb's has been invoked to explain the stability of the secondary structure in proteins (see, e.g., ref 6).

To quantitatively estimate this effect in proteins, a number of first-principles quantum-chemical studies have been performed. Van Duijnen and Thole<sup>6</sup> studied small peptide chains in the helical conformation, consisting of up to 10 peptide molecules, on the basis of Hartree–Fock (HF) calculations and found that cooperativity increases the electric field of hb's by 20–30%. Due to the limited computer resources available at that time, the basis set used was rather restricted. Suhai,<sup>9</sup> performing calculations at the MP2 (second-order Møller–Plesset perturbation theory) level and extensive checks of the basis set, found an increase in bond strength of 60–70% due to cooperativity for an infinite array of hydrogen bonded formamide (fm) molecules. Similar calculations (HF level) by Ludwig et al.<sup>8</sup> but for finite clusters of *N*-methylformamide and *N*-methylacetamide (nma) molecules showed an increase in bond strength by 38–42% due to cooperativity. The structures used in refs 8 and 9 are model structures where the molecules are

exclusively connected by hb's. Though this allows a straightforward extraction of the hb energies, the backbone of the peptide chain (which is an integral part of any protein) is missing. Thus, these studies give only a limited insight into the role hb cooperativity has in proteins. In the present paper we describe an approach that allows us to extract the energy of isolated and interacting hb's in peptide chains (consisting of one type of peptide unit only) taking the *full backbone* into account. We focus on peptide chains in  $\alpha$ -helical conformation (Figure 1a) and the fully extended structure (FES) (Figure 1b). More specifically we considered polyaniline because alanine is the simplest amino acid frequently found in  $\alpha$ -helical conformation in proteins. A single molecular (peptide) unit is shown in Figure 1c.

A prerequisite to extract hb energies is the knowledge of total energies for the various structures. We therefore use density-functional theory (DFT) and a plane-wave basis set. The use of the latter has for our purposes several advantages compared to a local basis set. It allows a systematic improvement of the basis set completeness, it is free of superposition errors (both aspects have been found to be crucial to obtain an accurate description of hb's),<sup>11</sup> and it gives the possibility to study both finite and infinite (periodic) peptide chains.

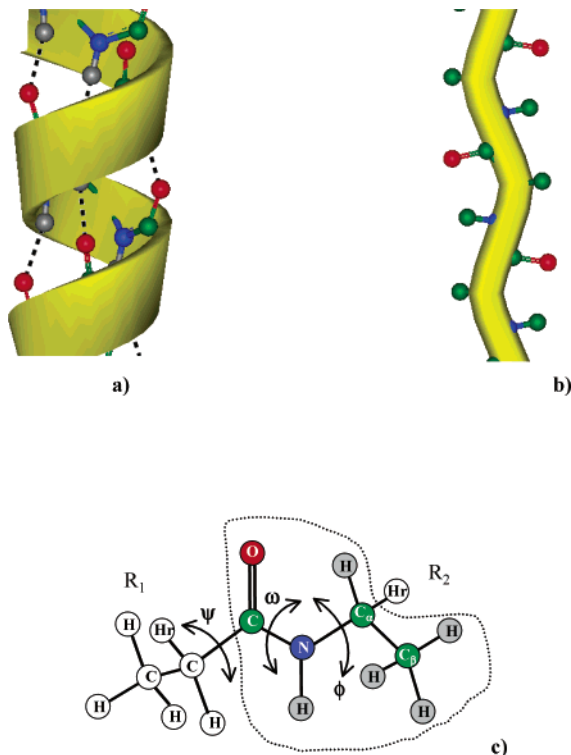
Recently, extensive studies have been performed to test the reliability and accuracy of DFT calculations for hb systems.<sup>12–16</sup> From those results some general conclusions can be drawn: (a) For an accurate description of systems with hb's it is mandatory to describe electronic exchange and correlation within the generalized gradient approximation (GGA) or with hybrid functionals.<sup>12,13</sup> (b) The performance/reliability of the employed GGA has to be carefully checked—some of the GGA functionals proposed in the literature give unsatisfactory results. (c) Also, some GGA functionals accurately describe the atomic geometries but grossly fail in the estimation of hb energies.<sup>14</sup> (d) Various studies indicate that the Perdew, Burke, and Ernzerhof functional (PBE)<sup>17</sup> describes hb's with an accuracy of 1 kcal/mol (0.04 eV).<sup>15,16</sup>

To further test the reliability of the PBE functional, we calculated equilibrium structures and hb interaction energies for

<sup>†</sup> Fritz-Haber-Institut der Max-Planck-Gesellschaft.

