

A Theoretical Evaluation of the pK_a for Twisted Amides Using Density Functional Theory and Dielectric Continuum Methods

Jon Iñaki Mujika, Jose M. Mercero,* and Xabier Lopez*

Kimika Fakultatea, Euskal Herriko Unibertsitatea, P.K. 1072, 20080 Donostia, Euskadi, Spain

Received: May 6, 2003; In Final Form: May 20, 2003

We present an ab initio study of the pK_a of a series of twisted amides in aqueous solution. The shift of the pK_a with respect to the known value for trimethylamine (TMA) is used in the evaluation. Calculations were made with density functional theory using the B3PW91 functional. Aqueous solvent effect is introduced by use of the polarizable continuum model. The protocol is tested on a series of tertiary amines and twisted amides, and a good agreement with the available experimental data is found. Finally, mechanistic implications of the change in basicity of the nitrogen as a function of the twist of the amide bond for the activation of C–N bond hydrolysis are discussed.

1. Introduction

The amide bond is of fundamental importance in biology as an essential element of the protein backbone. Structural distortion of the amide unit from the lowest energy planar configuration has been shown not only to alter the reactivity involving nucleophilic attack/hydrolysis^{1–6} but also to induce important changes in the basicity of the amide group.^{3,4,7,8} Planar amides have very low pK_a values (for instance, the pK_a of formamide is 0.12; ref 9), with a preference for the O-protonated tautomer. However, higher pK_a 's have been found for twisted amides. Namely, a pK_a of 5.3 has been reported for compound **2b** in Figure 1, and on the basis of the hydrolysis profile as a function of pH, Wang et al.^{3,4} have estimated that the pK_a of **2c** is 3.7. Moreover, the nature of the protonation in twisted amides is different from that of their undistorted counterparts. Gas-phase calculations by Greenberg et al.^{7,8} for twisted amides of the types **2a** and **3a,b** showed preferentially N-protonated tautomers rather than the O-protonated ones found for planar amides. This clearly can lead to different hydrolysis mechanisms for twisted amides at acidic pH's. We have previously suggested¹⁰ that this may be the origin of the very fast hydrolysis observed by Kirby et al.^{5,6} for compound **1** (Figure 1).

An accurate knowledge of the pK_a of twisted amides is thus of importance for an understanding of the differential reactivity of distorted versus undistorted compounds. Unfortunately, experimental determination of these pK_a 's is not always feasible; e.g., Kirby et al.^{5,6} were not able to determine the pK_a of compound **1** due to its fast hydrolysis in water. In other cases, the pK_a has been inferred indirectly from the hydrolytic profile as a function of the pH.³ Consequently, quantum-mechanical calculations are needed to complement and confirm the available experimental data. Gas-phase acidity/basicity can be calculated quite accurately, provided that extended basis sets are used and electron correlation effects are taken into account. In this regard, density functional theory (DFT) is a good compromise between efficiency and accuracy. However, the gas-phase results must be corrected for the effect of aqueous solvation, which is large for ionic systems. Solvation effects can be introduced by a

variety of approaches.¹¹ Computationally, the most efficient is the use of dielectric continuum models.^{12,13} These models properly account for long-range bulk solvent effects,¹⁴ although they fail to include short-range effects, such as hydrogen bonding, which can be important for determining accurate pK_a values.¹⁴ One possibility is to consider a few water molecules explicitly in the first solvation shell,^{15,16} and to then treat the rest of the solvent by a continuum model. A useful alternative¹⁷ is to calculate the pK_a 's with respect to a closely related compound for which the experimental pK_a is known. The calculation of the pK_a is thus reduced to the evaluation of a change in the free energy for a balanced chemical reaction which conserves the number of charged species. This leads to a cancellation of errors when evaluating the solvation contribution to the pK_a . It also avoids the need to introduce the solvation free energy of the proton, which is still somewhat uncertain.¹⁴ We use this latter approach in the present study to evaluate the pK_a 's of a series of distorted amides (compounds **1**, **2a–c**) and **3a,b** relative to the known pK_a of trimethylamine (TMA). We first determine the most stable protonated tautomer, and then, using the energy for that tautomer, we estimate the pK_a for the molecule. HF/6-31G* wave functions and the polarizable continuum model are used to calculate the solvation effects. We find good agreement with available experimental data for tertiary amines and twisted amides and predict the pK_a for systems whose pK_a 's are not known. Finally, the mechanistic implications for the hydrolysis reactions of the amides are briefly discussed.

2. Methodology

2.1. Ab Initio Calculations. All the structures were optimized in the gas phase at the B3PW91/6-31+G(d) level of theory^{18–23} using Gaussian98.²⁴ To confirm that the optimized structures were minima on the potential energy surfaces, frequency calculations were done at the B3PW91/6-31+G(d) level. The frequencies were then used to evaluate the zero-point vibrational energy (ZPVE) and the thermal ($T = 298$ K) vibrational corrections to the enthalpy and Gibbs free energy²⁵ in the harmonic oscillator approximation. These calculations were also made with Gaussian98.²⁴ To calculate the entropy, the different contributions to the partition function were evaluated using the

* Corresponding authors. E-mail: J.M.M., pobmelat@sq.ehu.es; X.L., poplopx@sq.ehu.es

