Solvent and Structural Effects in the N−H Bond Homolytic Dissociation Energy

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In this work, the gas-phase homolytic N−H bond dissociation enthalpy (BDE) was investigated for a large series of molecules containing at least one N−H bond by means of accurate density-functional theory calculations. The molecules studied belong to different classes of compounds, namely, amines, amides and anilines, amino acids, phenoxazines, indolamines, and other compounds of general interest, such as anti-inflammatory drugs. To achieve these purposes, the (RO)B3LYP/6-311+G(2d,2p)//(U)B3LYP/6-31G* level of theory was used. The calculated gas-phase N−H BDEs, at $T = 298.15$ K, are in the range 499.6−203.9 kJ/mol, for purine and HNO, respectively. Further, the calculated BDEs are in excellent agreement with a significant number of available experimental BDEs. Solvent effects were also taken in account, and rather significant differences are found among N−H BDEs computed in the gas phase and in heptane, DMSO, or water.

Introduction

Among the most fundamental aspects in chemical and biochemical studies are the concepts of structure, energetics, and reactivity, as well as their inter-relationships. In most chemical reactions, there are disruption and formation of chemical bonds, being essential, in this context, to establish databases with experimental reliable data of bond dissociation energies (BDEs) as a direct information of the strength of chemical bonds. There have been several attempts to achieve these purposes, and the recent literature reports two relevant studies on that field.[1,2] However, such important contributions are far from being complete for all the many possible different bonds and, additionally, it is a very hard task to select experimental BDEs from a list of measured and remeasured values for many of the key compounds.

Chemical species containing the N−H bond form an important class of compounds with a large variety of applications, from pharmaceutical agents[3−6] to toxic substances.[7−10] Thus, these compounds may be found in the building blocks of biomolecules as well as in a large number of chemical industry products. In fact, not only are they relevant in life processes but also can have very different roles in industry acting as antioxidants,[4,11−13] complexing agents,[14] or in the manufacture of herbicides, surfactants, dyes, pigments, rubber, polymers, and several biological materials.[4,13,15] The N−H bonds play a crucial role in many biological mechanisms as, for example, in the proton-transfer enzymatic reaction catalyzed by acetylcholinesterase, where N−H bonds are cleaved and formed at the imidazole ring from the Glu327-His440-Ser200 catalytic triad.[5,16] Also, they are important in the antioxidant activity of phenothiazine and related compounds to prevent premature polymerization or oxidation of plastics, lubricating oils, foods, or cosmetics[4,13,17−19] and are equally relevant in free radical reactions.[20]

Despite the great potential and wide application of chemicals containing the N−H bond, the information about the reactivity and strength of this chemical bond is still scarce. Moreover, several data from research studies reported in the literature are often contradictory.[4,11−13,21−34] In fact, even for the most studied and simple molecules such as NH_3, CH_3NH_2, $(CH_3)_2NH$, $PhNH_2$, and Ph_2NH, the experimental homolytic N−H BDE available in the literature may differ by more than 20 kJ/mol. The main causes for such differences in the gas-phase BDE are thought to be due to the application of several different experimental techniques such as photoacoustic calorimetry,[32] EPR measurements of equilibrium constants,[4] or cyclic voltammetry.[29,31] Further, the extrapolation of solution-phase data to gas-phase BDEs implies the introduction of corrections that could sometimes be inappropriate.

The strength of the N−H bond changes dramatically with the number and nature of the atoms attached to the nitrogen atom. Because of these changes, known experimental values vary by more than 100 kJ/mol, which may have important consequences on how easily nitrogen-centered free radicals are formed.[20] The rate of oxidation reactions is highly dependent on the formation of these free radicals and on the transfer of atomic hydrogen. The antioxidant effect is much more effective if RN−H bonds are cleaved at low energies. For example, vitamin E is an effective chain-breaking antioxidant in human blood plasma due to its low O−H BDE. The O−H BDE in vitamin E depends on the structure of tocopherol, but its value may be approximated by that in α-tocopherol, for which experimental results range from 323.4 to 330.1 kJ/mol, depending on the technique used.[35−38] Recently, it was pointed out that the N−H bond in phenothiazine is very weak, where the N−H BDE is at least similar to O−H BDE in vitamin E.[4] The O−H and N−H bond energies have also an important role in tautomeric equilibria such as that observed between a pyridone dimer and hydroxypiridine monomers.[39]

Despite the practical importance of N−H-containing compounds, information about their thermochemical properties is still scarce. Probably, this is due to several factors, different from compound to compound, such as the low stability of some amines, the difficulty of achieving high purity state, difficulties

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of handling of harmful compounds, etc. This is confirmed by experimental research in our group, namely, on the determination of standard enthalpies of formation of dialkylamines and substituted anilines.[40−42]

From what is stated above, it would be helpful if an accurate and systematic study was performed for a variety of compounds containing the N−H bond. However, none of the experimental techniques applied to determine N−H BDEs simultaneous combine the speed and the simplicity required to carry out such an investigation. Further, experimental techniques are not adequate to determine BDEs in compounds containing more than one N−H bond, and provide only either an average of the several N−H bonds, or the lowest N−H BDE in the molecule. Therefore, it is convenient to take advantage of a theoretical approach to obviate these experimental difficulties and also to predict and interpret N−H BDEs in different chemical species. In fact, theoretical approaches must be considered since, very recently, it was found that application of density-functional theory (DFT) is successful in the estimation of O−H BDEs in phenol derivatives.[43−49] The application of a DFT/AM1 model, a single-point calculation at the B3LYP/6-311+G(2d,2p) level on a geometry optimized by the semiempiric AM1 method, was found to be useful for the calculation of ΔBDEs between phenol derivatives and phenol.[33] Recently, this approximated model was applied in the study of N−H BDEs in *p*-substituted anilines, 3,7-disubstituted phenothiazines, and 4,4′-disubstituted diphenylamines.[50] It is shown that absolute N−H BDEs computed by the simplified method are far from those calculated if a full DFT procedure is used. For instance, these authors found that the N−H BDE in phenothiazine, computed by the, in principle, much more accurate (RO)B3LYP/6-311+G(2d,2p) approach, is 12.5 kJ/mol larger than that computed with the DFT/AM1 model. The value computed with the full DFT procedure is closer to the most recent experimental value, ∼330 kJ/mol, and also to those reported by other authors.[4,13,29] However, the approximated method is shown to provide ΔBDEs that are in excellent agreement with some of the available experimental results.

In the present paper, N−H BDEs are reported for a large series of R_nNH compounds estimated by accurate DFT-based calculations. The N−H-containing molecules studied include aliphatic amines and anilines, amides and benzamides, phenoxazines and related compounds, amino acids, indolamines, and nonsteroidal anti-inflamatory drugs (NSAIDs).

