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CHAPTER 12

CALCULATION OF PROTON AFFINITY, GAS-PHASE BASICITY, AND ENTHALPY OF DEPROTONATION OF POLYFUNCTIONAL COMPOUNDS BASED ON HIGH LEVEL DENSITY FUNCTIONAL THEORY

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12.1 INTRODUCTION

Protonation [Eq. (1)] and deprotonation [Eq. (2)] processes of poly-functional polar molecules play very crucial role in organic chemistry,

biochemistry, medicine, and pharmacy and are the first steps in many fundamental chemical rearrangements studies [1, 2].



where B and AH are the base and the acid, respectively. The capability of an atom or molecule in the gas phase to accept a proton can be characterized by calculating, from the above reaction, the proton affinity (PA), the molecular basicity in the gas phase basicity (GB), and the enthalpy of deprotonation, (ΔH_{dep}).

Using standard conditions, the PA is defined as the negative of the enthalpy change, ΔH , for the gas phase reaction (Eq. (1)) and the GB is defined as the negative of the free energy change, $\Delta_{base} G$, associated with the same reaction in (Eq. (1)), whereas the enthalpy of deprotonation is the energy associated with the deprotonation energy (Eq. (2)). The PA and GB quantities are site-specific values and therefore must be calculated at each chemically different binding site in the molecule. This means that some molecules will have multiple PAs and/or multiple GB values. Protonation and deprotonation give a deep understanding of the correlations between molecular structures, molecular stability, reactivity, prediction of the preferred site for nucleophilic and electrophilic attachment in the organic compounds, reaction mechanisms occurring in several biological systems and of the organic molecules [3], and the possible role played by the protonation processes in decreasing the activation barrier for the 1,3-hydrogen transfer process [4–7]. In addition, PA can be applied to different aspects such as determination of the stability of cationic species [8, 9], the hydrogen bonding ability, acidity of solid catalysts [10], and relation between PA and pKa [11, 12].

Recent years have witnessed a great progress in experimental and theoretical investigations of the protonation of polyfunctional compounds [3, 13–16]. Unfortunately, measuring of the proton affinities of polar polyfunctional molecules, an attribute common to most biologically interesting molecules, is an experimental challenge. It was pointed out that direct measurements of the PA are not easy, and are possible for only a few mol-

ecules, mainly olefins and carbonyl. The basis for this scale is described by Hunter and Lias [17]. On the other hand, based on the phenomenal growth in computational power in recent years, much attention has been given to the possibility of calculating these parameters by quantum methods. Ab initio approaches are very successful in providing reliable values of PA and GB for small molecules even at lower levels of theory [18, 19]. In the last two decades, the progress in the density functional theory (DFT) approaches makes this method another candidate for reliable calculation of proton affinities. It has been shown that the PA values computed using the B3LYP method are as effective as high level ab initio results, and the results were comparable up to ~1–2 kcal/mol in comparison with the measured values [20–29]. In addition to the direct calculation of the proton affinity and gas phase basicity, several descriptors were used to predict the proton affinity and gas phase basicities such as the molecular electrostatic potential (MEP) on the nuclei of the basic centers and the valence natural atomic orbital energies (NAO) of the basic centers [28, 30]. Yuang et al. [28] suggested that the more negative the MEP value, the stronger is the molecular basicity, and the larger is the proton affinity and gas phase basicity. They also proposed that for systems with multiple sites of the same basic element type, the most basic site (largest energy decrease) has the most negative MEP value.

Additionally, the ^1H NMR chemical shift ($\delta^1\text{H}$) of the incoming proton [31] and the topological properties at the bond critical point (BCP) of the B-H $^+$ bond (including electron density, ρ_{BCP} , and its Laplacian, $\nabla^2\rho$) calculated by means of the Bader theory of atoms in molecules [32]. Strong linear correlations were found between these descriptors and the values of PA or GB in the gas phase. These results suggested that these quantum descriptors (MEP, NAO, $\delta^1\text{H}$, and ρ_{BCP}) can be easily used to approximately estimate the PAs or GBs in the gas phase.