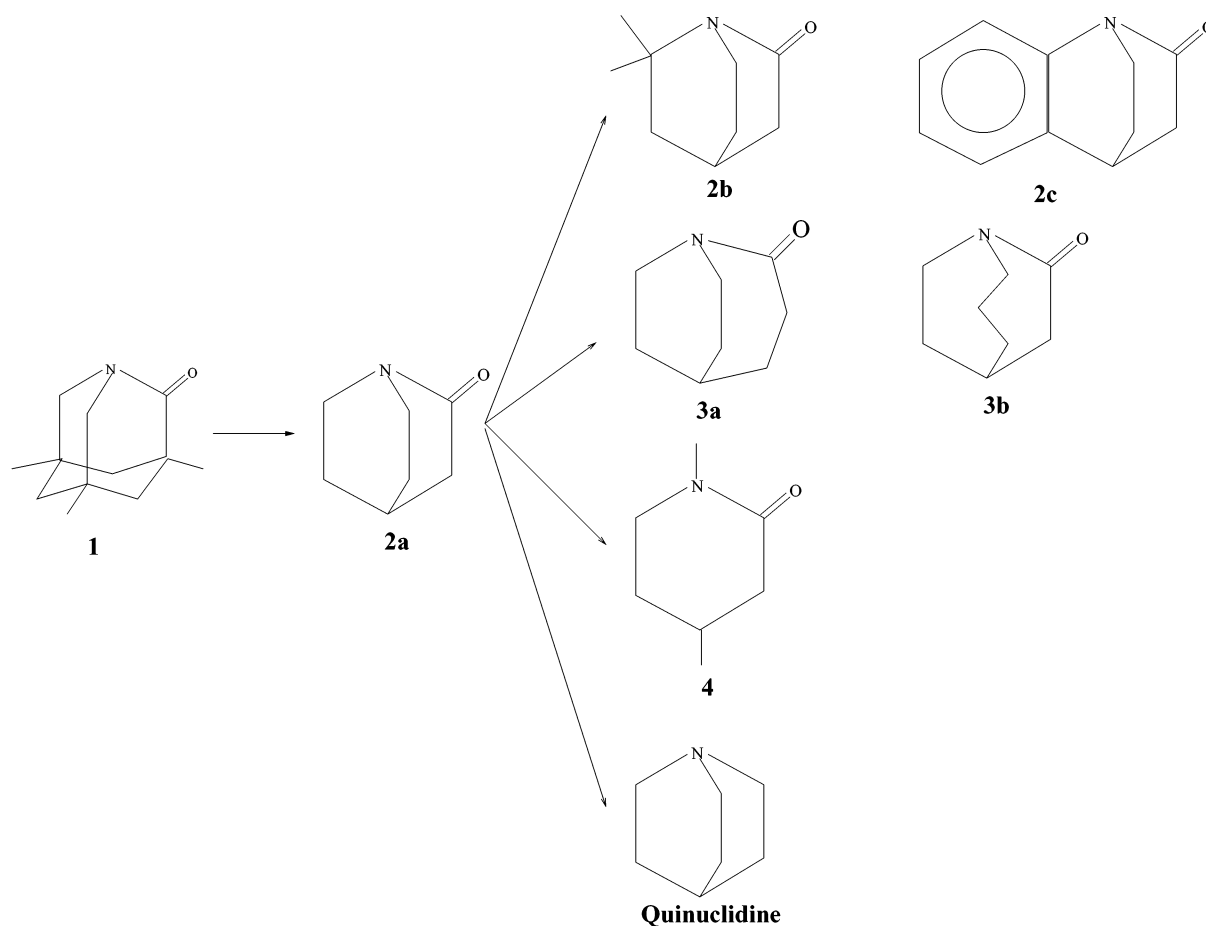


Figure 1. Scheme showing the twisted amides considered in the paper. Compound **1** has been synthesized by Kirby et al., and compound **2a** is a simplified version of compound **1**, for which we have recently investigated the alkaline hydrolysis.¹⁰ Compounds **2b** and **2c** are derivatives of **2a** which conserve the degree of twist of the amide bond. Compounds **3a** and **3b** are generated from elongations of the aliphatic chain in the cage of **2a**, which leads to a partial release of the twist of the amide bond. Compound **4** is the δ -lactam planar analogue of **2a**, and finally quinuclidine is a tertiary amine that is structurally related to **2a**.

standard expressions for an ideal gas in the canonical ensemble and the harmonic oscillator and rigid rotor approximation.²⁶ The electronic energy was refined by single-point energy calculations with a higher basis set, namely B3PW91/6-311++G(3df,2p). The final gas-phase enthalpy and free energy were obtained from the B3PW91/6-311++G(3df,2p) electronic energy and the enthalpic and entropic corrections evaluated at the B3PW91/6-31+G(d) level.

Other functionals, such as B3LYP, were also tried for the gas-phase calculations. However, B3LYP showed a slightly poorer agreement with experimental pK_a 's (the mean absolute deviation was 0.6 pK_a unit) than B3PW91 (mean absolute deviation of 0.4 pK_a unit). Therefore, we decided to use the B3PW91 functional, and only those results are presented.

2.2. Solvent Contributions. Solvation free energies at the gas-phase B3PW91/6-31+G(d) geometries were estimated with the polarizable continuum model (PCM) approach,^{27–30} using the HF/6-31G* wave function for the solute. We used the united atom Hartree–Fock (UAHF)²⁹ set of atomic radii to define the cavity. These radii have been optimized with the HF/6-31G* wave function to give accurate solvation free energies of a dataset of anionic/cationic and neutral organic and inorganic molecules. To obtain the relative energy of two tautomers in solution, the contributions of solvation were added to the corresponding gas-phase relative energies, calculated as described in section 2.1. The thermodynamic cycle shown in Figure 3 was employed to evaluate the relative free energies in

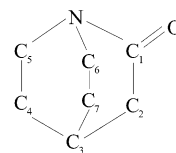


Figure 2. Scheme showing the atom numbering used in the definition of the dihedral angles for the calculation of τ , χ_C , and χ_N , according to formula 5, 6, and 7.

aqueous solvent (ΔG_{aq}) between the O- and N-protonated tautomers (designed as OH and NH):

$$\Delta G_{\text{aq}}^{\text{NH-OH}} = \Delta G_{\text{gas}}^{\text{NH-OH}} - G_s^{\text{A-OH}} + G_s^{\text{A-NH}} \quad (1)$$

Here, $\Delta G_{\text{aq}}^{\text{NH-OH}}$ is the free energy difference in aqueous solution between the N- and O-protonated tautomers, $\Delta G_{\text{gas}}^{\text{NH-OH}}$ is the relative free energy in the gas phase and is obtained by the methods described in section 2.1, and G_s^i is the solvation free energy for the i th molecule, calculated with the HF(PCM)/6-31G* approach.

2.3. Evaluation of pK_a Values. We have estimated the pK_a 's of twisted amides **1**, **2a–c**, and **3a,b** by means of quantum mechanical calculations. Considerable cancellation of errors is expected if, instead of evaluating absolute pK_a , relative pK_a 's are evaluated. This requires the choice of a similar reference molecule for which the experimental pK_a is known. Using a

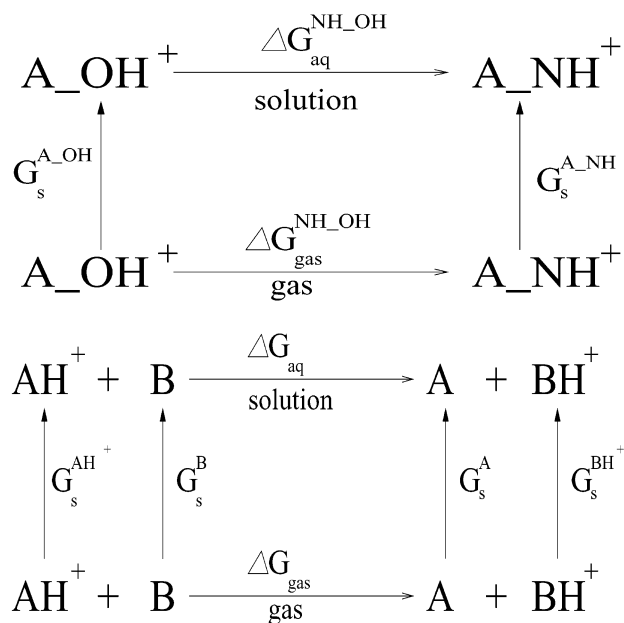
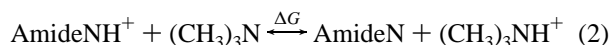