Computational Methods

DFT calculations were performed by means of the GAMESS-US and GAUSSIAN98 packages.[51,52] Accurate energies were computed in two steps, all using the B3LYP hybrid method proposed by Becke.[53] First, the geometries of all species were full-optimized at the (U)B3LYP/6-31G(d) level of theory, the unrestricted formalism used in the optimization of RN• radicals. Then, a single-point calculation was performed using the (RO)-B3LYP/6-311+G(2d,2p) approach, with the restricted open-shell, RO, formalism used to generate the DFT orbitals in the case of the RN• radicals. For comparison purposes, some calculations were also performed at the (RO)B3LYP/6-311++G-(3df,3pd)//(U)B3LYP/6-311+G(3df,3pd) level of theory.[54] Vibrational frequencies have also been calculated at the same levels of theory used in the optimization procedure in order to correct the electronic energy values by inclusion of zero-point energies, ZPE, as well as translation, rotational, and vibrational contributions to the enthalpy at $T = 298.15$ K. In the calculation of vibrational frequencies, a scale factor of 0.9804 was used to correct ZPEs as suggested by Scott et al.[55]

The homolytic N−H BDEs of the several compounds were estimated by subtracting the enthalpy at $T = 298.15$ K of the neutral molecules (RNH) from the sum of enthalpies of the radical (RN•) and that of hydrogen atom (H•). This scheme was shown to yield accurate BDEs for a series of phenol derivatives.[44−49]

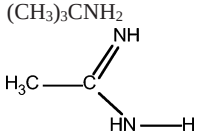
Solvent effects were introduced in the calculations considering an electrostatic influence by means of a self-consistent reaction-field (SCRF) method. In the present work, the solvent is defined by a continuous medium, which is characterized by its dielectric constant as suggested by the polarized continuum model, PCM, of Tomasi an co-workers.[56] In this model, the molecule under study, solute, is placed inside a cavity of a convenient shape. Since no explicit solvent molecules are included in the calculations, the effect of solvent is approximated and only the electrostatic part is taken into account. The calculations were performed by the polarizable conductor calculation model, CPCM,[57] and also used the integral equation formalism model, IEFPCM.[58] In these calculations, four different dielectric constants were used throughout the calculations in order to simulate the electrostatic influence of bulk water ($\epsilon = 78.4$), bulk DMSO, ($\epsilon = 46.7$), and bulk heptane ($\epsilon = 1.9$). These solvents were chosen in order to obtain information about the influence of solvent polarity in the N−H BDEs. The SCRF calculations followed a similar scheme to that employed for determination of N−H BDEs in a vacuum, i.e, geometry, frequencies, and final energy are calculated at the same levels of theory, namely, the (RO)B3LYP/6-311+G(2d,2p)//(U)-B3LYP/6-31G(d). Recently, it was found for formate anion in aqueous solution that the B3LYP calculated frequencies are in better agreement with experiment if a scale factor similar to the one used for the gas phase is used.[59] Therefore, in the present SCRF calculations, the 0.9804 scaling factor suggested by Scott et al. was introduced in the correction of ZPEs.[55]

Results and Discussion

The computed geometrical parameters, as well as energetic data for each species studied in the present work, will be supplied by the authors upon request. In a general way, full-optimized geometries are in excellent agreement with available data.[60] In the following subsections, computed results will be directly compared with experimental data from several different techniques and under different experimental conditions. Those experimental values extracted from solution-phase techniques already include the authors' correction for gas-phase conditions. As referred above, it is possible to find in the literature several results for N−H BDEs coming from two different experimental groups which do not closely agree with each other. Each group claims its value to be the correct one, but additional studies from other groups would be required to withdraw any final conclusions.[29,32,35]

The BDEs of the N−H Bonds in RNH_2 Compounds. The computed results for the gas-phase BDEs in aliphatic alkylamines are reported in Table 1. Computed N−H BDEs in ammonia and methylamine are in excellent agreement with experimental data, the computed numbers lie in the range of experimental values from different sources. The results herewith compiled show that there is not a significant variation in BDEs on this class of compounds, except in the case of ammonia. This fact is not related with a stronger bond in NH_3, since all N−H bond distances in this group of amines are calculated to be about 1.019−1.020 Å. Thus, the higher BDE value for the homolytic N−H bond scission in ammonia is due to a less efficient stabilization of the $•NH_2$ radical when compared with

TABLE 1: N−H Homolytic BDEs for RNH_2 Compounds with Values in kJ/mol Computed at Two Different Levels of Theory

compound	6-311+ G(2d,2p)[a]	6-311++ G(3df,3pd)[b]	exp
HNH_2	448.1	450.0	431.0;[c] 447.7;[d] 451.9;[e] 456.9 ± 7.1[f]
CH_3NH_2	413.2	413.6	384.9;[c] 418.4;[d] 425.1 ± 8.4[f]
$CH_3CH_2NH_2$	416.0	416.6	
$CH_3(CH_2)_2NH_2$	415.9	416.5	
$CH_3(CH_2)_3NH_2$	415.5		
$CH_3(CH_2)_5NH_2$	415.4		
$CH_3(CH_2)_7NH_2$	415.5		
$CH_3(CH_2)_9NH_2$	415.6		
$CH_3CH(NH_2)CH_3$	416.8		
$CH_3CH_2CH(NH_2)CH_3$	414.5		
$(CH_3)_3CNH_2$	409.6		397.5 ± 8.4[g]
	412.6	413.9	

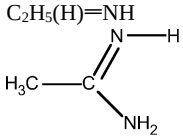
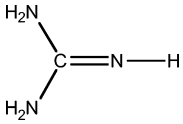
[a] (RO)B3LYP/6-311+G(2d,2p)//(U)B3LYP/6-31G(d). [b] (RO)B3LYP/6-311++G(3df,3pd)//(U)B3LYP/6-311++G(3df,3pd). [c] Reference 21. [d] Reference 22. [e] Reference 26. [f] Reference 23. [g] Reference 78.

the other amines shown in Table 1. In fact, the stabilization of the $^{\bullet}NH_2$ radical can be seen by the lower value of the N−H BDE in *tert*-butylamine when compared with the N−H BDE in 1-butylamine, and this may be correlated with the presence of three methyl groups attached to CNH_2 in $(CH_3)_3CNH_2$. These three CH_3 substituents are electron donors that destabilize the $(CH_3)_3CNH_2$ species and stabilize the $(CH_3)_3CNH^{\bullet}$ radical. Consequently, the N−H BDE is lowered, and if this value is compared with others reported in Table 1, it decreases by about 5−6 kJ/mol. In this same table, another comparison may be established with a significantly different compound; for ethanimidamide, these stabilization effects are also observed, but this time resonance effects must also be taken into account due to delocalization of the odd electron in the radical.

The size of the basis set and its influence both on geometry optimization and computation of N−H BDE was also explored. For that purpose, the 6-311++G(3df,3pd) basis set was used for full optimization of geometries and to obtain enthalpies at $T = 298.15$ K. By analyzation of data in Table 1, it is shown that differences in computed BDEs at the (RO)B3LYP/6-311++G(3df,3pd)//(U)B3LYP/6-311++G(3df,3pd) level of theory differ by a maximum of 1 kJ/mol from the computed BDEs by the (RO)B3LYP/6-311+G(2d,2p)//(U) B3LYP/6-31G(d) approach. Thus, it may be concluded that the less demanding computing approach is enough to obtain accurate N−H BDEs. This will be further supported in the subsequent sections by the excellent agreement between computed and available experimental data.