Understanding of the influence of the substituents on proton affinities and gas phase basicities has been studied experimentally and theoretically (see Ref. [22] and Refs. therein). Extensive works have been conducted to study the presence of the substituent on the aromatic ring, not necessarily a phenyl ring [33–35]. Kukol et al. [33] summarized the effect of the *ortho*-, *meta*-, and *para*-substituents on aromatic carbonyl compounds on the proton affinity and gas phase basicity. Substituent effects were subdi-

vided into polar and steric effects. In general, polar effects were rather in terms of strong resonance interaction with electron donating/withdrawing characteristic of the substituent.

A lot of heterocycles have many acidic and basic centers in their structures; therefore, the study of the protonation and deprotonation of these systems will be a subject of interest, particularly, for the biologically important heterocycles. This chapter deals mainly to test the validity of the DFT method to calculate the intrinsic properties of polyfunctional compounds. This aim is achieved by firstly, calculating the proton affinity, gas phase basicity, and the enthalpy of deprotonation of some polyfunctional compounds in gas phase and in solution; secondly, comparing our calculated results with the available experimental data; and finally, studying the influence of the substituent effect on the PA and GB of the compounds under probe proton affinities. The selected compounds are hydantoin, isorhodanine, rhodanine and their thio derivatives, and benzamide and its m- and p- derivatives. All calculations were performed using the famous DFT at the B3LYP and BP86 6–311++G(2df,2p)//6–311+G(d,p) level of theory in the gas phase and in solution (water). Another important aspects that will be presented in this chapter is calculation of some quantum descriptors, namely, molecular electrostatic potential (MEP) on the nuclei of the base, natural atomic orbital energy (NAO) of the base, proton ^1H NMR chemical shifts ($\delta^1\text{H}$) of the incoming proton, and the electron density at the O-H $^+$ bond critical point (ρ_{bcp}) and examine the possibility of using them to estimate/predict the intrinsic basicity of the polyfunctional compounds. The systems under consideration are hydantoin and its thio derivatives; mono and di-substituted hydantoin derivatives; and rhodamine, isorhodanine, and benzamide and their derivatives.

12.2 COMPUTATIONAL DETAILS

The standard hybrid DFT in the framework of B3LYP [36, 37] functional at the 6–311+G(d,p) [38, 39] basis function was used for geometry optimization. The harmonic vibrational frequencies of the different stationary points of the potential energy surface (PES) were calculated at the same level of theory that was used to check that all the structures are minima

with no imaginary frequencies as well as to estimate the corresponding zero point energy corrections (ZPE) that were scaled by the empirical factor 0.9806 proposed by Scott and Radom [40]. In order to obtain more reliable energies for the local minima, final energies were evaluated by using the same functional combined with the 6-311++G(2d,2p) basis set. It has been shown that this approach is well suited for the study of this kind of systems, yielding PAs, GBs, and ΔH_{dep} in good agreement with the experimental values. A single point calculation was used to compute the molecular electrostatic potential (MEP) on each of the nuclei followed by a full natural bonding orbital (NBO) calculations [41] to obtain the natural atomic orbital energies. The molecular electrostatic potential (MEP) of a molecule is a real physical property, and it can be determined experimentally by X-ray diffraction techniques [42]. The MEP on the nuclei of a molecule is originally invoked to study electrophilic reactivity. $V(\vec{r})$ (MEP) that is created at a point \vec{r} by electrons and nuclei of a molecule is given as (Eq. (3)):

$$MEP = V(\vec{r}) = \sum_A \frac{Z_A}{|R_A - \vec{r}|} - \int \frac{\rho(\vec{r}')}{|\vec{r}' - \vec{r}|} d\vec{r}' \quad (3)$$

where Z_A is the charge on nucleus A, located at R_A , and $\rho(\vec{r})$ is the molecule's electron density [43].

In order to compute the ^1H NMR absolute shielding constants ($\delta^1\text{H}$ values) of the associated proton, another single point calculation at the B3LYP/6-311+G(d,p) level with the gauge-independent atomic orbital (GIAO) method [44] was performed. Furthermore, the calculated chemical shielding was converted into chemical shift by subtracting 32.5976, the ^1H shielding of tetramethylsilane computed at the same level of theory and basis set.