<sup>‡</sup> Universidad Autónoma Metropolitana Iztapalapa.

<sup>§</sup> Programa de Simulación Molecular, IMP.



**Figure 1.** (a) Schematic geometry of a polypeptide in right-handed  $\alpha$ -helical conformation. The dashed lines mark the hydrogen bonds (hb's), and the color code used to mark the atoms is defined in (c). (b) Schematic structure of a FES. In (a) and (b) only atoms forming the protein backbone are shown. (c) Schematic geometry of an alanine monomer. The structure enclosed in the dotted line is an alanine peptide unit. R $_1$  and R $_2$  mark the two rest groups that terminate the ends of the finite peptide chains. Also shown are the torsional (dihedral) angles  $\phi$ ,  $\psi$ , and  $\omega$ , which are commonly used to describe the atomic geometry relaxations within a peptide unit.

an extensive set of hydrogen bonded dimers containing the peptide functional group and compared these results with MP2 calculations in the literature. As discussed in section 3, the difference in the hb energy in all cases was smaller than 1.1 kcal/mol. As a further test, we repeated the MP2 calculations by Suhai<sup>9</sup> for an infinite array of hydrogen bonded formamide molecules using PBE. The calculated hb cooperativity and hb strength are within 13% of error and 0.3 kcal/mol, respectively. As a final test we calculated the hb strength in finite polyalanine  $\alpha$ -helices consisting of up to eight peptide units (for structural details see below), using the Becke exchange functional and the Lee–Yang–Parr functional for correlation (BLYP),<sup>18</sup> the Becke hybrid functional for exchange and the Lee–Yang–Parr functional for correlation (B3LYP)<sup>19</sup> and PBE. For the  $\alpha$ -helix BLYP and B3LYP lead to slightly larger hb energies (by  $\sim 0.8$  kcal/mol). Because the shift is almost constant, it has a negligible effect on energy differences ( $\sim 0.03$  kcal/mol) and hb cooperativity.

## 2. Computational Aspects

On the basis of the above-described convergence checks, we have employed DFT PBE-GGA to study infinite polyalanine chains in  $\alpha$ -helical and FES conformations, as well as alanine peptide chains from one up to four units. Specifically, we employed ab initio pseudopotentials<sup>20</sup> with the parallel version of the FHI98md code.<sup>21</sup> The calculations have been performed with a plane wave basis set (energy cutoff: 70 Ry). The Brillouin zone has been sampled at the  $\Gamma$ -point, except for the infinite fully extended structure where a smaller unit cell has

**TABLE 1: Structural Parameters (Bond Lengths, Angles, and Dihedral Angles) for the Peptide Unit in the Fully Relaxed Infinite  $\alpha$ -Helix and FES Chain<sup>a</sup>**

parameter	$\alpha$ -helix	FES
CC $_{\alpha}$	1.539	1.536
CN	1.346	1.343
CO	1.236	1.232
NH	1.029	1.025
C $_{\alpha}$ C $_{\beta}$	1.525	1.533
C $_{\alpha}$ N	1.453	1.448
C $_{\alpha}$ H	1.102	1.103
C $_{\beta}$ H	1.098	1.098
C $_{\alpha}$ CN	116.7	115.3
OCN	123.1	123.8
CNC $_{\alpha}$	120.8	123.7
CNH	120.5	122.5
NC $_{\alpha}$ C $_{\beta}$	110.6	112.4
NC $_{\alpha}$ H	109.0	108.7
HC $_{\alpha}$ C	104.1	109.9
C $_{\alpha}$ C $_{\beta}$ H	110.5	111.1
HC $_{\beta}$ H	108.7	109.0
OCNH	174.7	-177.4
OCNC $_{\alpha}$	-3.1	-4.5
CNC $_{\alpha}$ C $_{\beta}$	172.3	78.8

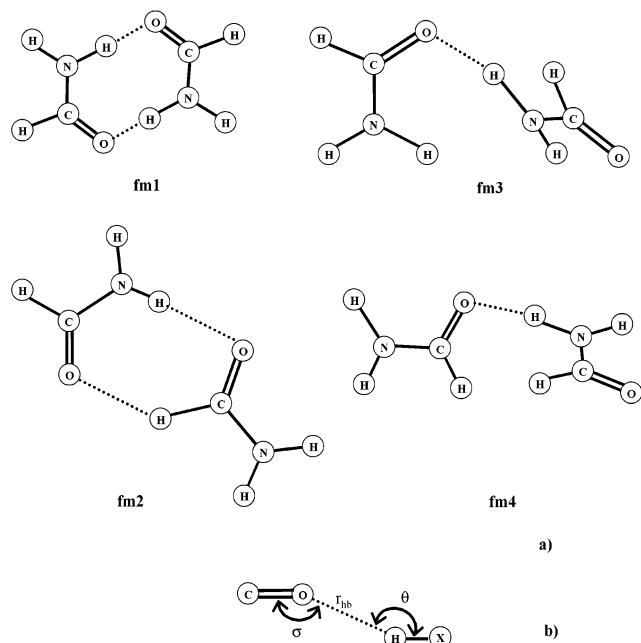
<sup>a</sup> All bond lengths are in  $\text{\AA}$  and angles in degrees. The structural parameters are defined in Figure 1c.