The BDEs of the N−H Bonds in R_2NH Compounds. The computed results for the gas-phase BDEs in aliphatic dialkylamines are, as expected from stereoelectronic effects, somewhat lowered when compared with numbers reported in Table 1. As far as we know, only the experimental N−H BDE for dimethylamine, $(CH_3)_2NH$, is available in the literature. For this compound, three different values are found, one being (359.8 ± 12.5) kJ/mol,[21] another one of 382.8 kJ/mol,[22] and a more recent one, which is (395.8 ± 8.5) kJ/mol.[23] The computed N−H BDE is 387.4 kJ/mol, right between the two most recent numbers.[22,23] In fact, the accuracy of the first value was doubtful if one considers the large interval of uncertainty given. Since a significantly low value was also reported for the N−H BDE in ammonia and methylamine, cf. Table 1, it may be concluded that N−H BDEs included in the review of Kerr[21] are, in principle, not accurate and have to be handled with extreme care. As done for the preceding group of alkylamines, the effect of the alkyl ligand on the N−H BDE of dialkylamines was studied. For the *N*,*N*-ethylmethylamine ($CH_3NHC_2H_5$) compound and when compared with dimethylamine, the N−H BDE is reduced to 386.4 kJ/mol, while for methylpropylamine ($CH_3NHC_3H_7$) it is reduced to 385.9 kJ/mol. Interestingly, the variation in the N−H BDE is not similar to those reported in Table 1 for methylamine, ethylamine, and propylamine, where an increase was found when replacing CH_3 by C_2H_5. Now, replacing the CH_3 group in $CH_3NHC_2H_5$ and in $CH_3NHC_3H_7$ by a C_2H_5 ligand, the computed N−H BDEs are 388.4 and 387.7 kJ/mol for the resulting products, $C_2H_5NHC_2H_5$ and $C_2H_5NHC_3H_7$, respectively. This effect in computed N−H BDEs (∼+2 kJ/mol) is opposed to what is expected if one only considers the larger destabilization due to inductive effects when going from a CH_3 to a C_2H_5 group. However, since R−N (R = CH_3, C_2H_5, C_3H_7, etc.) bond lengths are shorter in radical RNR species than in their parent RNHR molecules, radical destabilization due to the presence of two bulky alkyl ligands becomes the most important factor. This is further confirmed by the increase in the N−H BDE computed for $CH_3NHCH(CH_3)_2$ and $CH_3NH(CH_3)_3$ compounds, when compared with the N−H BDE in dimethylamine. For these two species, the N−H BDE values are 389.3 and 391.4 kJ/mol, respectively.

TABLE 2: N−H Homolytic BDEs, in kJ/mol, for R=NH Compounds

compound	calcd	exp
$H_2C{=}NH$	369.2	
$CH_3C(H){=}NH$	368.7	
$(CH_3)_2C{=}NH$	377.5	
$C_2H_5(H){=}NH$	373.2	
	393.2; 412.6[a]	426.8[b]
	402.2; 406.5[a]	435.1[b]
$PhC(=NH)NH_2$	404.4; 429.0[a]	426.8[b]

[a] BDE of N−H bond from the NH_2 group. [b] Reference 26.

The BDEs of the N−H Bonds in RC=NH Compounds. Gas-phase N−H BDEs for imines are reported in Table 2. Direct comparison between the simplest imine, $H_2C{=}NH$, and methylamine shows that the presence of a double bond in the imine lowers the energy required to extract the hydrogen bond attached to the nitrogen atom. This is certainly due to the fact that the C=N double bond implies a more elongated N−H bond in the imine, whereas the longer C−N bond in methylamine allows for a better accommodation of the nitrogen atom electron lone pair. In imines, the substitution of a hydrogen atom attached to carbon seems to significantly affect the energy required to remove the imine group hydrogen. However, differences are smaller than those computed for R_2NH amines. Interestingly, the introduction of NH_2 substituents, yielding ethanimidine, $CH_3C(=NH)NH_2$, or guanidine, $(NH_2)_2C{=}NH$, increases the N−H BDE, while substitution of one CH_3 group by NH_2 in dimethylamine, $CH_3N(-H)CH_3$, yielding methylhydrazine,

$CH_3N(-H)NH_2$, decreased the energy needed for N−H bond scission; the computed BDE for methylhydrazine is 326.0 kJ/mol. This may be explained by the well-known basicity of the guanidine moiety, as illustrated, for instance, in the side chain of amino acid arginine. N−H BDEs estimated from the acidities of the N−H bond and oxidation potentials in DMSO, are also found in the literature. Peculiarly, the experimental value for $PhC(=NH)NH_2$ is exactly the same reported for $CH_3C(=NH)NH_2$, cf. 426.8 kJ/mol, and denotes that the phenyl group does not introduce any influence in the N−H dissociation energy.[26] When compared with $CH_3C(=NH)NH_2$, it seems rather difficult that the N−H bond in $PhC(=NH)NH_2$ and $CH_3C(=NH)NH_2$ does not suffer any effect by the proximity of the aromatic ring in which some electron delocalization is possible. From the present calculations, it seems that this N−H bond is somewhat affected by the proximity of the aromatic ring as can be concluded by the two different N−H BDEs computed for these two compounds. The calculated values are 393.2 and 412.6 kJ/mol for N−H bond scission of the =NH and $-NH_2$ groups in $CH_3C(=NH)NH_2$ and 404.4 and 429.0 kJ/mol for N−H bond scission of the =NH and $-NH_2$ groups in $PhC(=NH)NH_2$. Only the computed BDE for the NH_2 group in $PhC(=NH)NH_2$ is in agreement with the experimental value. But, the lower BDE calculated for the =NH group is in agreement with the higher acidity of the N−H bond in this group, when compared with the N−H bond in ammonia.[26] Because of the unexpected determination of exactly the same experimental N−H BDE for $PhC(=NH)NH_2$ and $CH_3C(=NH)NH_2$ and also due to the significantly large differences found between experimental and theoretical N−H BDEs, further experimental investigation on this kind of molecules is required.

The BDEs of the N−H Bonds in Small Molecules. The N−H BDE was also calculated for a series of small molecules, namely, HN, HNC, HNO, HNCO, H_2NNO_2, and H_2NNH_2. The experimental N−H BDE of H_2NNH_2 had been determined by photoionization mass spectrometry, corresponding to (338.1 ± 1.3) kJ/mol at $T = 0$ K.[61] This result has been corrected to $T =$ 298.15 K by DiLabio and co-workers, yielding a BDE of 343.9 kJ/mol.[33] For this same compound, another experimental N−H BDE was reported by Grela and Colussi,[62] but their value, of about 366 kJ/mol, seems too high since the former values are in excellent agreement with the computed BDE, which is 340.4 kJ/mol. When compared with ammonia, this reduction in BDE is due to strong delocalization of the odd electron between the two nitrogen atoms, forming a two-center three-electron bond. For the other compounds, computed N−H BDEs are as follows: HN, 412.1 kJ/mol; HNC, 486.0 kJ/mol; HNO, 203.9 kJ/mol; HNCO, 491.1 kJ/mol; and H_2NNO_2, 444.7 kJ/mol. These numbers may be compared with the experimental BDEs for HNO, (196.2 ± 0.4) kJ/mol,[63] and for HNCO, (458.7 ± 1.7) kJ/mol.[63] For the HNCO species, there is a huge deviation between the experimental and the computed number. The N−H BDE of these two compounds, HNO and HNCO, was recomputed by using the Gaussian-3 approach,[64] and similar numbers to those obtained with the B3LYP method were found, 201.4 and 496.6 kJ/mol, respectively. In the case of the HNCO species, the difference between theory and experiment is even larger when the G3 approach is used.