Figure 3. Scheme showing the thermodynamic cycles used to evaluate the free energy difference in solution between N- and O-protonated tautomers in amides (top diagram), and the relative proton affinity with respect to trimethylamine (bottom diagram; compound B refers to trimethylamine).

thermodynamic cycle with the reference molecule (Figure 3b) avoids the need to deal with the proton solvation free energy.¹⁴ It is also important that the number of charged species is conserved on both sides of the chemical equation for which the free energy difference is calculated. One can expect that inaccuracies of the continuum models for describing the strong hydrogen bonds of the first solvation shell around ions will cancel approximately, providing the charged species have similar first solvation shells. We have used this protocol to evaluate pK_a 's for phosphoranes,¹⁷ and we obtained results that are nearly coincident with experimental estimates and density functional-based ab initio molecular dynamics calculations.³¹ In the present work, we follow this approximation and use trimethylamine (TMA) as the reference molecule. This molecule is a tertiary amine with a pyramidal nitrogen that accepts the proton, as is the case for the twisted amides **1**, **2a–c**, and **3a,b**. The experimental pK_a of TMA has been measured³² ($pK_a = 9.8$), and there is a single protonation site. In addition, very good agreement with the experiments is obtained for the solvation free energies of charged and neutral amines when using the polarizable continuum model with the UAHF set of radii.²⁹ For instance, the experimental solvation free energy of trimethylamine is -3.2 kcal/mol, and it is -59 kcal/mol for the protonated species. These values are well reproduced with the HF(PCM)/6-31G* method,²⁹ which gives -2.8 and -58.9 kcal/mol, respectively. Therefore, our choice of reference system and method is justified.

We evaluated the free energy change corresponding to the reaction



where ΔG for the reaction is evaluated according to the methods described in sections 2.1 and 2.2, and the thermodynamic cycle of Figure 3b; i.e., ΔG_{aq} is given by

$$\Delta G_{aq} = \Delta G_{gas} - G_s^{AH} - G_s^B + G_s^{BH} + G_s^A \quad (3)$$

where A and B are the amide of interest and $(\text{CH}_3)_3\text{N}$, respectively. The gas-phase free energy is evaluated according to the methods described in section 2.1, and G_s^i , the solvation free energy of compound i , is estimated with the polarizable continuum model, as described in section 2.2. The pK_a of the amide group being studied (i.e., **1**, **2a–c**, **3a,b**) is determined from the calculated ΔG_{aq} values for the above equilibria and the experimental pK_a of TMA, according to

$$pK_a = \frac{\Delta G_{aq}}{\ln_{10} RT} + pK_a^{\text{TMA}}(\text{exp}) \quad (4)$$

3. Structural Results

Several untwisted and twisted amides are considered in this study. Formamide, acetamide, propamide, and butamide are used as examples of untwisted amides with different numbers of C–C and C–N bonds. As twisted amides we have chosen the compounds **1**, **2a–c**, and **3a,b** shown in Figure 1. Compound **1** has been synthesized by Kirby et al.^{5,6} and showed a highly accelerated hydrolysis when dissolved in water. Compound **2a** can be considered as a prototype of a twisted amide, which combines a high amide distortion and simplicity. We have recently characterized the barriers for its alkaline hydrolysis;¹⁰ the rate of hydrolysis was found to be significantly accelerated with respect to that of its planar amide analogue compound **4**. Compounds **2b,c** can be viewed as derivatives of **2a** by double methylation of a carbon vicinal to the nitrogen (**2b**), or by addition of a phenyl ring in the structure (**2c**). For compounds **2b,c** experimental estimates of the pK_a 's exist.^{3,5} Compounds **3a,b** can also be viewed as derivatives of **2a** corresponding to different elongations of the aliphatic chain determining the cage structure, but they are expected to have different twists of the amide group. These compounds, along with **2a**, have been characterized in the gas phase at the HF/6-31G* level of theory by Greenberg et al.,^{7,8} who reported intermediate twisting of the amide bond. For each of these amides, we have studied the neutral, N-protonated, and O-protonated species. First, we describe the structures with a particular focus on the twisting of the amide bond. Then, we consider the changes in structure that are caused by N- and O-protonation. In section 4, we describe the relative stability of the N- and O-protonated tautomers in the gas phase and in solution, and the latter are then used to calculate the pK_a values with eq 4.

Selected bond distances and angles optimized at the B3PW91/6-31+G* level of theory are shown in Table 1 for untwisted amides and in Table 2 for twisted amides. For all the compounds studied, the C–N versus C–O bond lengths are shown in Figure 4. The out-of-plane deformations and amide bond twisting are described by the angles τ , χ_C , and χ_N , following the definitions of refs 33 and 34. The angle τ characterizes the mean twisting angle around the C–N bond and ranges from 0° (planar amide group) to 90° (when the two planes defined by the $\text{O}_1\text{--C}_1\text{--C}_2$ and $\text{C}_5\text{--N--C}_6$ atoms are perpendicular); χ_C and χ_N are measures of the degree of pyramidalization at the C and N atoms, respectively. They range from approximately 0° (planar sp^2 atoms) to 60° (tetrahedral sp^3 atoms). The combination of dihedrals used to define τ , χ_C , and χ_N is as follows. Defining the four torsion angles $\omega_1 = \text{O}_1\text{--C}_1\text{--N--C}_5$, $\omega_2 = \text{C}_2\text{--C}_1\text{--N--C}_6$, $\omega_3 = \text{C}_2\text{--C}_1\text{--N--C}_5$, and $\omega_4 = \text{O}_1\text{--C}_1\text{--N--C}_6$ (for the atom numbering definition, see Figure 2), we can write

TABLE 1: B3PW91/6-31+G* Geometrical Parameters for the Untwisted Planar Amides (Distances in Ångstroms and Angles in Degrees)

molecule	bond distances				angles			improper dihedral	
	C ₁ N	C ₁ O	OH	NH	τ	χ_C	χ_N	N	C ₁
formamide	1.358	1.217			0.0	0.0	0.0	180.0	180.0
N-protonated	1.565	1.174		1.030	30.1	0.0	60.2	121.7	180.0
O-protonated	1.295	1.291	0.975		0.0	0.0	0.0	180.0	180.0
acetamide	1.365	1.223			0.0	0.0	0.0	180.0	180.0
N-protonated	1.615	1.177		1.027	44.6	0.0	62.1	119.9	180.0
O-protonated	1.304	1.304	0.974		0.0	0.0	0.0	180.0	180.0
propamide	1.367	1.226			1.3	0.9	8.9	171.9	179.1
N-protonated	1.591	1.181		1.027	15.8	0.4	56.0	123.1	179.5
O-protonated	1.302	1.313	0.973		0.0	0.0	0.0	180.0	180.0
butamide	1.372	1.229			0.0	0.0	0.0	180.0	180.0
N-protonated	1.571	1.185		1.025	30.9	0.0	61.8	119.1	180.0
O-protonated	1.304	1.317	0.972		2.0	0.5	1.8	178.3	179.4
4	1.370	1.228			2.6	1.6	17.2	162.9	178.4
N-protonated	1.569	1.188		1.027	45.8	1.0	51.5	128.0	178.8
O-protonated	1.302	1.316	0.972		1.3	1.0	0.5	179.5	179.0