been used. For the latter, two  $k$ -points [(0, 0, 0.25), (0, 0, 0.75)] have been found sufficient to achieve energy convergence.

We start discussing the infinite chains. The atomic structure of an infinite helix can be described in terms of a one-dimensional crystal with lattice vector:  $\mathbf{R}_n = r \cos(\theta n)\mathbf{e}_x + r \sin(\theta n)\mathbf{e}_y + n\Delta z\mathbf{e}_z$ . Here,  $r$  is the perpendicular distance of the lattice site to the helix axis,  $\theta$  is the helix twist, and  $\Delta z$  corresponds to the increment in the  $z$ -axis per peptide unit. For an infinite chain the site index  $n$  goes from minus to plus infinity. We describe this system within a supercell approach where periodic boundary conditions are assumed. Thus, for a unit cell consisting of  $N$  peptide units we have  $\mathbf{R}_n + N\Delta z\mathbf{e}_z = \mathbf{R}_{n+N}$ . From this we get  $\theta = 360^\circ m/N$  with  $m$  the number of helix turns per supercell. For our calculations we have used a structure with three turns and 11 peptide units per cell, giving a helix twist of  $98.2^\circ$  close to the experimental value of  $99.57^\circ$ .<sup>22</sup> The helix was modeled in an ( $a \times a \times c$ ) orthorhombic supercell with the helix axis parallel to the  $c$  lattice side. A side length  $a = 13.0 \text{ \AA}$ , has been chosen and found to be sufficiently large to ensure that interactions with the periodic images of the helix are negligible. An optimum lattice constant,  $c = 16.45 \text{ \AA}$ , has been calculated by minimizing the total energy. The helix geometry was fully relaxed. For the torsional angles (see Figure 1c) we get  $\phi = -63.8^\circ$ ,  $\psi = -42.4^\circ$ , and  $\omega = 178.0^\circ$ . The hb length between hydrogen and the oxygen atoms is  $1.95 \text{ \AA}$ . These results agree with previous experimental and theoretical values in the literature.<sup>2,16,23,24</sup> The calculated geometry parameters for the peptide unit in the infinite  $\alpha$ -helix chain are given in Table 1.

The infinite FES chain was modeled using two peptide units per unit cell in an orthorhombic ( $a \times b \times c$ ) supercell. The lattice parameters  $a = 8.1 \text{ \AA}$ ,  $b = 8.62 \text{ \AA}$ , and  $c = 7.21 \text{ \AA}$  have been obtained by following the same criteria described above for the infinite  $\alpha$ -helix. The chain axis is parallel to the  $c$  lattice side. The FES geometry was fully relaxed. The calculated torsional angles are  $\phi = -159.7^\circ$ ,  $\psi = 164.4^\circ$ , and  $\omega = -174.1^\circ$ . The calculated geometry parameters for the peptide unit in the infinite FES chain are given in Table 1.

The finite chains were modeled in an orthorhombic supercell. A vacuum region of the same length as the chain along the



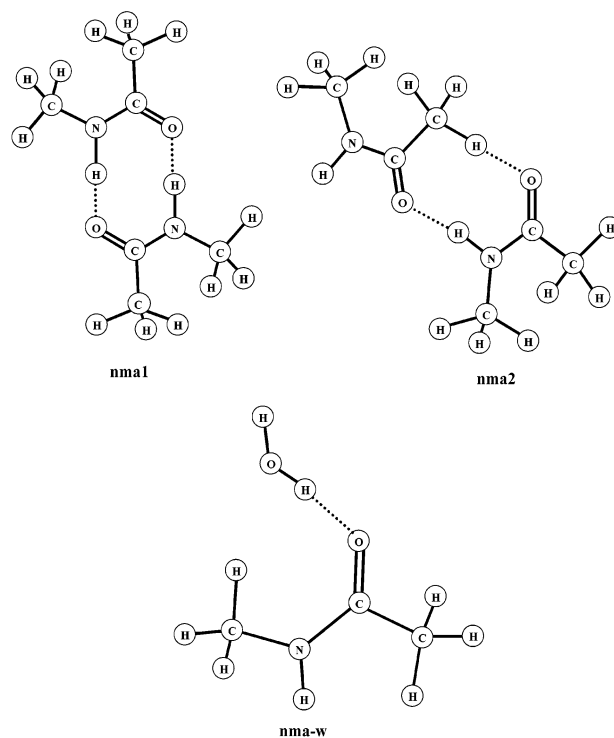
**Figure 2.** (a) Schematic geometry of the formamide (fm) dimers. The dotted lines mark the hydrogen bonds (hb's). (b) Geometry parameters used to describe the hb. X stands for C or N.