Analysis of the electron densities at bond critical points (bcps) of the optimized structures was performed by generating the wave functions through a single point calculation on the geometrized structures and analyzing these wave functions by means of the atoms-in-molecules (AIM) theory proposed by Bader et al. [32] as implemented in AIM2000 program package [45]. We have additionally carried out calculations in solution using the integral equation formalism polarizable continuum model

(IEF-PCM) in which the solvent is represented by an infinite dielectric medium at the same level of theory. All calculations were performed with the Gaussian 09 program [46] with tight self-consistent field convergence, and in addition, ultrafine integration grids were used for MEP calculations.

The gas phase PA of a molecule B was estimated from the reaction involving the addition of a proton to the neutral species (protonation reaction) (Eq. (1)); the equation for the PA is written as (Eq. (4)):

$$PA = -\Delta H^{298} = H^{298}(BH^+_{(g)}) - \left[H^{298}(B_{(g)}) + H^{298}(H^+_{(g)}) \right], \quad (4)$$

where $H^{298}(BH^+_{(g)})$ is the sum of electronic and thermal enthalpies for the protonated species and $H^{298}(B_{(g)})$ is the sum of the electronic and thermal enthalpies for the neutral species under investigation. Under the standard state conditions, the values of the enthalpy and entropy of the gas-phase proton are $\Delta_g^0 H(H^+) = 2.5RT = 1.48 \text{ kcal/mol}$. This value corresponds to the translational proton energy (a loss of three degrees of freedom is $3/2(RT)$ plus the PV work-term ($=RT$ for ideal gas)).

Thermodynamically, GB is related to PA and the change of entropy ΔS at constant temperature (298.15 K) by (Eq. (5)):

$$GB = PA - T\Delta S \quad (5)$$

For proton, only the translational entropy $S_{translational}(H^+)$ is not equal to zero and is determined to be 26.04 cal/mol and the value of Gibbs free energy of the gas has been used as shown in (Eq. (6)) [47–49].

$$\Delta_g^0 G(H^+) = \frac{5}{2}RT - T\Delta S^0 = 1.48 - 7.76 = -6.28 \text{ kcal/mol} \quad (6)$$

To calculate the proton affinity and molecular basicities in the solvent (water in our case), the reaction to be considered is identical to one used in the gas phase (Eq. (1)), except that all constituents are solvated. PCM thermodynamic results, obtained from the harmonic frequency analysis, were used to evaluate the PA value according to the following equation (Eq. (7)):

$$PA = -\Delta_{prot}H^{298} = -[H^{298}(BH_{solv}^+) - H^{298}(B_{solv}) - H^{298}(H_{solv}^+)] \quad (7)$$

In this case, the proton enthalpy is determined from summing the solvation enthalpy of the proton $\Delta_{solv}H^{298}(H^+) = -275.12$ kcal/mol [50], which is very close to the experimental value (-275.14 kcal/mol)[51], with proton gas-phase enthalpy $H^{298}(H^+(g)) = 1.48$ kcal/mol. In order to calculate the molecular basicity in solution, Eq (the constant $pK_b(B)$) for a base B is given by the well-known thermodynamic relation (Eq. (8)):

$$pK_b(B) = \frac{\Delta_{prot}G(solv)}{2.303RT} \quad (8)$$

where R , T , and $\Delta_{prot}G(solv)$ (1 atm, standard state) are the gas phase constant, the temperature (298.15 K), and the standard free enthalpy of base protonation reaction in solution, respectively. $\Delta_{prot}G(solv)$ is determined from the following equation (Eq. (9)):

$$\Delta_{prot}G^{298}(solv) = G^{298}(BH_+(solv)) - G^{298}(B(solv)) - G^{298}(H^+(solv)) \quad (9)$$

In water, the aqueous free enthalpy $G^{298}(H^+(aq))$ is determined by summing $\Delta_{aq}G^{298}(H^+) = -266.13$ kcal/mol[51, 52] and $G^{298}(H^+(g)) = -6.3$ kcal/mol [53].