TABLE 2: B3PW91/6-31+G* Geometrical Parameters for the Twisted Pyramidal Amides (Distances in Ångstroms and Angles in Degrees)

molecule	bond distances				angles			improper dihedral	
	C ₁ N	C ₁ O	OH	NH	τ	χ_C	χ_N	N	C ₁
1	1.450	1.208			89.7	0.2	60.0	119.4	179.8
N-protonated	1.546	1.191		1.026	90.0	0.0	56.7	122.4	180.0
O-protonated	1.365	1.294	0.981		67.3	14.7	59.7	117.3	165.1
2a	1.447	1.207			89.8	0.1	62.1	117.1	177.9
N-protonated	1.543	1.188		1.026	90.0	0.0	58.0	120.9	180.0
O-protonated	1.359	1.289	0.982		61.8	13.6	63.7	113.3	166.4
2b	1.448	1.207			88.5	1.9	59.7	118.6	178.1
N-protonated	1.532	1.190		1.026	89.7	1.5	55.6	122.3	178.5
O-protonated	1.344	1.297	0.977		62.0	13.4	60.3	116.9	165.6
2c	1.461	1.204			86.2	1.6	64.7	114.5	178.4
N-protonated	1.561	1.186		1.025	88.2	0.5	60.0	118.0	179.5
O-protonated	1.379	1.286	0.983		70.1	4.5	65.5	105.4	175.5
3a	1.402	1.221			36.0	11.5	50.9	129.4	168.4
N-protonated	1.561	1.189		1.026	53.1	0.2	53.2	126.3	179.8
O-protonated	1.314	1.313	0.973		31.0	17.8	44.5	137.0	161.3
3b	1.403	1.219			39.9	11.2	46.0	134.4	168.8
N-protonated	1.545	1.190		1.026	70.2	0.3	50.0	128.5	179.6
O-protonated	1.316	1.311	0.973		33.1	16.8	40.4	139.8	163.2

$$\tau = (\omega_1 + \omega_2)/2 \quad (5)$$

$$\chi_C = \omega_1 - \omega_3 + \pi(\text{mod}2\pi) = -\omega_2 + \omega_4 + \pi(\text{mod}2\pi) \quad (6)$$

$$\chi_N = \omega_2 - \omega_3 + \pi(\text{mod}2\pi) = -\omega_1 + \omega_4 + \pi(\text{mod}2\pi) \quad (7)$$

The absolute values of these angles with projection on the 0–90° quadrant are shown in Tables 1 and 2; the improper dihedrals for C and N, defined as O–C₁–N–C₂ and C₁–N–C₅–C₆ dihedral angles, respectively, are also reported.

3.1. Neutral Amides. The values of τ , χ_C , and χ_N are very low for neutral untwisted amides, indicating that both the nitrogen and the carbonyl carbon show a planar configuration. Formamide, acetamide, and butanamide show values of τ , χ_C , and χ_N of 0.0°, whereas propanamide shows only slight deviations, namely, values of 1.3° for τ , 0.9 for χ_C , and 8.9 for χ_N . The situation is very different for the twisted amides **1** and **2a–c**. The geometrical constraints imposed by the “cage” structure of these compounds lead to calculated τ values between 85° and 90°. The crystallographic structure⁵ of **1** has τ of 90.5°. An intermediate twist is observed for compounds **3a,b**, with values for τ of 36° (**3a**) and 40° (**3b**). There is a general agreement with the results of Greenberg et al.⁸ for these

compounds, although the theoretical level they used is different (HF/6-31G*). They reported values of τ of 39.2° and 44.0° for **3a** and **3b**, and a value of 90.0° for **2a**. These twisted structures have planar carbonyl carbon ($\chi_C = 0^\circ$), but the planarity at nitrogen is lost (e.g., $\chi_N = 62.1$ for **2a**), in accord with the breakdown of the $n_N \rightarrow \pi_{CO}^*$ resonance. Interestingly, structures **3a** and **3b** show slight deviations from planarity for the carbonyl carbon, with χ_C values around 11°.

As expected, the twist about the C–N bond has a substantial effect on its length. Amides **1** and **2a–c** show the longest C–N bonds among the neutral amides, between 1.450 Å for **1** and 1.461 Å for **2c**. These bond lengths are almost 0.1 Å longer than any of the C–N bonds in the undistorted planar amides (Table 1). Correspondingly, the C–O bond lengths shorten, although the differences are not as dramatic; they are on the order of 0.02 Å. For instance, the C–N bond length in **2a** is 1.447 Å and the C–O bond length is 1.207 Å, whereas in butamide the values are 1.372 and 1.229 Å, respectively. Amides **3a** and **3b**, with intermediate twisting, have C–N and C–O bond lengths between those of planar amides and twisted amides; the C–N bond length for **3a** is 1.402 Å, and the C–O bond length is 1.221 Å. The calculated values for the C–N

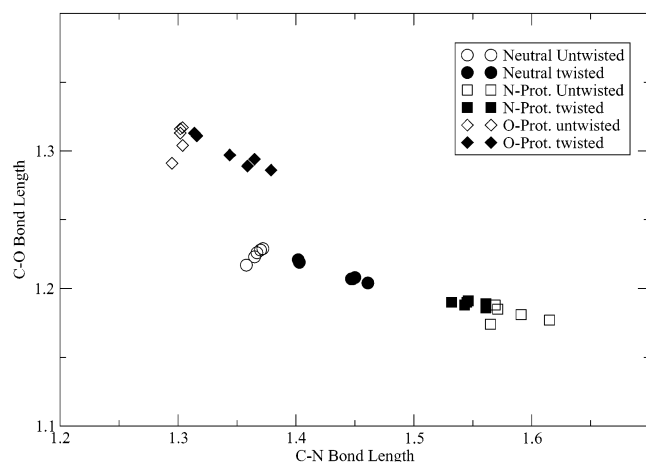


Figure 4. C–N versus C–O bond lengths (in Å) for twisted and untwisted amides in the neutral state (circles) and in the two protonated states, N-protonated (squares) and O-protonated (diamonds). The bond lengths are in angstroms and are calculated using the B3PW91/6-31+G(d) level of theory.

and C–O bond lengths compare well with the available crystallographic data; e.g., in the case of **1**, we obtain 1.450 and 1.208 Å for the C–N and C–O bond lengths, respectively, while the experimental values are 1.475 and 1.196 Å. The present results are also in general agreement with those of Greenberg et al.,⁸ although we get somewhat longer bond lengths in general, as expected when electron correlation is introduced.