axis and of 5.3 Å perpendicular to the chain axis direction has been used. Because the peptides have a large dipole moment ( $\sim 3$  D) along the helix axis we introduce a dipole compensation layer (with the isosurface normal parallel to the helix axis) in the middle of the vacuum region.<sup>25</sup> This eliminates the dipole–dipole interaction along the helix axis. The lateral dipole–dipole correction is taken into account explicitly by calculating the corresponding electrostatic energy. To avoid unsaturated peptide bonds, the ends of the finite chains have been chemically passivated by two capping groups  $R_1 = \text{CH}_2\text{--CH}_3$  and  $R_2 = \text{H}$  (see Figure 1c). The capping groups have been designed to preserve the nearest neighbor groups that a peptide bond has in the infinite peptide chain.

The fm and nma dimers were modeled in an orthorhombic supercell with a vacuum region of at least 6 Å along three axes. The calculations have been performed with an energy cutoff of 70 Ry and the Brillouin zone has been sampled at the  $\Gamma$ -point. Dipole–dipole interactions between neighboring cells have been corrected as described above.

### 3. Results

Let us first discuss the reliability and accuracy of PBE calculations for hb systems. We have therefore calculated the association energies of a set of hydrogen bonded dimers. The association energy has been calculated as the difference between the total energy of the fully relaxed isolated molecules constituting the dimer and of the fully relaxed hydrogen bonded dimer. Using this definition the hb energy is the negative association energy. We have focused on various dimers of fm (Figure 2a) and nma (Figure 3) because these structures contain N–H $\cdots$ O hb's that are structurally similar to those found in an  $\alpha$ -helix. The results together with MP2 association energies as reported by Vargas et al.<sup>26</sup> are listed in Table 2. We find that PBE generally underestimates the hb strength with a maximum error bar of 1.1 kcal/mol. We note that the MP2 calculations against which we compare our results have been performed on different levels of accuracy. The association energies for the smaller fm structures have been calculated by employing a larger basis set



**Figure 3.** Schematic geometry of the *N*-methylacetamide (nma) dimers. The dotted lines mark the hydrogen bonds (hb's). At the bottom a nma–water (nma–w) dimer is shown.

**TABLE 2: Association Energies in kcal/mol for Formamide (fm), *N*-Methylacetamide (nma), and *N*-Methylacetamide–Water (nma–w) Hydrogen Bonded Dimers<sup>a</sup>**

dimer	hbs	Best value	PBE	PBE error per hb
fm1	2	−14.35 <sup>b</sup>	−14.34	0.01
fm2	2	−9.70 <sup>b</sup>	−9.11	0.30
fm3	1	−7.34 <sup>b</sup>	−6.78	0.56
fm4	1	−6.76 <sup>b</sup>	−6.28	0.48
nma1	2	−17.18 <sup>c</sup>	−15.27	0.96
nma2	2	−10.76 <sup>c</sup>	−8.57	1.10
nma–w	1	−7.2 <sup>d</sup>	−7.51	−0.31

<sup>a</sup> The corresponding structures are shown in Figures 2a and 3. Best value gives the best (with respect to the basis set) available MP2 value.

<sup>b</sup> Extrapolation of the MP2/aug-cc-pVXZ for X = D, T, and Q total energies to the complete basis set limit (ref 27). <sup>c</sup> MP2/aug-cc-pVTZ single point energy calculation on the MP2/aug-cc-pVDZ optimized geometry.<sup>27</sup> <sup>d</sup> MP2/aug-cc-pVDZ single point calculation considering valence electrons only on the HF/DZP optimized geometry.<sup>28</sup> A basis set superposition error correction has been applied in (c) and (d).