To calculate the deprotonation enthalpy (DPE, ΔH^{298}) for removing H^+ according to the deprotonation reaction (Eq. (2)), we follow (Eq. (10)):

$$\Delta H_{DPE}^{298} = H^{298}(AH_{(g)}) - [H^{298}(A_{(g)}^-) - H^{298}(H_{(g)}^+)] \quad (10)$$

where $H^{298}(AH_{(g)})$ is the sum of electronic and thermal enthalpies for the isolated molecules under probe, $H^{298}(A_{(g)}^-)$ is the sum of the electronic and thermal enthalpies for the anion species for the corresponding molecules, and $H^{298}(H_{(g)}^+)$ is the translational energy term for the H^+ (i.e., the thermal correction term), whose value is 0.889 kcal/mol.

12.3 RESULTS AND DISCUSSION

12.3.1 HYDANTOIN AND ITS THIO DERIVATIVES

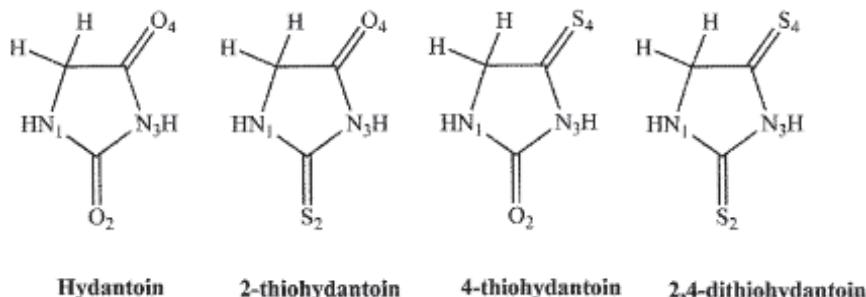
12.3.1.1 Proton Affinity of Hydantoin and its Thio Derivatives

To our knowledge, there is no experimental data related to the proton affinity of hydantoin. The available data are from the study of Silva et al. [54] and Bouchoux [55, 56] who used the G3MP2B3 and G4MP2 level of theory, respectively. In Table 12.1, we list the DFT B3LYP results of PAs of hydantoin and its thio derivatives (Scheme 1), together with the avail-

TABLE 12.1 Proton Affinities of Different Basic Sites of Hydantoin Calculated Using Different Theoretical Methods

Species	Method	O2(S2)	O4(S4)	N1	N2
Hydantoin	B3LYP*	197.8	193.7	186.1	175.9
	G3MP2B3 ^a	196.5	192.1	185.7	175.7
	G4MP2 ^b	198.0	198.0		
2-thiohydantoin	B3LYP*	205.9	192.9	186.2	174.5
	G3MP2B3 ^a	203.3	191.9	186.4	175.8
4-thiohydantoin	B3LYP*	197.8	202.3	187.2	176.4
2,4-dithiohydantoin	B3LYP*	206.0	202.0	186.2	174.5

^aValues taken from Ref [54]; ^bValues taken from Ref[55]; *Results of this work



SCHEME 1 Schematic representation of hydantoin and its thio derivatives.

able theoretical results [54–56]. Results revealed that the calculated PAs using the B3LYP method are in good agreement with those of G3MP2B3 and G4MP2. An excellent linear relationship was observed between the B3LYP and G3MP2B3 results (see Figure 12.1).

The reported results show a very strong linear relationship with correlation coefficients $R^2 = 0.999$, reflecting the validity and effectiveness of the DFT B3LYP method in calculating the intrinsic basicity of the polyfunctional molecules. It is worth mentioning that DFT methods consume much lower computation time than the ab initio method. Analysis of Table 12.1 indicates that thiohydantoin derivatives are more basic than the hydantoin one and the sulfur atom at position 2 (S2), which is located between two amidic groups, is more basic than the one at position 4 (S4). The PA trend of the heteroatoms in hydantoin and its thio derivatives can be arranged from highest to lowest basicity as follows: S2 > S4 > O2 > O4 > N1 > N4. These results agree with those reported for analogue systems [3, 13].