The BDEs of the N−H Bonds in Compounds of Formula $RC(=X)NH_2$ (X = O, S, and Se). Computed BDEs are reported in Tables 3 and 4 for aliphatic and for aromatic amides, respectively. Again, for the aliphatic compounds, computed results are far from the estimated values of Bordwell et al. based on acidities and on oxidation potentials in DMSO.[26] For acetamide and thioacetamide, differences are of about 15 and 30 kJ/mol, respectively. The computed N−H BDEs for these two compounds are larger than the experimental values. Further, opposite variations between experimental and computed data are found for urea and thiourea. For urea, the calculated value is shown to be lower than the estimated BDE by 15 kJ/mol, while for thiourea, the calculated value is 13 kJ/mol higher than the estimated number. Because of some similarity between acetamide and urea and also between thioacetamide and thiourea, it is not probable that DFT gives an incorrect description of N−H BDEs for these two similar families of compounds. Previously, it was considered that DFT always underestimates X−H BDEs, but this seems to be not correct. If this conclusion is correct, then it is possible to conclude that the experimental N−H BDEs for acetamide, thioacetamide, and thiourea are incorrect since they are lower than DFT computed numbers. Also interesting, in the works of Bordwell and co-workers[31,65] it is mentioned that N−H BDEs are the same for NH_3, $CH_3C(=O)NH_2$, and $PhC(=O)NH_2$, their values being about 448 kJ/mol. This behavior contrasts with our computed energies for these species, where a notorious energetic variation of about 20 kJ/mol exists. Since it is expected a different behavior for the stabilization of atomic charge in the conjugate bases or the odd electron in the corresponding radicals, different N−H BDEs are also predictable. In the experimental works of Bordwell et al.,[31,65] it is reported that the equilibrium acidities and oxidation potentials of the conjugate bases of acetamide and benzamide are almost the same but a significant difference is found for ammonia. Attempting to obtain more information about what is happening here, gas-phase acidities for these three neutral molecules and ionization energies for the conjugate bases were computed. The calculated gas-phase acidities are 1690.5 kJ/mol for NH_3, 1533.3 kJ/mol for $CH_3C(=O)NH_2$, and 1482.6 kJ/mol for $PhC(=O)NH_2$. These results are in excellent agreement with available experimental data for NH_3, (1690.3 ± 1.7) kJ/mol,[66] (1687.8 ± 0.4) kJ/mol,[67] and (1688.7 ± 3.3) kJ/mol;[68] for $CH_3C(=O)NH_2$, (1515 ± 9) kJ/mol,[69] (1500 ± 5) kJ/mol,[70] and (1561 ± 13)[71] kJ/mol; and for $PhC(=O)NH_2$, (1481 ± 9) kJ/mol.[72] Because of the large interval of the experimental values

TABLE 3: N−H Homolytic BDEs, in kJ/mol, for Carboxamide and Urea Derivatives

compound	calcd	exp
$CH_3C(O)NH_2$	467.0	447.7;[a] 451.9[b]
$CH_3C(S)NH_2$	410.2	380.7[b]
$CH_3C(Se)NH_2$	377.6	
NH_2CONH_2	449.8	464.4[b]
NH_2CSNH_2	402.5	389.1[b]
NH_2CSeNH_2	398.9	
$CH_3N(H)CONH_2$	423.5	
$CH_3NHCON(H)H$	444.1	

[a] Reference 65. [b] Reference 26.

TABLE 4: N−H Homolytic BDEs, in kJ/mol, for Different Substituted Benzamides[a]

substituent	ortho calcd	para calcd
−H (benzamide)	459.2	
−F	476.3 (+17.1)	458.6 (−1.0)
−Cl	463.6 (+4.4)	459.3 (+0.1)
−CN	470.8 (+11.6)	462.4 (+3.2)
$-NH_2$	449.3 (−9.9)	452.6 (−6.6)
$-NO_2$	457.5 (−1.7)	463.3 (+4.1)
$-CH_3$	451.8 (−7.4)	457.8 (−1.4)
$-OCH_3$	472.7 (+13.5)	455.7 (−3.5)

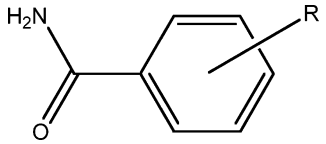
[a] The experimental value for benzamide is 447.7 kJ/mol.[65] Δ = N−H BDE in substituted benzamide and N−H BDE in benzamide, given in parentheses. Please see Chart 1.

TABLE 5: Comparison between Computed and Experimental BDE(N−H) (kJ/mol) for Different Substituted Anilines

	ortho		meta		para	
substituent	calcd	exp	calcd	exp	calcd	exp
−H (aniline)	385.8					375.3 ±6.3;[a] 386.2;[b] 372.8 ± 4.2;[c,d] 368.2 ± 8.4[e]
−F	385.2 (−0.5)		391.6 (+5.8)		381.3 (−4.5)	371.5[a] (−3.8)
−Cl	388.7 (+2.9)	389.5[b] (+3.3)	390.8 (+5.0)	387.4[b](+1.2)	383.7 (−2.1)	386.6[b] (+0.4)
−OH	349.5 (−36.3)		387.1 (+1.3)		369.7 (−16.1)	
−CN	399.7 (+13.9)	397.9[b] (+11.7)	396.1 (+10.3)	393.7[b] (+7.5)	398.3 (+12.5)	398.3[b] (+12.1); 384[c] (+11.2)
$-NH_2$	363.6 (−22.2)		384.8 (−1.0)		359.5 (−26.3)	360[c] (−12.8)
$-NO_2$	415.1 (+29.3)		396.5 (+10.7)		403.2 (+17.4)	404.6[b] (+18.4)
$-CH_3$	380.9 (−4.9)	379.0[d] (+6.2)	384.7 (−1.1)		379.0 (−6.8)	366.1[a] (−9.2); 384.9[b] (−1.3); 371[c] (−1.8)
$-CF_3$	397.6 (+11.8)	387.0[d] (+14.2)	393.4 (+7.6)	400.4[b] (+14.2); 390[d] (+17.2)	396.8 (+11.0)	403.8[b] (+17.6); 385[c] (+12.2)
−COOH	409.3 (+23.5)		391.8 (+6.0)		396.5 (+10.7)	
$-OCH_3$	376.5 (−9.3)	371[d] (−1.8)	389.6 (+3.8)	392.9[b] (+6.7)	368.6 (−17.2)	378.2[b] (−8.0); 365[c] (−7.8)
$-C(CH_3)_3$	375.5 (−10.3)		382.9 (−2.9)		380.1 (−5.7)	372[c] (−0.8)

[a] Gas phase, ref 32. [b] Measured in DMSO, ref 29. [c] Measured in water, ref 11. [d] Measured in water, ref 12. [e] Review value, ref 22. Δ = N−H BDE in substituted aniline and N−H BDE in aniline, given in parentheses.

CHART 1



for acetamide, if a mean of the two most recent experimental values is taken,[70,71] experimental and computed numbers are identical! The computed energies required to extract one electron from these anions, obtaining the corresponding radicals, are 70.4 kJ/mol for NH_2^- yielding $NH_2^\bullet$, 246.5 kJ/mol for $CH_3C(=O)NH^-$ giving $CH_3C(=O)NH^\bullet$, and 289.3 kJ/mol for $PhC(=O)NH^-$ yielding $PhC(=O)NH^\bullet$. These results show significant differences between these three species, but since acidities decrease from ammonia to benzamide and an opposite effect is found for ionization potentials, these differences may be attenuated in DMSO solution. These differences between experimental and computed data are not meaningful if comparison is done for similar species such as substituted benzamides, cf. Chart 1. N−H BDEs for this class of compounds and effects of various substituents at ortho and para positions are compiled in Table 4. For substitution at the para position, the N−H BDE depends on the character of the group attached, increasing from electron-donating to electron-withdrawing groups, i.e., $-NH_2 < -OCH_3 < -CH_3 < -F < -Cl < -CN < -NO_2$. For substitution at the ortho position, the analysis of the computed values is more difficult due to stereochemical effects between adjacent substituents. In some cases, the ortho-substituted compounds have a lower N−H BDE than the corresponding para-substituted benzamides. This is an interesting fact that may be useful for the design of new antioxidants. It is shown that the introduction of these electron-donating or electron-withdrawing groups in the aromatic ring has an effect in N−H BDEs similar to that observed for aniline derivatives, cf. next section and Table 5.