(extrapolation of the MP2/aug-cc-pVXZ for X = D, T, and Q total energies to the complete basis set limit) than the one used for the nma dimers (MP2/aug-cc-pVTZ single point calculation on MP2/aug-cc-pVDZ optimized geometries).<sup>26</sup> Interestingly, when the comparison is restricted to structures where the extrapolation to the complete basis set limit has been applied, the error bar becomes even smaller (0.6 kcal/mol). At the moment we can therefore not say whether the slightly larger discrepancies between PBE and MP2 results found for the nma dimers are due to PBE or due to the incompleteness of the basis set for the nma dimer MP2 calculations.

Table 3 compares the hb-related optimized geometry parameters. In general, differences in the hb distances are less than 0.02 Å and in the angles less than 6° with respect to MP2 optimized geometry parameters. The largest deviation is for the nma–water complex (nma–w) where the error in the hb length

**TABLE 3: Geometry Parameters (hb Length, Angles) for Formamide (fm), *N*-Methylacetamide (nma), and *N*-Methylacetamide–Water (nma-w) Hydrogen Bonded Dimers<sup>a</sup>**

dimer	parameter	best value		PBE		PBE error	
		NH $\cdots$ O	CH $\cdots$ O	NH $\cdots$ O	CH $\cdots$ O	NH $\cdots$ O	CH $\cdots$ O
fm1 <sup>b,c</sup>	$r_{\text{hb}}$	1.825		1.81		-0.015	
	$\theta$	174.2		174.0		-0.2	
	$\sigma$	120.1		120.2		0.1	
fm2 <sup>c</sup>	$r_{\text{hb}}$	1.825	2.234	1.84	2.28	0.015	0.046
	$\theta$	174.2	144.9	168.9	142.6	-5.3	-2.3
	$\sigma$	0.0	0.0	1.0	0.0	1.0	0.0
fm3 <sup>c</sup>	$r_{\text{hb}}$	1.935		1.92		-0.015	
	$\theta$	158.4		160.8		2.4	
	$\sigma$	110.3		113.0		2.7	
fm4 <sup>c</sup>	$r_{\text{hb}}$	1.904		1.90		-0.004	
	$\theta$	165.8		166.3		0.5	
	$\sigma$	108.9		110.9		2.0	
nma1 <sup>b,d</sup>	$r_{\text{hb}}$	1.799		1.78		-0.019	
	$\theta$	177.7		178.1		0.4	
	$\sigma$	118.6		119.5		0.9	
nma2 <sup>d</sup>	$r_{\text{hb}}$	1.867	2.249	1.87	2.25	0.003	0.001
	$\theta$	169.0	177.4	169.9	176.0	0.9	-1.4
	$\sigma$	122.2	117.4	123.2	118.6	1.0	1.2
nma-w <sup>e</sup>	$r_{\text{hb}}$	1.979		1.84		-0.139	
	$\theta$			176.2			
	$\sigma$			134.2			

<sup>a</sup> The structures are shown in Figures 2a and 3. The structural parameters are defined in Figure 2b. Best value gives the best available value. All lengths are given in Ångströms, and all angles in degrees. <sup>b</sup> Our geometry optimization show the two hb's to be identical. <sup>c</sup> MP2/aug-cc-pVTZ optimized geometry.<sup>27</sup> <sup>d</sup> MP2/aug-cc-pVDZ optimized geometry.<sup>27</sup> <sup>e</sup> HF/DZP optimized geometry.<sup>28</sup>

is about 0.1 Å. We relate this to the fact that the geometry optimization for the reference structure<sup>27</sup> has been performed on a HF level, which is well-known to overestimate the hb length.<sup>28</sup> On the basis of the above discussion we are confident that PBE in combination with a plane-wave basis set allows a description of the hb strength with an error bar <1 kcal/mol per hb.

We will now turn to the estimate of the hb strength. A finite chain  $R_1P_NR_2$  consisting of  $N$  identical peptide units  $P$  and the two capping groups  $R_1$  and  $R_2$  can be obtained by the reaction  $R_1P_{N-1}R_2 + P \rightarrow R_1P_NR_2$ . The enthalpy of the reaction at temperature  $T = 0$  K, and pressure  $p = 0$  is

$$\Delta H_{\sigma}^N = E_{\sigma}^N - E_{\sigma}^{N-1} - \mu_p \quad (1)$$

Here,  $E_{\sigma}^N$  is the total energy of a chain consisting of  $N$  peptides. The index  $\sigma$  marks the conformation of the chain: for an extended structure  $\sigma = \text{FES}$ , and for a helical conformation  $\sigma = \alpha$ .  $\mu_p$  is the chemical potential and defines the energy cost to take out a peptide unit from its corresponding chemical reservoir. In general, the chemical potential is given by the specific environment in which the reaction takes place. For the following discussion we use as a chemical reservoir the fully relaxed infinite polyalanine chain in FES conformation ( $\mu_p = E_{\text{FES}}^{\infty}/2$ ), because it is free of chain edge effects and hb interactions. The factor  $1/2$  takes into account that we have two peptide units per supercell.