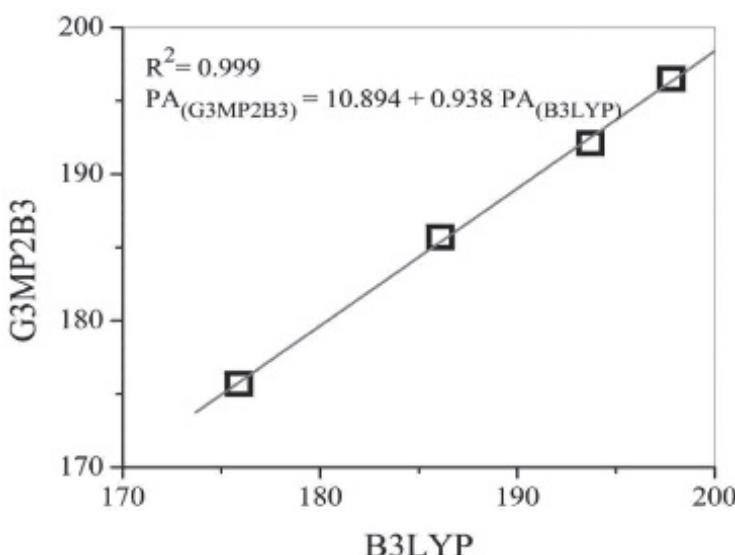
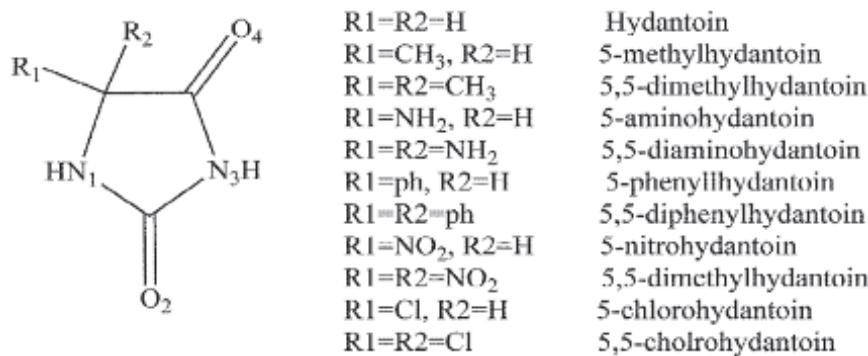


FIGURE 12.1 Linear relationship between the proton affinity calculated using B3LYP and the PAs calculated using the G3MP2B3 method of the basic centers of the hydantoin molecule. All values are in kcal/mol.

12.3.1.2 Substituent Effect on the Proton Affinity of Hydantoin

This subsection focuses on studying the influence of the mono- and di-substituent(s) on the proton affinity of hydantoin molecules. The species under probe are shown in Scheme 2. The results of this study are presented in Table 12.2. As can be observed in the table, ongoing from electron with drawing substituents to electron donating ones, the proton affinity of



SCHEME 2 Schematic representation of mono and di-substituted hydantoins.

TABLE 12.2 Proton Affinities (kcal/mol) of Mono- and Di-Substituted Hydantoin Calculated Using B3LYP Method

Species	O2	O4
5-phenylhydantoin	200.5	199.8
5,5-diphenylhydantoin	206.2	203.8
5-amino hydantoin	197.7	197.3
5,5-diamino hydantoin	202.7	201.3
5-methylhydantoin	183.8	179.3
5,5-dimethylhydantoin	201.0	196.1
Hydantoin	197.8	193.7
5-chlorohydantoin	188.4	186.5
5,5-dichlorohydantoin	184.6	183.9
5-nitrohydantoin	182.9	183.9
5,5-dinitrohydantoin	173.5	177.6