Overall, the results indicate that the C–N bond is more sensitive to the twist of the amide group than is the C–O bond. The same trend was observed when analyzing the rotation barrier in formamide and derivatives.^{35–40} This fact has been used to challenge the traditional amide $n_N \rightarrow \pi_{CO}^*$ resonance model.⁴⁰ However, the data can be reconciled with the $n_N \rightarrow \pi_{CO}^*$ resonance model if one takes into account the strong polarization of the C=O bond and its ionic bond character.⁴⁰ In fact, Glendening and Hrabal⁴¹ have re-examined the role of the resonance interactions in formamide by using natural population analysis⁴² and natural resonance theory (NRT).⁴³ They found that the NRT representation of planar amides consists primarily of two resonant structures, one with a formal double C=O bond and a single C–N bond (contributing 60–65%) and another resonant structure with a formal C=N double bond and a single C–O bond (contributing 28–30%). This situation corresponds to the traditional $n_N \rightarrow \pi_{CO}^*$ resonance model.

3.2. Structural Effects of N- and O-Protonation. The effect of N- and O-protonation on the amide structure for both twisted and untwisted amides is quite important, and follows opposite trends. As shown by Greenberg et al.,^{7,8} O-protonation lengthens the C–O bond and shortens the C–N bond, affecting untwisted and twisted amides in a similar way. If we look at the diagram in Figure 4, O-protonated amides are shown in the top left corner, where the longest C–O bonds and the shortest C–N ones occur, in agreement with the results of Greenberg et al.

On the other hand, N-protonation has the opposite effect: it elongates the C–N bond and shortens the C–O bond, since

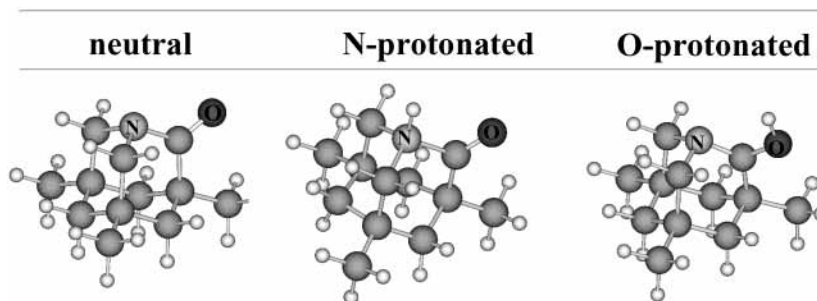


Figure 5. B3PW91/6-31+G(d) structures for twisted amide **1** in three protonation states: neutral, N-protonated, and O-protonated.

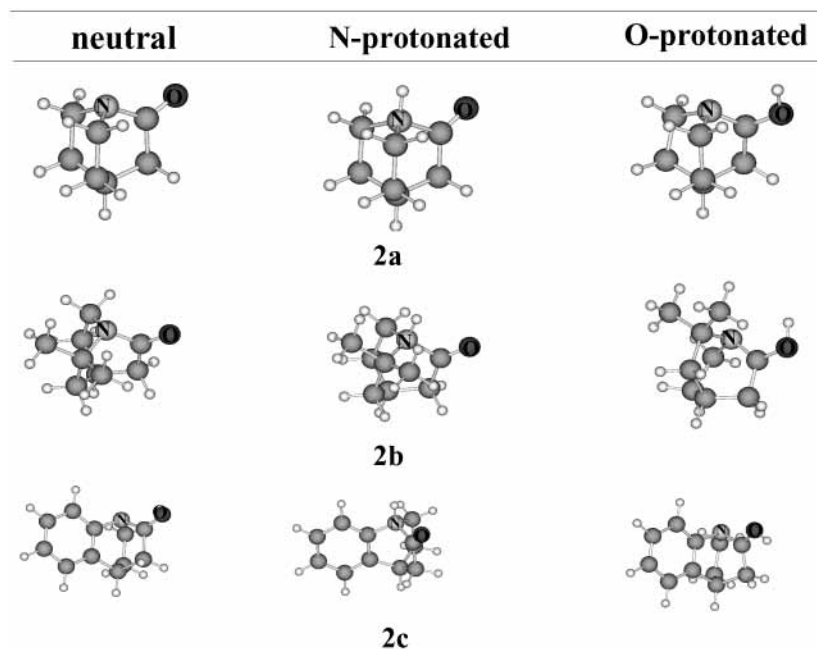


Figure 6. B3PW91/6-31+G(d) structures for twisted amides **2a–2c** in three protonation states: neutral, N-protonated, and O-protonated.

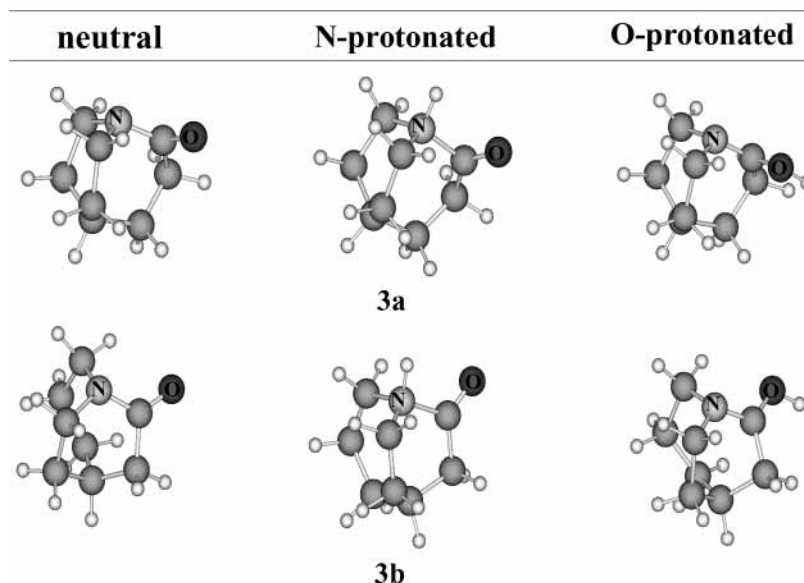


Figure 7. B3PW91/6-31+G(d) structures for twisted amides **3a,b** in three protonation states: neutral, N-protonated, and O-protonated.

the proton binds to the unique lone pair of the nitrogen and prevents the $n_N \rightarrow \pi_{CO}^*$ resonance. The τ and χ_N angles reflect this change in resonance, and in the case of planar amides, χ_N goes from values close to 0° to around 60° upon N-protonation. There is also a significant elongation of the C–N bond for twisted amides⁸ for compounds **2a**, **3a**, and **3b**. The C–N bond in N-protonated amides is the most “activated” bond (its length ranges from 1.55 to 1.62 Å); these amides are shown in the bottom right corner of the diagram in Figure 4.