For the construction of the finite chains we use the equilibrium structures (see Table 1) of the peptide unit in the infinite chains; i.e., we select the atomic positions of the passivating group  $R_1 = \text{CH}_2\text{-CH}_3$  such that they match the positions of the  $\text{C}_{\alpha}\text{H-C}_{\beta}\text{H}_3$  atoms in the peptide neighbor and allow only the atoms  $\text{H}_r$  (which have no equivalent in the infinite chain; see Figure 1c) to relax. This constraint simulates that the hb's are surrounded by the same peptide bonds such as in an infinite chain.

Using the above scheme we have calculated the reaction enthalpy (eq 1) of finite chains in both conformations. As can

**TABLE 4: Reaction Enthalpies (Eq 1) To Add One Peptide to Finite and Infinite Polyalanine Chains in Fully Extended ( $\Delta H_{\text{FES}}$ ) and  $\alpha$ -Helical ( $\Delta H_{\alpha}$ ) Conformations<sup>a</sup>**

$N$	$\Delta H_{\text{FES}}$	$\Delta H_{\alpha}$	$E_{\text{hb}}$
2	0.92	6.32	
3	0.59	5.89	
4	0.50	2.38	3.5
$\infty$	0.0	-2.71	8.6

<sup>a</sup> In the last column the hb energies, as extracted from the  $\alpha$ -helices (eqs 3 and 4), is listed. All energies are in kcal/mol.

be seen in Table 4, the enthalpy for chains in the FES conformation is close to zero; i.e., the energy to add a peptide to a monomer or dimer is the same (within an error of less than 1 kcal/mol (0.04 eV)) as to add it to the infinite chain. This implies that the interaction between two nearest neighbor peptide bonds is negligible (<1 kcal/mol); i.e., *the peptide bonds do not interact and the bond energy is additive and not cooperative*.

We now discuss the helical conformation. For small chains ( $N = 2, 3$ ) the reaction enthalpy is  $\sim 5.9$  kcal/mol (0.26 eV) (with an error less than  $\sim 1$  kcal/mol; see Table 4). Because small chains are free of any hb's (hb's form between fourth nearest neighbor peptides thus they are present only in chains with  $N \geq 4$ ), this is the energy to bend a peptide-peptide bond from the extended structure into the  $\alpha$ -helical conformation. Although this energy has been derived only for the small chains, the noncooperative behavior in the extended structure and its  $N$ -independence for small  $\alpha$ -helices implies that this value applies also to large chains. We thus get the chemical potential of a hypothetical infinite  $\alpha$ -helix without hb's (but with the hydrogens and all other atoms at the correct position):

$$\tilde{\mu}_{\alpha}^{\infty} \approx \mu_{\text{FES}}^{\infty} + 5.9 \text{ kcal/mol} \quad (2)$$

The fact that a peptide unit in such a (hypothetical) structure has a 5.9 kcal/mol higher chemical potential than in an extended conformation reflects that the peptide unit has to be significantly strained to go from an extended to an  $\alpha$ -helical conformation.

Using the chemical potential for the infinite hb-free  $\alpha$ -helix, we can immediately determine the hb energy. We therefore



consider the reaction where we take out one peptide unit from this chemical reservoir and add it to an  $\alpha$ -helix with  $N - 1$  peptide units. In this reaction and for  $N \geq 4$  one hb (but no net peptide-peptide bond) is formed. The energy of this reaction is thus the (negative) bond energy of the hb:

$$-E_{\text{hb}}^N = \Delta H_{\text{hb}}^N = E_{\text{hb}}^N - E_{\alpha}^{N-1} - \tilde{\mu}_{\alpha}^{\infty} \quad (3)$$

For  $N = 4$  we get  $E_{\text{hb}}^N = 3.5$  kcal/mol (0.15 eV).

Using this value, we can check the validity of common model structures that contain hb's but no peptide bonds. In such a model the energy of an isolated hb is simply the energy difference between a dipeptide (consisting of two peptide units connected by a hb) and two isolated peptides. In the dipeptide structure the positions of the peptides were chosen to be identical to the positions of fourth nearest neighbors in an infinite  $\alpha$ -helix. The resulting hb energy is 5.9 kcal/mol (0.26 eV) per hb; i.e., the energy of an isolated hb is overestimated by more than 60%. We therefore conclude that the presence of peptide-peptide bonds that form the protein backbone significantly affects the strength of neighboring hb's. Model systems where the peptide units are connected solely by hb's have therefore only a limited applicability on realistic biomolecules.