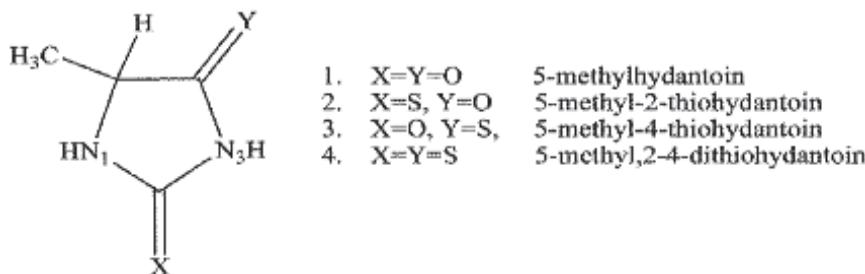
hydantoin is increased. For example, the proton affinity of 5-aminohydantoin (197.7 kcal/mol) is higher than that of 5-nitrohydantoin (182.9 kcal/mol).

It is also obvious that proton affinities of the 5,5-di-substituted species are larger than those of the 5-monosubstituted ones. For example, the proton affinity of 5,5-diaminohydantoin is ~5 kcal/mol higher than that of 5-aminohydantoin. In contrast, the proton affinity of 5,5-dinitrohydantoin is found to be ~9.5 kcal/mol lower than that 5-nitrohydantoin. This finding indicates that the presence of two electron withdrawing groups largely decreases the intrinsic basicity of the basic center, whereas the reverse is true in the case of the electron donating groups.

12.3.1.3 5-Methylhydantoin and Its Thio Derivatives

In this part, we introduce the results obtained by Safi and Frenking [24] for 5-methylhydantoin and its thio derivatives shown in Scheme 3. The PAs were obtained by using the two level of theory, B3LYP and BP68, with 6-311+G(2fd,2p)//6-311+G(d,p) basis set.

Table 12.3 shows that the agreement between both two levels of theory is satisfactory. Our results in **Table 12.3** deduced that the atom with the most intrinsic basic character is the heteroatoms of the carbonyl and/or thiocarbonyl group attached to position 2 and/or 4. The intrinsic basicity of these ranges between 193 and 205 kcal/mol. These results led us to conclude that the four hydantoin systems are bases with moderate strength in the gas phase. In addition, it was found that the strongest base among



SCHEME 3 5-methylhydantoin and its thio derivatives.

TABLE 12.3 Calculated Gas Phase Proton Affinities of 5-Methylhydantoin and Its Thio Derivatives at B3LYP/6–311+G(3df,2p)//B3LYP/6–311+G(d,p) and BP686–311+G(3df,2p)//B3LYP/6–311+G(d,p) Levels of Theory

		N1	O2	N3	O4	S2	S4
1	B3LYP	187	197	175	193	--	--
	BP68	188	197	--	193	--	--
2	B3LYP	186	--	177	192	204	--
	BP68	188	--	176	193	204	--
3	B3LYP	187	197	174	--	--	200
	BP68	188	197	176	--	--	201
4	B3LYP	188	--	--	--	205	200
	BP68	189	--	--	--	204	200

Results are taken from Ref. 24.

the four is compound **4**, but the basicity gap is small when compared with the other molecules.

The PA values in Table 12.3 indicate that the basicities of the lone pairs at O4 and S4 are lower than that of the lone pairs of O2 and S2 by 4 and 5 kcal/mol, respectively. These results are in agreement with those obtained for the analogue systems, namely uracil [27], thiouracil derivatives [57], triazepinethio derivatives [58], and aliphatic amides [59]. Furthermore, the difference between the PAs of the heteroatoms of the carbonyl and thiocarbonyl groups and the two nitrogen atoms, N1 and N3, is quite substantial and ranges between 10 to 20 kcal/mol. This is in agreement with ab initio calculations, which showed that amides derived from weak acids protonate preferentially at the acid residue rather than at the nitrogen with energy differences between 10 and 30 kcal/mol [27, 60]. In summary, for 5-methylhydantoin and its thio derivatives, the most basic site is always sulfur atom at position 2, which leads us to classify the order of basicity sites in these molecules as follows: S2 > S4 > O2 > O4 > N1 > N3. To compare the accuracy of the DFT results with highly accurate coupled cluster calculations, the proton affinities of water and hydrogen sulfide were calculated. Table 12.4 summarizes the results at B3LYP/6–311+(2df,2f), B3LYP/6–311+(d,f), CCSD(T)/6–311+(2df,2f), and CCSD(T)/6–311+(d,f), together with experimental data [61]. The data show that the B3LYP results deviate only slightly from the CCSD(T) val-