As shown in Figure 4, there is a strong anticorrelation between the C–N and C–O bond lengths as a function of twisting in the amide bond. The longer the C–N bond, the shorter is the C–O bond when strong $n_N \rightarrow \pi_{CO}^*$ resonance exists, as in neutral and O-protonated untwisted amides. However, in N-protonated species, there is no such effect because of the absence of the $n_N \rightarrow \pi_{CO}^*$ resonance after protonation. Finally, protonation has a strong effect on the amide bond structure. Whereas protonation at O tends to strengthen the C–N amide bond, protonation at nitrogen leads to a big activation of the C–N bond. To determine whether O- or N-protonation will be more likely, the relative stability of each of the tautomers should be analyzed. This is done in the following section.

4. Free Energy Results and pK_a Values

4.1. Relative Stability of N- versus O-Protonation in the Gas Phase and in Solution. The relative stabilities of the N- versus O-protonated tautomers are listed in Table 3. Values calculated in the gas phase and in solution are shown. For all planar amides, the ΔG_{aq}^{NH-OH} defined in eq 1 is positive, indicating that O-protonated tautomers are more stable than N-protonated tautomers. The ΔG_{gas}^{NH-OH} values range from 14 to 18 kcal/mol. This preference for O-protonated tautomers confirms earlier ab initio studies.⁴⁴ It appears unlikely that higher levels of theory would change this qualitative behavior. Solvent has only a small effect on the relative affinities for the proton between nitrogen and oxygen in these systems; i.e., the ΔG_{aq}^{NH-OH} values are in the range from 11 to 14 kcal/mol, indicating that the preference for O-tautomers is preserved in solution.

Twisted amides show a preference for N-protonation, as already pointed by Greenberg et al.,⁸ and there is a correlation between the degree of twist and N-tautomer stabilization.

TABLE 3: Relative Free Energy (ΔG_{NH-OH}) of the N-Protonated Species versus the O-Protonated Species (in kcal/mol) in the Gas Phase and in Solution

species	gas phase	solution
Untwisted Planar Amides		
formamide	18.8	13.4
acetamide	16.7	13.7
propamide	15.5	11.8
butamide	14.3	12.5
4	16.2	14.0
Twisted Pyramidal Amides		
1	−19.4	−22.0
2a	−19.7	−21.0
2b	−21.4	−21.7
2c	−18.6	−20.0
3a	−4.8	−5.9
3b	−6.0	−7.0
3c	−4.1	−5.7

Amides **1** and **2a–c**, with nearly a 90° twist, have ΔG^{NH-OH} values ranging from -18.6 to -21.4 kcal/mol in the gas phase, and from -20.0 to -22.0 kcal/mol in solution. Again, the solvent has only a small effect on the relative stabilities of the tautomers. Consistent with this, the ΔG^{NH-OH} values for amides **3a** and **3b** are between those for planar amides and **2a–c**, amides but they do show a preference for N-protonations: it is -5.7 kcal/mol for **3a** and -7.0 kcal/mol for **3b**.

In summary, O-protonation is favored for planar amides, whereas N-protonation is preferred for the twisted amides **2a–c** and **3a,b**.

4.2. pK_a Values. Planar amides show a sufficiently low pK_a that ensures they remain unprotonated at a wide range of pH values. However, twisted amides can have very different pK_a values. On the basis of the hydrolytic profile as a function of pH, Wang et al.³ estimated a value of 3.7 for the pK_a of **2c**. In addition, they gave values of -0.3 and 0.5 for compounds analogous to **3a** and **3b**, but with an additional phenyl ring as in **2c**. Also, Pracejus has measured an apparent pK_a of 5.3 for amide **4**.⁴⁵

The theoretical pK_a 's were obtained for the molecules and the model systems according to the protocol described in section 2.3. To validate the method, a series of tertiary amines with known experimental pK_a values were studied. The theoretical and experimental values are compared in Table 4 and Figure 8

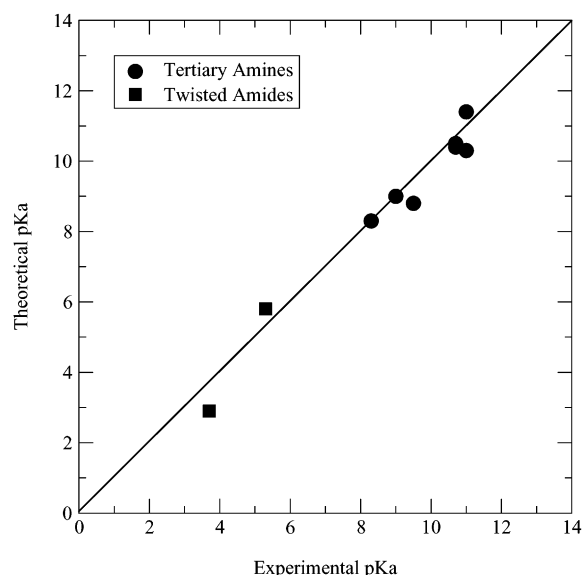


Figure 8. Experimental versus theoretical pK_a . Data are taken from Table 4.

TABLE 4: Estimated Values of pK_a for Tertiary Amines and Twisted Amides

molecule	ΔG_{gas}	ΔG_{soln}	pK_a	
			theor	exp
Tertiary Amines				
triethylamine	8.3	0.7	10.3	11.0
tripropylamine	10.5	0.8	10.4	10.7
triallylamine	7.7	-2.0	8.3	8.3
dimethylcyclohexylamine	8.2	0.9	10.5	10.7
dimethylbenzylamine	4.8	-1.0	9.0	9.0
diethylbenzylamine	7.1	-1.3	8.8	9.5
quinuclidine	8.8	2.2	11.4	11.0
Twisted Amides				
1	6.3	-4.2	6.7	
2a	2.5	-4.5	6.5	
2b	5.9	-5.5	5.8	5.3
2c	1.0	-9.4	2.9	3.7
3a	-4.0	-12.2	0.8	
3b	-3.0	-10.7	1.9	

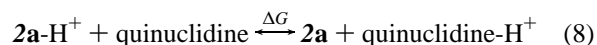
for this series of amines and for compounds **2b** and **2c**. In the case of tertiary amines, we obtain pK_a values that are within 0.7 unit of the experimental mark; the mean absolute error is 0.4 pK_a unit. Particularly encouraging is the result obtained for quinuclidine (see Figure 1), an amine with a cage structure analogous to that of amides **1** and **2a–c**. For quinuclidine, we obtain a pK_a value of 11.4, in very close agreement with the experimental value ($pK_a = 11.0$). Good agreement is also obtained for the twisted amides **2b** and **2c**. The experimental estimates for the pK_a values of **2b** and **2c** are 5.3 and 3.7, respectively, which compare well with the calculated values of 5.8 and 2.9. However, it should be noted that these experimental values are only estimates, as described in the Introduction. For the rest of the twisted amides, the values are 6.7 (**1**), 6.5 (**2a**), 0.8 (**3a**), and 1.9 (**3b**).