The BDEs of the N−H bonds in Substituted Anilines. Table 5 lists the variation of the N−H BDE with the substituent placed at ortho, meta, and para positions in monosubstituted anilines. It is possible to find in the literature several works devoted to the N−H bond dissociation energy in aniline derivatives.[11,12,22,29,32] Experimental results are also included in Table 5, and in general they are in excellent agreement with computed data. A close inspection of Table 5 shows that experimental values obtained by consideration of both equilibrium acidities and oxidation potentials of the conjugate bases in DMSO[29] or water[11,12] yield significantly different N−H BDEs. However, if their differences with respect to aniline are considered, these two approaches yield the same results. Thus, differences between the absolute BDEs from these works are probably due to improper introduction of C_3 in the equation $BDE_{HA} = C_1 pK_{HA} + C_2 E_{OX}(A^-) + C_3$ (see refs 11 and 29 for further details). Interestingly enough for this kind of compounds, computed BDEs are in close agreement with the results estimated from Bordwell and co-workers work on the combination of equilibrium acidities and oxidation potentials of these substituted anilines and conjugate anions.[29] However, differences may reach 7−10 kJ/mol as for example those found for *m*- and *p*-trifluoromethylaniline and *p*-methoxyaniline. A significantly low N−H value is found for *o*-hydroxyaniline, and this is due to H−N····H−O hydrogen-bonding interaction in the radical, in which the optimized structure of this species resembles that from the catechol molecule.[43] When compared with aniline, this hydrogen-bonding stabilization causes the most dramatic effect in computed N−H BDEs, even larger than that verified for the presence of the NO_2 group also in the ortho position.

The BDE results computed for the meta- and para-substituted anilines are plotted against σ^+ Hammett parameters in Figure 1. A good correlation is found ($R^2 = 0.97$), and clearly the electron donors placed at para positions, $-NH_2$, −OH, $-OCH_3$, and $-CH_3$, destabilize the corresponding substituted anilines, and hence, the computed BDE in these substituted *p*-anilines are lower than that computed for aniline. This effect due to electron donors is much less pronounced if these substituents appear at meta positions. Stabilization of the *p*-anilines is found for the other cases, especially in the case of NO_2 and CN both at the meta and para positions, and consequently, the computed N−H BDE reaches the highest values. For ortho derivatives, similar results to those computed for para derivatives are obtained, except in the cases where the substituents have oxygen atoms, −OH, $-NO_2$, −COOH, and $-OCH_3$. In these cases, differences between N−H BDEs computed for ortho and para derivatives are larger than 8 kJ/mol and may be attributed to

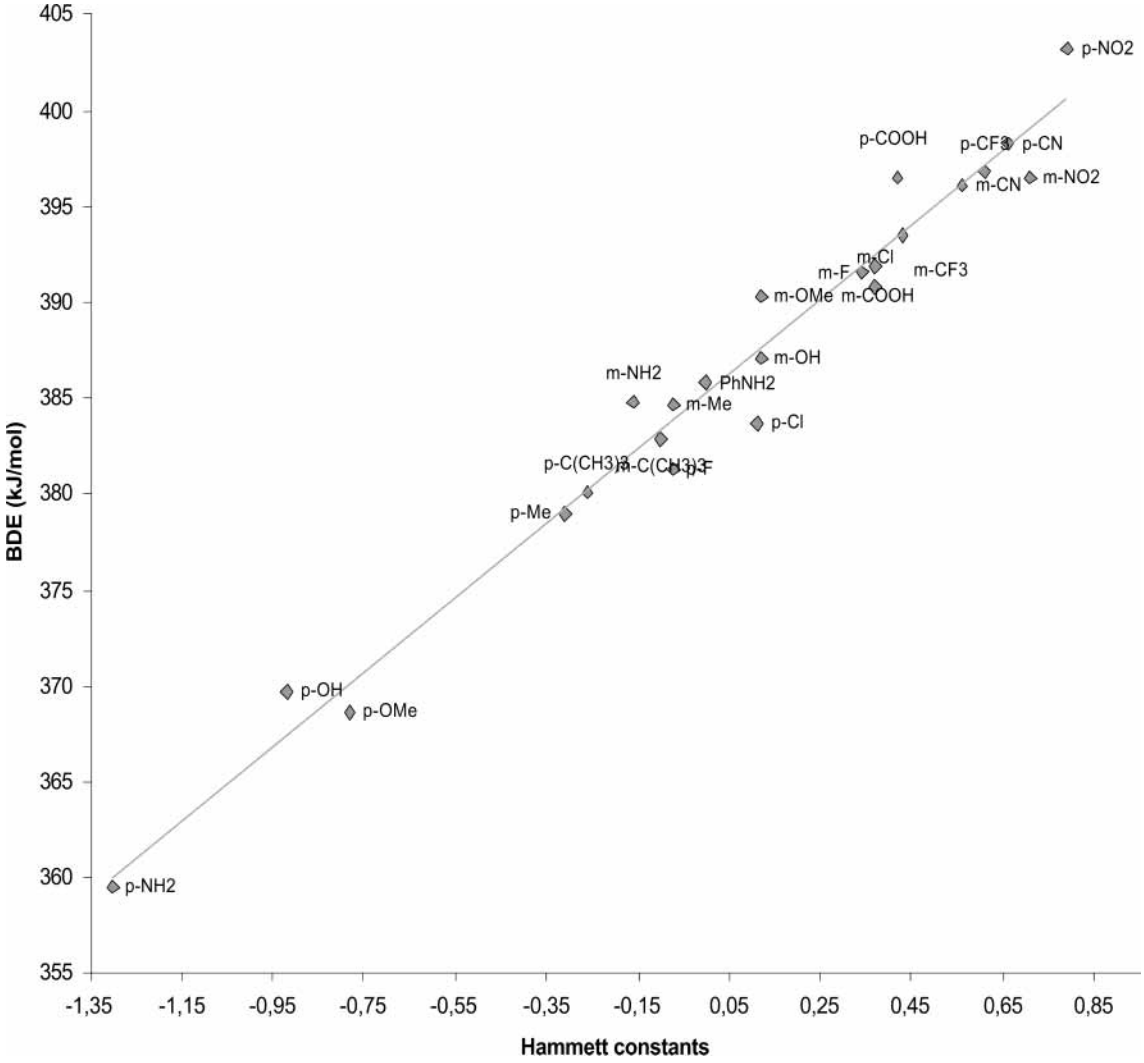
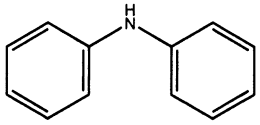
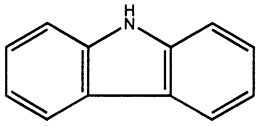
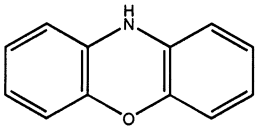
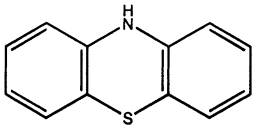
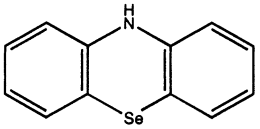
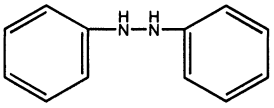


Figure 1. Correlation of calculated BDE(N−H) for different meta- and para-substituted anilines against Hammett σ^+ constants ($R^2 = 0.97$).

stabilization effects in the neutral molecules due to formation of hydrogen bonds between oxygen lone pairs and one hydrogen atom in the amino group. Finally, comparison of ΔBDEs reported in Table 5 with those calculated previously by Pratt and co-workers[50] shows that these two approaches yield similar values but with rather large differences found for the $-NH_2$, −COOH, −F substituents. The maximum difference between the ΔBDEs calculated with these two approaches is 5.7 kJ/mol. The most important conclusion from data reported in Table 5 is that *o*-hydroxyaniline is the aniline derivative with the most interesting antioxidant activity.