TABLE 12.4 Proton Affinity Values (kcal/mol) of H₂O and H₂S Obtained at DFT and CCSD(T) Levels of Theory, with Experimental Values Given for Calibration

Species	DFT ^a	CCSD(T) ^b	Expt ^c
H ₂ O	164.2	164.9	165.2
H ₂ S	169.8	169.7	168.5

^a Calculated at B3LYP/6–311+G(2df,2p)// B3LYP/6–311+G(d,p) level of theory.

^b Calculated at CCSD(T)/6–311+G(2df,2p)// B3LYP/6–311+G(d,p).

^c Data taken from Ref. [61].

ues, which in turn agree very well with the experimental findings. The results suggest that our DFT values for the heterocyclic compounds should be highly accurate.

Table 12.5 displays the calculated acidities for neutral 5-methylhydantoin and its thio derivatives (Scheme 3) together with their radical cations. The deprotonation energies were obtained using two levels of theory, B3LYP and BP86, with 6–31G(d), 6–311G(d,p) and B3LYP/6–311+G(2df,2p) basis functions. For sake of comparison, we included the acidity of the protonated molecule obtained at the same basis sets. As it is found in literature [62–64], data reported in Table 12.5 indicate that

TABLE 12.5 Calculated 298 K Deprotonation Energies, ΔH²⁹⁸, of the 5-Methylhydantoin and Its Thio Derivatives (Scheme 3)

Species*	Method	Neutral		Radical	
		N1	N3	N1	N3
1	B3LYP ^a	356	351	201	196
	B3LYP ^b	348	343	199	193
2	B3LYP ^a	341	341	216	214
	B3LYP ^b	338	337	221	219
3	B3LYP ^a	346	335	220	214
	B3LYP ^b	341	336	220	217
4	B3LYP ^a	334	334	218	217
	B3LYP ^b	333	332	226	222

^aB3LYP/6–311G(d,p).

^bB3LYP/6–311+G(2df,2p)//6–311G(d,p).

All values are in kcal/mol.

ΔH²⁹⁸ = ΔE_{elec} + ΔZPVE + Δ(H²⁹⁸–H⁰) + 6.2 kJ; scaled ZPVE by 0.9806 empirical factor.

Results are taken from Ref. 23.

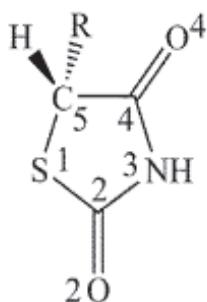
the most acidic site of 5-methylhydantoin and its thio derivatives is the N3-H group. For hydantoins, the imide proton N3-H is more acidic than N1-H, and hence, this position is more reactive toward electrophiles. It is noted that there is an inverse relationship between the magnitude of ΔH^{298} and the strength of the acid. The larger the value of ΔH^{298} , the weaker is the acid. The first conspicuous fact is that the agreement between both two levels of theory is satisfactory, and the energy gap between the two levels is 2–3 kcal/mol. Another conspicuous fact is that the acidity values obtained from the 6–31G(d) and 6–311G(d,p) basis are more than ~10 and 8 kcal/mol, respectively, which are higher than those obtained using 6–311+G(2fd,2p)//6–311+G(d,p) basis functions, in agreement with those results reported for uracil [65]. These findings show that diffuse functions are required to lower computed deprotonation energies of anions [66].

For compounds 1 and 3, it is found that the acidity difference between N3 and N1 atoms is quite substantial and amounts to about 5.0 kcal/mol in favor of the former. For compounds 2 and 4, this acidity difference decreases to about 1.0 kcal/mol. The reason for this behavior is probably due to the high polarizability and size of the sulfur atom over the oxygen. In summary, our results suggest that the gas phase acidity trend of the molecules under investigation is as follows: 4 > 2 > 3 > 1. These results agree with those reported experimentally [64], which showed that compound 2 ($pK_a=8.5$) is slightly stronger acid than compound 1 ($pK_a=9.0$). Again, these results argued the validity and efficiency of the DFT method to predict and estimate the gas phase acidity of the polyfunctional compounds.