Following the same procedure used to derive the hb energy for finite  $\alpha$ -helices, we are now able to extract the hb energy in an infinite helix:

$$-E_{\text{hb}}^{\infty} = \Delta H_{\text{hb}}^{\infty} = \mu_{\alpha}^{\infty} - \tilde{\mu}_{\alpha}^{\infty} \quad (4)$$

where  $\mu_{\alpha}^{\infty}$  is the total energy of the infinite  $\alpha$ -helix per peptide unit. Using this equation we obtain  $E_{\text{hb}}^{\infty} = 8.6$  kcal/mol (0.37 eV).

#### 4. Discussion

From the above results we can draw a number of conclusions: first, in an infinite polyaniline  $\alpha$ -helix the hb interaction is strongly cooperative and strengthens each individual bond by more than a factor of 2 compared to an isolated hb. It is interesting to note that the hb cooperativity for a realistic helix structure (where the helix backbone is fully taken into account) is significantly larger than for previously studied model structures where an enhancement of 38–42%<sup>8</sup> or 60–70%<sup>9</sup> has been reported. A closer analysis shows that two effects, which have not been considered in previous studies, give rise to the large enhancement in the hb cooperativity: (i) the bond energy of an isolate hb reduces by including the interaction with the helix backbone (by  $\sim 40\%$ ) and (ii) the hb energy in the infinite  $\alpha$ -helix increases because the macro dipole is completely compensated. Previous estimates of the hb cooperativity were made by using chains of rather limited size. In these chains the dipole moment of the peptide units add up to a large macro dipole along the helix axis.<sup>10</sup> In nature, however, these macro dipoles are largely compensated by solvents, charged groups, or charge transfer. In our calculations compensation of the macro dipole has been directly taken into account by assuming periodic boundary conditions for the infinite chain.

An important implication of the large cooperativity is that, within a single protein, hb's with very different strengths may coexist: In regions where the hb is essentially isolated, the hb is in the weak limit ( $\sim 3$ – $4$  kcal/mol) whereas in regions with a high density of hb's (e.g., in an  $\alpha$ -helix region) it may be in the strong limit ( $\sim 9$  kcal/mol). Second, it is important to notice that without hb-cooperativity the helix would be energetically less stable than the extended conformation, i.e., the energy of

an isolated hb is not enough to force a peptide unit into an  $\alpha$ -helical conformation. Based on our calculated energies, the critical length of an  $\alpha$ -helix can be estimated. Assuming a maximum cooperativity for all hb's, the  $\alpha$ -helix must consist of at least 10 peptide units to be stable against transformation into the extended structure. This result is consistent with recent experiments according to which small polyaniline chains do not form helical structures in vacuum and solution.<sup>29,30</sup>

The calculated hb energy in the polyaniline chain can be compared with hb's in other systems. Using the same method we find for a water dimer a hb energy of 5.4 kcal/mol; i.e., it is larger than the energy of the isolated hb in polyaniline ( $\sim 54\%$ ) but lower ( $\sim 59\%$ ) than in the infinite helix. Further, we find the hb energy between water and a peptide unit (nma-w, see Figure 3 and Table 2) is 7.5 kcal/mol. This energy is significantly larger than that of an isolated hb; i.e., in water isolated hb's are unstable against hb formation between peptides and water. Only the large energy gained due to cooperativity stabilizes  $\alpha$ -helices against the formation of water-polypeptide hb's.

#### 5. Conclusions

In conclusion, calculating the energy for finite and infinite polyaniline chains we are able to extract the energy of isolated and interacting hb's by taking the full secondary structure into account. We find that hb cooperativity is significantly stronger than expected from previous studies on model structures where the protein backbone and periodicity of the secondary structure have been neglected. Finally, we note that the method to extract bond energies is general; i.e., it can be applied to any linear or helical polymer consisting of chemically identical molecules and in combination with any total energy formalism.

**Acknowledgment.** J.I. thanks to the Alexander von Humboldt Foundation for a fellowship support. A.R. thanks CONACYT and TWAS for financial support under contracts No. 400200-5-29124E and 98-252 RG/CHE/LA, respectively. M.G. thanks CONACYT for financial support under contract No. 400200-5-36482E.

**Supporting Information Available:** Total energies in hartrees and Cartesian coordinates of the optimized structures in ångströms. This material is available free of charge via the Internet at <http://pubs.acs.org>.