The BDEs of the N−H Bonds in Diphenylamine and Related Compounds. Substitution of one hydrogen atom by a phenyl group in the NH_2 group of aniline, yielding diphenylamine, reduces the N−H BDE from 385.8 to 355.0 kJ/mol, cf. Table 6. This computed value is in rather good agreement with experimental results, which range from 359 to 379 kJ/mol.[4,13,25,29,32] By introduction of a bridge between the two rings yielding carbazole, entry 2 in Table 6, the computed BDE energy raises again to a value closer to the computed N−H BDE in aniline. Two experimental N−H BDE values for carbazole have been reported, both higher than those reported for diphenylamine and close to the experimental N−H BDE in aniline.[13,29] A N−H BDE lower than that in diphenylamine would be expected for carbazole due to a, in principle, much more effective radical stabilization in the former species. This is based on the coplanarity of the two phenyl rings imposed by the extra C−C bond in carbazole when compared with diphenylamine. However, homolytic bond scission will produce loss of aromaticity, therefore causing destabilization of the resulting carbazole radical. This is supported by the significant energetic difference computed for removal of one electron from carbazolide or from diphenylamide anions, yielding the corresponding radical species. It is much more difficult to withdraw one electron from a carbazolide anion than from a diphenylamide anion. The difference between the energy required to remove one electron from these two anions is 45.7 kJ/mol. These energetic differences are in agreement with the oxidation potentials measured for the conjugate bases of carbazole and diphenylamine.[29] The energetic variation caused by the introduction of oxygen, sulfur, or selenium bridges between the aromatic rings in diphenylamine was also computed. Computed N−H BDEs for these new compounds are much lower than the BDE computed for diphenylamine as observed experimentally.[4,29] However, differences between theoretical and experimental numbers may arise to 20 kJ/mol. The N−H dissociation energies in phenoxazine, phenothiazine, and phenoselenazine are lower than, or at least equal, to those in vitamin E tocopherols.[35−38] In these molecules, a behavior distinct from that found in carbazole could be observed and also related to differences in the oxidation potentials of the conjugate bases of these compounds.[29] Since a significantly large difference is found between experimental and computed BDE in phenoxazine, its geometry has been reoptimized using a larger basis set, namely, the 6-311+G*

TABLE 6: N−H Homolytic BDEs, in kJ/mol, for Diphenylamine, Carbazole, Phenoxazine, and Derivatives and Also for Diphenylhydrazine

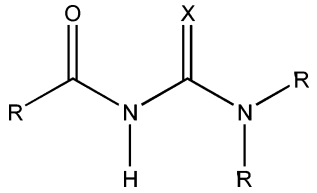
compound	calcd.	exp.
	355.0	364.8±6.3[a]; 366.1±4.2[b]; 359.0±2.9[c]; 365.7[d]; 379[e]
	377.8	388.3[b]; 398[e] 371.6[f]
	307.4	333.5[b]; 323.0±1.3[c]
	320.5	344.3[b]; 331.8±1.3[c] 328[e]
	327.2	336.4±1.7[c]
	333.1	290.0[g] 305.8[h]

[a] Reference 32. [b] Reference 29. [c] Reference 4. [d] Reference 25. [e] Reference 13. [f] Reference 79. [g] Reference 31. [h] Reference 80.

basis; now calculations include diffuse functions to determine if differences were due to an incorrect description of the phenoxazine structure. The new computed BDE differs from those reported in Table 6 by only 0.1 kJ/mol. Zhao et al. have estimated a significantly low N−H dissociation energy for diphenylhydrazine.[31] In fact, the computed N−H BDE value for diphenylhydrazine is close to the phenoselenazine N−H BDE and also to that found in tocopherols.[35−38] Its value is 331.1 kJ/mol, ∼7 kJ/mol lower than the calculated value for hydrazine, H_2NNH_2. This decrease in N−H BDE is due to the possibility of addition delocalization of the unpaired electron into the aromatic rings. However, this finding contrasts with the difference of ∼47 kJ/mol between the experimental values for these two species. These N−H BDEs, close to O−H BDE in tocopherols, explain the good polymerization inhibitor behavior of phenothiazines. Further, at the present moment, some phenoxazine, phenothiazine, and phenoselenazine derivatives are being used in photodynamic therapy.[73]

The BDEs of the N−H Bonds in *N*,*N*-Dialkyl-*N*′-acylurea and in *N*,*N*-Dialkyl-*N*′-acyl(aryl)thiourea Ligands. These compounds have found large interest since they are particularly prone to form coordination complexes with transition metals, TM. Thus, their use in liquid−liquid extraction, for example, of TMs in the mining industry is an important application of these compounds. A schematic representation of these molecules is depicted in Chart 2. These ligands are found to coordinate to TMs in a bidentate O,O or S,O manner, with simultaneous loss of the NH hydrogen atom. For this type of metal complexes,

CHART 2



metal−ligand BDEs were not known until very recently.[74] This lack of information was mainly due to the absence of N−H BDEs for these urea-based ligands. Therefore, these parameters were also estimated from accurate theoretical calculations, and the results herewith obtained are reported in Table 7. Computed results for a large series of thiourea derivatives range in the interval comprised between 337 and 348 kJ/mol. The N−H BDE increases slightly with the size of the alkyl substituent attached to the amino group. Computed values for the two considered urea derivatives are much larger, by almost 100 kJ/mol, than those computed for the thiourea compounds.

The BDEs of the N−H Bonds in Drug Analogues. In this subsection, N−H dissociation energies in a series of heterocyclic compounds common in drugs and other biologically relevant molecules are presented in Table 8, which includes aromatic and nonaromatic compounds and also a nonheterocyclic molecule. For example, pyrrolidine may be found in nicotine, and indole and piperidine may be found in drugs, etc. In Table 8, BDEs for NH and NH_2 groups present in some biologically important compounds are given in two different columns. A

TABLE 7: N−H Homolytic BDEs, in kJ/mol, for a Series of Alkyl and Acyl Urea and Thiourea Derivatives[a]

X	R	R′	computed value
O	phenyl	C_2H_5	435.7
O	phenyl	C_4H_9	434.2
S	phenyl	CH_3	346.2
S	phenyl	C_2H_5	336.8
S	phenyl	C_3H_7	336.8
S	phenyl	C_4H_9	336.6
S	phenyl	$^iC_4H_9$	336.8
S	furoyl	C_2H_5	346.4
S	furoyl	$^iC_4H_9$	347.9
S	$^iC_3H_7$	C_2H_5	343.1
S	$^iC_4H_9$	C_2H_5	341.4
S	$^tC_4H_9$	C_2H_5	340.4
S	$^tC_4H_9$	C_3H_7	344.4
S	$^tC_4H_9$	C_4H_9	345.9

[a] Three different classes of compounds were studied, acylalkylureas, acylalkylthioureas, and alkylthioureas, depending on the substituents R and R′ used and shown in Chart 2.