The calculated values indicate interesting qualitative trends. First, the calculations show a tendency for twisted amides to have higher pK_a 's than untwisted amides. The fully distorted amides (τ close to 90°) **1** and **2a,b** show values between 5.8 and 6.7, whereas undistorted amides such as formamide show values between 1 and 3, although one has to take into account that the protonation state of reference in untwisted amides is the O-protonated tautomer. Following this trend, amides with intermediate twisting, **3a** and **3b**, have lower pK_a values, 0.8

and 1.9, respectively. The values for gas-phase and solution free energy differences for equilibrium 2 can be found in Table 4. These free energy differences measure the relative proton affinity of each species with respect to TMA. In the gas phase, the numbers are positive for the fully twisted amides **1** and **2a–c** and negative for the intermediate twisted amides **3a,b**. After solvent corrections have been included, all numbers are negative, indicating the larger proton affinity of TMA in solution with respect to any of these amides. However, in terms of relative proton affinities between twisted and partially twisted amides, the results are similar in the gas phase and in solution. In both cases, partially twisted amides show lower proton affinities than fully twisted amides. The origin of this shift in proton affinities can be easily explained in terms of the $n_N \rightarrow \pi_{\text{CO}}^*$ resonance model. Amides with a high degree of bond twist do not show the $n_N \rightarrow \pi_{\text{CO}}^*$ stabilizing effect for the neutral state, and therefore, they have larger proton affinities in the gas phase and larger pK_a 's in solution than partially twisted amides, for which there is a certain degree of $n_N \rightarrow \pi_{\text{CO}}^*$ resonance.

Another remarkable trend observed is the important effect that a phenyl group has on the calculated pK_a 's. On going from **2a** to **2c**, a significant lowering in the pK_a is observed, from 6.5 to 2.9. This effect is confirmed when comparing the results obtained for amides **3a,b** (0.8 and 1.9, respectively) with the estimates inferred by Brown et al.^{3,4} for analogous compounds but with a phenyl group attached to them. Based on the hydrolytic profile as a function of pH, their estimates of the pK_a for **3a,b-Phe** were -0.3 and 0.6, respectively. Thus, their numbers are lower by 1–1.5 units than the calculated pK_a values of **3a,b**, consistent with the effect expected from phenyl substitution when comparing **2a** and **2c**.

Finally, we compare the results between twisted amides and amines of similar size. For instance, if we compare the pK_a values for quinuclidine and amide **2a**, we observe that the pK_a of quinuclidine is between 4.5 and 5 units larger than that of **2a**. If we compare the free energies for the following equilibrium,



we obtain values of -6.3 and -6.7 kcal/mol in the gas phase and in solution, respectively. This indicates that the lower proton affinity of these twisted amides compared to that of structurally related amine compounds has only a small solvent effect, and that the carbonyl group destabilizes the N-position for protonation.

5. Discussion: Mechanistic Implications

The calculations have shown that, in neutral or slightly acidic media, there is a high probability for twisted amides to be found in their N-protonated state. This is expected to have implications for the hydrolysis mechanism of twisted amide compared to undistorted amides. Planar amides undergo very slow hydrolysis in neutral media,⁴⁶ although the reaction can be substantially accelerated by general and specific acid–base catalysis. This is why the breakdown of an amide bond requires enzymatic catalysis in biological systems.⁴⁷ The inherent stability of the amide bond has been explained by the resonance stabilization occurring between the p-type N lone pair and the carbonyl π orbitals. This leads to a partial double bond character for the C–N bond, in accord with theoretical analysis by Glendening and Hrabal⁴¹ using natural population analysis and natural resonance theory. As a consequence, the inherent stability of the amide bond can be substantially altered if the amide

resonance is broken. This can be accomplished if the amide reactant is twisted, as in compounds **1**, **2a–c**, and **3a,b**. Early kinetic experiments^{1–3} supported this idea and determined that twisted amide **2c** was hydrolyzed faster by a factor of 10^7 than planar amide analogues. The activation of the C–N bond in twisted amides is in accord with structural analyses of twisted amides. Both X-ray data and ab initio studies have shown that there is substantial elongations of the C–N bond upon twisting.^{3,4,7,8} In addition, our theoretical investigations have shown that the twisting of the amide bond with nitrogen pyramidalization decreases the barrier with respect to alkaline hydrolysis of model planar amides by about 8–9 kcal/mol, a factor on the same order as that observed experimentally.^{1–3} Interestingly, Kirby et al.^{5,6} found that amide **1** hydrolyzes much faster. Brown et al.^{3,4} observed that the degree of rate acceleration of twisted amides is pH dependent; i.e., compound **2c** showed an increase in rate by a factor of 10^7 under basic conditions, with respect to untwisted analogues, while the rate acceleration was up to a factor of 10^{11} under acid-catalyzed conditions. This suggests that a different mechanism is involved in the latter, in accord with the observation of Kirby et al.

Another factor related to the additional activation of the C–N bond under acidic media is the differential protonation of twisted amides with respect to untwisted ones. In the case of undistorted amides, the protonated species are not very likely at a wide range of pH, since these amides have small pK_a values. Moreover, at low pH, when protonated, the O-protonated tautomer is preferred, which strengthens the C–N bond. However, as established by the gas-phase calculations of Greenberg et al.^{7,8} and by our results in solution, twisted amides have a very different protonation scheme, with preference for the N-protonated tautomer, which leads to a weakening of the C–N bond. This, along with the high pK_a values between 5 and 7 for certain twisted amides (compounds **1**, **2a**, and **2b**), can lead to substantial populations of N-protonated amides in only slightly acidic media, with the resulting activated states of the C–N bond. In this regard, recall that **1** has one of the highest pK_a 's of the series investigated in the present paper and, as reported by Kirby et al.,^{5,6} hydrolyzes extremely fast. The mechanistic consequences of such protonation would be significant, and for a full understanding of the mechanism, further theoretical characterization of the resultant transition states and intermediates will be necessary.