#### References and Notes

- (1) Scheiner, S. *Hydrogen bonding a theoretical perspective*; Topics in Physical Chemistry; Truhlar, D. G., Ed.; Oxford University Press: Oxford, U.K., 1997.
- (2) Baker, E. N.; Hubbard, R. E. *Prog. Biophys. Mol. Biol.* **1984**, *44*, 97.
- (3) Perrin, C. L.; Nielson, J. B. *Annu. Rev. Phys. Chem.* **1997**, *48*, 511.
- (4) Weinhold, F. *J. Mol. Struct. (TEOCHEM)* **1997**, *398*–*399*, 181.
- (5) Sheridan R. P.; Lee, R. H.; Peters, N.; Allen, L. C. *Biopolymers* **1979**, *18*, 2451.
- (6) van Duijnen, P. T.; Thole, B. T. *Biopolymers* **1982**, *21*, 1749.
- (7) Elstner, M.; Jalkanen, K. J.; Knapp-Mohammady, M.; Frauenheim, Th.; Suhai, S. *Chem. Phys.* **2000**, *256*, 15.
- (8) Ludwig, R.; Weinhold, F.; Farrar, T. C.; *J. Chem. Phys.* **1997**, *107*, 499. Ludwig, R.; Weinhold, F.; Farrar, T. C. *J. Phys. Chem. A* **1997**, *101*, 8861.
- (9) Suhai, S. *J. Phys. Chem.* **1996**, *100*, 3950.
- (10) Park, C.; Goddard W. A. *J. Phys. Chem. B* **2000**, *104*, 7784.
- (11) del Bene, J. E. *Hydrogen bonding: 1. Encyclopedia of computational chemistry Vol. 2*; Schleyer, P., Ed. in Chief; John Wiley: Chichester, U.K., 1998.

- (12) Laasonen, K.; Csajka, F.; Parrinello, M. *Chem Phys. Lett.* **1992**, *194*, 172. Laasonen, K.; Sprik, M.; Parrinello, M. *J. Chem. Phys.* **1993**, *99*, 9080.
- (13) Sirois, S.; Proynov, E. I.; Nguyen, D. T.; Salahub, D. R. *J. Chem. Phys.* **1997**, *107*, 6770.
- (14) Vargas, R.; Garza, J.; Dixon, D. A.; Hay, B. P. *J. Phys. Chem. A* **2000**, *104*, 5115.
- (15) Tuma, C.; Boese, A. D.; Handy, N. C. *Phys. Chem. Chem. Phys.* **1999**, *1*, 3939.
- (16) Kaschner, R.; Hohl, D. *J. Phys. Chem. A* **1998**, *102*, 5111.
- (17) Perdew, J.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865.
- (18) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
- (19) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
- (20) Troullier, N.; Martins, J. L. *Phys. Rev. B* **1991**, *43*, 1993. Fuchs, M.; Scheffler, M. *Comput. Phys. Commun.* **1999**, *119*, 67; <http://www.fhi-berlin.mpg.de/th/fhi98md/fhi98pp>.
- (21) Bockstedte, M.; Kley, A.; Neugebauer, J.; Scheffler, M. *Comput. Phys. Commun.* **1997**, *107*, 187; <http://www.fhi-berlin.mpg.de/th/fhi98md/>.
- (22) Arnott, S.; Dover, S. D. *J. Mol. Biol.* **1967**, *30*, 209.
- (23) Presta, L. G.; Rose, G. D. *Science* **1988**, *240*, 1632.
- (24) MacArthur, M. W.; Thornton, J. M. *J. Mol. Biol.* **1996**, *264*, 1180.
- (25) Neugebauer, J.; Scheffler, M. *Phys. Rev. B* **1992**, *46*, 16067.
- (26) Vargas, R.; Garza, J.; Friesner, R. A.; Stern, H.; Hay, B. P.; Dixon, D. A. *J. Phys. Chem. A* **2001**, *105*, 4963.
- (27) Dixon, D. A.; Dobbs, K. D.; Valentini, J. J. *J. Phys. Chem.* **1994**, *98*, 13435.
- (28) Del Bene, J. E.; Jordan, M. J. T. *J. Mol. Struct. (THEOCHEM)* **2001**, *573*, 11.
- (29) Hudgins, R. R.; Ratner, M. A.; Jarrold, M. F. *J. Am. Chem. Soc.* **1998**, *120*, 12974.
- (30) Speck, E. J.; Olson, C. A.; Shi, Z.; Kallenbach, N. R. *J. Am. Chem. Soc.* **1999**, *121*, 5571.