significantly large variation is shown in computed BDEs for this class of compounds, and differences are not easily attributed to a specific factor. In fact, for the heterocyclic and saturated molecules considered, namely, pyrazolidine, pyrrolidine, and piperidine, the N−H BDE changes between 301.7 and 392.6 kJ/mol. For the other compounds listed in this table, the computed values range also in a large interval, from 372 to 500 kJ/mol. Aromaticity plays an important role in the computed N−H BDEs as may be concluded by the increase in the N−H BDE, of about 30 kJ/mol, when going from pyrrolidine to pyrrole. In fact, the presence of π electrons in the ring increases the energy required for homolytic N−H bond scission. However, for seratonine, the N−H BDE is lower than the computed number in piperidine, and this seems to be due to the presence of a hydroxyl substituent in the benzene ring. This is supported by the observed decrease in the N−H BDE calculated for aniline substituted by one OH group at any position but especially in *p*-hydroxyaniline. Also of interest, the presence of a second nitrogen atom in the imidazole ring, when compared with that for pyrrole, also causes an increase in the N−H BDE. However, this increase is less important than the one reported above when going from pyrrolidine to pyrrole. The computed N−H BDE in compounds containing only a five-membered ring reaches its maximum value for pyrazole. The computed N−H BDE in this compound is 499.5 kJ/mol, almost 100 kJ/mol higher than the computed number for imidazole, which differ from pyrazole by the position of the nitrogen atoms in the five-membered ring. In pyrazole, the two N atoms are adjacently connected, while in imidazole, there is one carbon atom between the two nitrogens. Thus, this significative increase in the N−H BDE is due to a strong interaction between the two adjacent N atoms in the case of pyrazole. The influence of π electrons in the N−H BDE is so important that a strong decrease in N−H BDEs is found when going from pyrazole to pyrazoline (one double bond is saturated) and to pyrazolidine (two double bonds are saturated) molecules. For these two species, the calculated N−H BDEs are even lower than those reported for pyrrolidine and seratonine. If one compares imidazole and purine directly, it is also shown that the additional six-membered ring in purine increases the N−H BDE by almost 80 kJ/mol. Finally, the computed value for indole is in good agreement with the experimental N−H BDE obtained by Bordwell et al.[28]

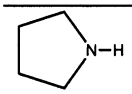
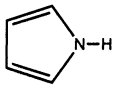
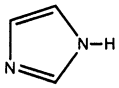
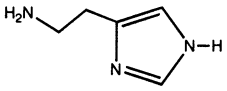
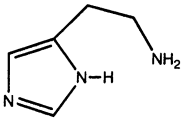
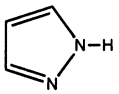
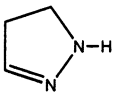
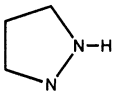
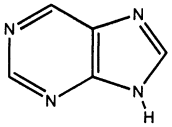
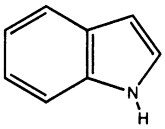
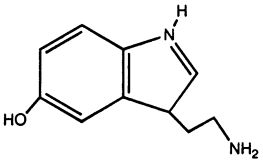
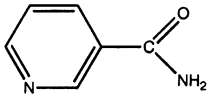
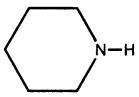
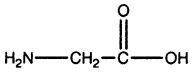
Turning our attention for the N−H bonds in the NH_2 group, it is noticed for compounds containing both NH and NH_2 groups that N−H bond scission always occurs with a lower energetic cost for the NH_2 group. For the molecules containing one NH_2 group, the largest value is found for nicotinic acid, N−H BDE is 463.0 kJ/mol, which is ∼30 kJ/mol larger than that computed for benzamidine (see Table 2). For glycine, the calculated N−H BDE is close to that reported in Table 1 for RNH_2 compounds.

Finally, for the compounds presented in this subsection, the computed BDEs vary in a large interval, ranging from values lower than those reported above for phenoxazine and phenothiazine, ∼300 kJ/mol in the case of pyrazolidine, to the largest computed N−H BDE, ∼500 kJ/mol, in the case of purine, which shows that simple chemical modifications may change the antioxidant activity drastically.

Solvation Effects in the BDEs of the N−H Bonds. Whereas some of the compounds studied in the present work have therapeutical properties and are of current use as drugs, others have just the opposite role and act as poisons on living organisms. For example, carbazole derivatives are known to intercalate in the DNA structure, leading to cell destruction. In the previous subsection, computed BDEs were reported for gas-phase conditions and it is expected that these values suffer variation in different environments such as those in living organisms. So, it would be interesting to know what happens to these dissociation energies in the presence of a solvent, namely, the major constituent of these organisms, water. The N−H BDE in methylamine and aniline was computed considering the solvent effects of heptane, DMSO or water, and two different computational strategies. These are the CPCM models of Barone and Cossi[57] and also the IEFPCM model of Tomasi et al.[58] These two computational strategies were found to yield practically the same N−H BDEs for these two compounds and required almost the same computer time. Therefore, we have chosen only one of these approaches, namely, the polarizable conductor calculation model, CPCM, from Barone and Cossi, mainly due to better SCF convergence. In the determination of solvent effects in the computed N−H BDEs, two approaches were considered, one in which the energy and geometry of both the neutral and of the radical was computed at the CPCM:(RO)-B3LYP/6-311+G(2d,2p)//(U)B3LYP/6-31G(d) level of theory and, in another approximation, one where only the energy of both the neutral and radical was computed using the CPCM model at the frozen gas-phase-optimized geometries. In the last case, corrections to $T = 298.15$ K were taken from frequencies computed in the gas phase. These two approaches were tested for methylamine, aniline, and imidazole, and it was found that the N−H BDEs of the solvated species computed using the simplest approach are negligibly corrected by full optimization within the CPCM model, cf. values given in parentheses. For these species, N−H BDEs differ by less than 2 kJ/mol. Therefore, to save some computer time, the N−H BDEs of the other compounds listed in Table 9 were obtained by calculation of the energy using the CPCM model at the geometry optimized in the gas phase. Thermal corrections were introduced considering the frequencies previously calculated in a vacuum.

The validity of the CPCM approach and of the use of frozen geometry was tested for phenol's O−H BDE. This is mainly due to the existence of several experimental works concerning the determination of O−H BDE in phenol either in the gas phase or in solution. The calculated gas phase O−H BDE is 366.6 kJ/mol, while experimental results lie in the 361.4 ± 8.5 to 375.0 ± 2.9 kJ/mol interval.[75] The recommended value in the review of Santos and Simões is 371.3 ± 2.3 kJ/mol,[75] while in a previous work, Wayner et al.[76] estimated 364 kJ/mol as the best value for the O−H BDE in phenol. The computed O−H BDEs in solution are 370.8 kJ/mol in heptane, 372.8 kJ/mol in DMSO, and 384.2 kJ/mol in water. These results may be compared with

TABLE 8: N−H Homolytic BDEs, in kJ/mol, for Some Drug Analogues[a]

		N-H	NH_2
	Pyrrolidine	371.2	
	Pyrrole	401.6	
	Imidazole	407.0	
	Histamine	395.0	410.9
	Histamine (tautomer)	401.9	413.3
	Pyrazole	495.5	
	Pyrazoline	364.1	
	Pyrazolidine	301.7	
	Purine	499.6	
	Indole	386.9	
	Seratonine	372.1	410.2
	Nicotinic acid		463.0
	Piperidine	392.6	
	Glycine		418.2

[a] The experimental value for indole is 392.5 kJ/mol, taken from ref 28.