6. Conclusions

Density functional theory was used in combination with dielectric continuum methods to estimate the pK_a values for a series of twisted amides. To avoid the inherent difficulties in calculating absolute pK_a 's, we have employed a protocol based on the calculus of a relative pK_a . Trimethylamine was taken as the reference molecule, and the relative pK_a 's for a series of tertiary amines and twisted amides were evaluated. Good agreement was found between theory and experiment for the systems for which experimental data exist. Our calculations confirmed that twisted amides have higher pK_a 's in solution than untwisted amides, and that the preferential protonation site is at the nitrogen in twisted amides. In addition, we estimated the pK_a values for highly twisted amides for which experimental data are not available, due to their fast hydrolysis which makes experimental measurements very challenging. They showed the highest pK_a values (between 6 and 7) in the series. This suggests that at neutral or slightly acidic pH, there will be a significant population of the N-protonated twisted amides, with the resultant activation of the C–N bond for the hydrolysis. This could be

an important contribution to the faster hydrolysis rates of twisted versus undistorted amides. Theoretical studies to determine the details of the mechanism are in progress.

Acknowledgment. This research was funded by Euskal Herriko Unibertsitatea (the University of the Basque Country), Gipuzkoako Foru Aldundia (the Provincial Government of Guipuzkoa), and Eusko Jaurlaritza (the Basque Government). We also thanks Prof. Martin Karplus for very useful discussions and kind advice. J.I.M. thanks the University of the Basque Country for a predoctoral grant.

References and Notes

- (1) Blackburn, G. M.; Plackett, J. D. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1366–1371.
- (2) Blackburn, G. M.; Skaife, C. J.; Kay, I. T. *J. Chem. Res.* **1980**, 294–295.
- (3) Wang, Q.-P.; Bennet, A.; Brown, R.; Santarsiero, B. *J. Am. Chem. Soc.* **1991**, *113*, 5757–5765.
- (4) Brown, R. *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry and Materials Science; Studies in Amide Hydrolysis: The Acid, Base, and Water Reactions*; John Wiley and Sons: New York, 2000.
- (5) Kirby, A. J.; Komarov, I. V.; Wothers, P.; Feeder, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 785–786.
- (6) Kirby, A. J.; Komarov, I. V.; Feeder, N. *J. Am. Chem. Soc.* **1998**, *120*, 7101–7102.
- (7) Greenberg, A.; Venanzi, C. A. *J. Am. Chem. Soc.* **1993**, *115*, 6951–6957.
- (8) Greenberg, A.; Moore, D. T.; DuBois, T. D. *J. Am. Chem. Soc.* **1996**, *118*, 8658–8668.
- (9) *Dictionary of Organic Compounds*, 5 ed.; Chapman and Hall: New York, 1982; Vol. 3.
- (10) Lopez, X.; Mujika, J.; Blackburn, G.; Karplus, M. *J. Phys. Chem. A* **2003**, *107*, 2304–2315.
- (11) Orozco, M.; Javier, L. F. *Chem. Rev.* **2000**, *100*, 4187–4225.
- (12) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027–2094.
- (13) Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161–2200.
- (14) Chipman, D. M. *J. Phys. Chem. A* **2002**, *106*, 7413–7422.
- (15) Pliego, J. R.; Riveros, J. M. *J. Phys. Chem. A* **2001**, *105*, 7241–7247.
- (16) Pliego, J. R.; Riveros, J. M. *J. Phys. Chem. A* **2002**, *106*, 7434–7439.
- (17) Lopez, X.; Schaefer, M.; Dejaegere, A.; Karplus, M. *J. Am. Chem. Soc.* **2002**, *124*, 5010–5018.
- (18) Becke, A. *Phys. Rev. A* **1988**, *38*, 3098.
- (19) Lee, C.; Yang, W.; Parr, R. *Phys. Rev. B* **1988**, *37*, 785.
- (20) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200.
- (21) Becke, A. *J. Chem. Phys.* **1993**, *98*, 5648.
- (22) Perdew, J. P.; Chevary, J. A.; Vosko, S. H.; Jackson, K. A.; Pederson, M. R.; Singh, D. J.; Fiolhais, C. *Phys. Rev. B* **1992**, *46*, 6671–6687.
- (23) Perdew, J.; Burke, K.; Wang, Y. *Phys. Rev. B* **1996**, *54*, 16533.
- (24) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; O. Farkas, J. T.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian98*, Revision A.2; Gaussian, Inc.: Pittsburgh, PA, 1998.
- (25) Hehre, W.; Radom, L.; Schleyer, P.; Pople, J. *Ab Initio Molecular Orbital Theory*; Wiley-Interscience: New York, 1986.
- (26) McQuarrie, D. A. *Statistical Mechanics*; University Science Books: Mill Valley, CA, 2000.
- (27) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *225*, 327–335.
- (28) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032–3041.
- (29) Barone, V.; Cossi, M.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3210–3221.
- (30) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404–417.

- (31) Davies, J.; Doltsinis, N. L.; Kirby, A.; Roussev, C.; Sprik, M. *J. Am. Chem. Soc.* **2002**, *124*, 6594–6599.
- (32) Hall, H. J. *J. Am. Chem. Soc.* **1957**, *79*, 5441.
- (33) Gilli, G.; Bertolasi, V.; Belluccu, F.; Ferretti, V. *J. Am. Chem. Soc.* **1986**, *108*, 2420–2424.
- (34) Ferretti, V.; Bertolasi, V.; Gilli, P.; Gilli, G. *J. Phys. Chem.* **1993**, *97*, 13568–13574.
- (35) Wiberg, K.; Laidig, K. *J. Am. Chem. Soc.* **1987**, *109*, 5935.
- (36) Wiberg, K.; Laidig, K. *J. Am. Chem. Soc.* **1992**, *114*, 831.
- (37) Wiberg, K.; Hadad, C.; Rablen, P.; Cioslowski, J. *J. Am. Chem. Soc.* **1992**, *114*, 8644.
- (38) Wiberg, K. B.; Rablen, P. R. *J. Am. Chem. Soc.* **1993**, *115*, 9234–9242.
- (39) Wiberg, K. B.; Rablen, P. R. *J. Am. Chem. Soc.* **1995**, *117*, 2201–2209.
- (40) Wiberg, K. B.; Rush, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 2038–2046.
- (41) Glendening, E. D.; Hrabal, J. A., II. *J. Am. Chem. Soc.* **1997**, *119*, 12940–12946.
- (42) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735–746.
- (43) Glendening, E. D.; Badenhop, J. K.; Weinhold, F. *J. Comput. Chem.* **1998**, *19*, 628–646.
- (44) Howard, A.; Kollman, P. *J. Am. Chem. Soc.* **1988**, *110*, 7195.
- (45) Pracejus, H. *Chem. Ber.* **1959**, *92*, 988–993.
- (46) Radzicka, A.; Wolfenden, R. *J. Am. Chem. Soc.* **1996**, *118*, 6105–6109.
- (47) Wolfenden, R.; Snider, M. J. *Acc. Chem. Res.* **2001**, *34*, 938–945.