TABLE 9: Solvent Effects in Computed N−H BDEs for Some Drug Analogues[a]

	gas phase	heptane	DMSO	water
CH_3NH_2	413.2	416.0 (416.0)	416.4 (416.4)	414.7 (414.5)
$PhNH_2$	385.8	389.8 (390.2)	392.2 (392.9)	395.5 (397.6)
imidazole	407.0	414.0 (413.5)	420.4 (419.5)	422.8 (423.4)
pyrrolidine	371.2	378.6	378.6	380.3
pyrrole	401.6	404.4	404.8	400.1
pyrazole	495.5	499.0	497.8	501.1
pyrazoline	364.1	366.6	365.9	370.7
pyrazolidine	301.7	303.1	302.3	306.2
indole	386.9	390.0	390.7	386.4
seratonine	372.1/410.2	374.9/413.0	375.0/413.2	372.7/410.1
nicotinic acid	463.0	470.7	477.6	481.6
piperidine	392.6	395.1	395.2	396.1

[a] In parentheses is given the N−H BDEs computed by full optimization within the SCRF model. The calculated enthalpy of solvation of the hydrogen atom is 4.0 kJ/mol in heptane, 6.1 kJ/mol in DMSO, and 6.2 kJ/mol in water.

the experimental results available for isooctane, 369.0 kJ/mol; DMSO, 378.1 kJ/mol; benzene, 373.6, 378.7, or 380.3 kJ/mol; and acetonitrile, 388, 397.5, or 402.3 kJ/mol.[75−77] From these results, it is clearly concluded that the effect of solvent in the O−H BDE is also not known from experimental studies and clearly it is not easy to conclude if the theoretical approach is capable to simulate the solvent. Thus, this range of experimental O−H BDEs may be used to qualitatively test the methods. If a comparison of theoretical and experimental values available for a solvent with a similar ϵ_0 is made, it is possible to conclude that the approach used is capable to describe qualitatively the effect of the solvent. The computed O−H BDE in heptane is not far from the experimental results obtained in benzene or isooctane. Some other methods may be applied to extract the solvation effect on the N−H BDE such as those recently used by Guedes and co-workers.[77] Elegantly, these authors used both microsolvation and Monte Carlo calculations to calculate the O−H BDE of phenol in benzene and acetonitrile. In that work, differences between calculated and experimental O−H BDEs are similar to the ones obtained by using the CPCM model to describe solvent effects.

The most striking feature from the results reported in Table 9 is that in some cases the N−H BDE increases due to the inclusion of solvent effects while for other compounds an influence in the opposite direction is noticed. As expected, the N−H BDE computed in nonpolar heptane solvent is closest to the computed value in a vacuum and differences increase with the polarity of the solvent considered except in some special cases where differences are larger when the DMSO solvent is considered. This atypical trend is found for pyrazole and similar compounds. The maximum influence of the solvent in the computed N−H BDE is found for nicotinic acid, in which the consideration of water as the solvent increases the N−H BDE by ∼19 kJ/mol. This is certainly caused by the presence of a C═O bond near the amino group. The N−H BDE in aniline is rather affected by the presence of solvent, the gas-phase value is 4.0, 6.4, and 9.7 kJ/mol lower than the calculated N−H BDE in heptane, DMSO, and water, respectively. Therefore, differences of more than 10 kJ/mol found in the literature, cf. Table 5, obtained using different experimental techniques are not only due to solvent effects. In terms of antioxidant activity, the most interesting substituted aniline is *o*-hydroxyaniline. Interestingly enough, in this case the N−H BDE is not affected by the polarity of the solvent and the computed numbers are 379.9 kJ/mol in heptane, 379.5 kJ/mol in DMSO, and 379.9 kJ/mol in water. Thus, for the compounds reported in this section, due to the different variation of N−H BDE with the polarity of solvent, it seems that the number and type of atoms placed in the vicinity of the N−H bond may have a particular influence on the BDE and caution must be taken when corrections are introduced.

Conclusions

The N−H BDEs for a large variety of N−H bond containing compounds of great interest to biochemistry, to environmental chemistry, to inorganic, and organic chemistry are reported. The DFT-based B3LYP hybrid method has been applied, and several different basis sets were used. The N−H BDE in RNH_2 compounds is of about 410−415 kJ/mol except in the case of ammonia, for which a somewhat larger energy was computed, 448−450 kJ/mol depending on the approach used. For the dialkylamines, R_2NH with R = CH_3, C_2H_5, and C_3H_7, the N−H BDE is lowered to 387−391 kJ/mol. The energy required for N−H homolytic dissociation in the case of R═NH compounds varies in a large interval when compared with computed N−H BDEs in alkylamines and dialkylamines, which are RNH_2-type molecules. In imines, the N−H BDE is ∼370 kJ/mol for the smallest imine, methanimine, and increases with the size of the R group of the imine. The computed value for the R═NH bond in benzamidine is 404.4 kJ/mol. The variation in the N−H BDE is even more dramatic in the case of small species containing one N−H bond, and the lowest computed value in the present work occurs for HNO. The effect of the substituent in the aromatic ring of substituted benzamides and anilines was also studied in the present work. The effects due to the presence of electron-donating or electron-withdrawing groups vary largely with the position considered, i.e., ortho, meta, and para. Both in substituted benzamides and substituted anilines, electron donors destabilize the parent-substituted molecules, and hence, there is a decrease in the N−H BDE when compared with the computed values for benzamide or aniline. Electron-withdrawing groups stabilize the neutral-substituted molecules and therefore, the N−H BDE increases with respect to benzamide and aniline. For substituted benzamides, the N−H BDE ranges from 450 to 477 kJ/mol, while for substituted anilines, a large interval was obtained, ranging from 349 to 415 kJ/mol. Interestingly, it is shown that for some substituents, the ortho-substituted anilines are expected to be more efficient antioxidants than the corresponding meta or para isomers. Further, DFT-computed N−H BDEs for anilines are not consistently lower than experimental results as found previously in the case of phenols and substituted phenols. In the present study, the effect due to the presence of R═O, R═S, and R═Se bonds or R−O−R, R−S−R, and R−Se−R in some species was also analyzed. It was observed that for acetamide and similar S- or Se-substituted molecules and, for urea and similar S- or Se-substituted molecules, the N−H BDE decreases from oxygen to selenium, while for phenoxazine derivatives, the N−H BDE increases. In the former cases, the computed N−H BDEs range from 467.0 kJ/mol for acetamide to 377.6 kJ/mol calculated for selenamide. For the phenoxazine derivatives (O, S, or Se) and for diphenylhydrazine, the computed N−H BDE values are close to those found in tocopherols. Thus, this class of compounds may find important applications as antioxidants. The N−H BDEs in an important class of ligands, with important applications as transition metals complexing agents, were also determined. It was found that for the urea derivatives, the N−H BDE is almost 100 kJ/mol larger than that in thiourea derivatives. A small variation is found between reported numbers for urea and for the alkylbenzoylthiourea (alkyl = ethyl or *n*-butyl), N−H BDEs are 449.8 and ∼435 kJ/mol, respectively, while a significant difference is noticed between thiourea and the alkylacylthioureas considered, N−H

BDEs are 402.5 and ∼340 kJ/mol, respectively. Finally, the N−H BDEs in some biologically relevant molecules were also computed. The computed values are varying between 300 kJ/mol, computed for pyrazolidine, and 500 kJ/mol, computed for purine.

Solvent effects in computed N−H BDEs were also considered in the present work. To account for these effects, the polarizable continuum model was taken into account and the solvent effects of heptane, DMSO, or water were introduced by specification of their dielectric constants. The computed N−H BDEs in solution for some of the compounds considered in the gas phase show that significant variations occur and that these depend largely on the compound considered. The computed variation of N−H BDE with solvent is not easily understood in terms of dipolar moments of the molecules considered. In fact, the computed N−H BDE of the polar *o*-hydroxyaniline molecule is found to be almost the same in any of the three solvents referred to above. This is an extremely important conclusion from the present work. Further, corrections in N−H BDEs are not easily predicted since these effects vary randomly.

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