12.3.2 THIAZOLIDINE-2,4-DIONE AND ITS 5-SUBSTITUTED DERIVATIVES

In this subsection, we introduce and discuss the DFT B3LYP results of the proton affinities (PAs), molecular electrostatic potential (MEP), and natural valence atomic orbital energies (NVAO) of the possible basic centers (O2, N3, and O4) existing for thiazolidine-2,4-dione (Scheme 4) [64].

Table 12.6 presents the PAs of the basic centers (O2, O4, and N3) existing for the system under probe. The PAs were calculated using the DFT method at the B3LYP/6–311++G(3df,2p)//B3LYP/6–311+G(d,p) level of theory. An analysis of Table 12.6 indicates that the most basic center is O2.

**SCHEME 4** Thiazolidine-2,4-dione and their 5-substituted derivatives.**TABLE 12.6** Proton Affinities (PAs) of the Basic Sites (in kcal mol⁻¹), Molecular Electrostatic Potential on the Nuclei of the Basic Sites (MEP) (in a.u.) and the Valence Natural Atomic Orbital Energies (NNAO) (in a.u.) of the Thiazolidine-2,4-dione and Its Derivatives

	PA		MEP				NVAO		
	O2	O4	N3	O2	O4	N3	O2	O4	N3
H	192	190	168	-22.356	-22.358	-18.313	-1.842	-1.823	-1.525
CH ₃	195	192	171	-22.359	-22.36	-18.316	-1.829	-1.814	-1.511
Cl	187	186	163	-22.343	-22.343	-18.301	-1.89	-1.873	-1.571
CN	181	179	156	-22.335	-22.334	-18.29	-1.92	-1.911	-1.611
F	185	183	161	-22.341	-22.341	-18.299	-1.898	-1.879	-1.577
NO ₂	181	184	158	-22.33	-22.33	-18.288	-1.935	-1.921	-1.615
NH ₂	199	197	-	-22.356	-22.355	-18.313	-1.841	-1.834	-1.525

Results are taken from Ref. 40.

The calculated PA of O₂ of the parent thiazolidine-2,4-dione compound is ~192 kcal/mol and it is ~ 2 and 23 kcal/mol higher than that of O₄ and N₃, respectively. Furthermore, it is found that the PA is increased when changing from the electron withdrawing group to the electron releasing group. Our results show that the highest PA corresponds to 5-amino derivatives (~199 kcal/mol), whereas the smallest one corresponds to the 5-cyano derivatives (181 kcal/mol). The electron releasing group makes the electron pairs on the oxygen atom more available by donating the electron to the system. The reverse is true in the case of the electron withdrawing group. These results

lead us to classify the compound under probe as a moderate basic compound, and the basic centers in this compound can be arranged in order of its strength as follows: O₂ > O₄ > N₃. Based on our results of MEP and NVAO values from [Table 12.6](#), it is found that the MEP trend order is $\text{MEP}(\text{O}_2) > \text{MEP}(\text{O}_4) > \text{MEP}(\text{N}_3)$. The absolute value of the $\text{MEP}(\text{O}_2)$ is higher than that of $\text{MEP}(\text{N}_3)$ by about 4.042–4.045 a.u. These results are in agreement with PA values, which suggest that O₂ is the most basic center among all the centers existing for the thiazolidine-2,4-dione and its derivatives. The same conclusion can be also reached when the NVAO results are considered.

An adequate linear relationship between the proton affinity and MEP is shown in [Figure 12.2](#). The correlation coefficient ($R^2 = -0.9419$) and the linear equation are shown in the figure. Based on these findings, one expects that the two oxygen atoms should be the site to preferably bond with the incoming proton. These numerical data led us to suggest, in accordance with our studies on benzamide derivatives, that the analysis of MEP on the nuclei of the basic centers can be used as a good descriptor to estimate the intrinsic basicities of the heterocyclic compounds containing different type of the basic centers.

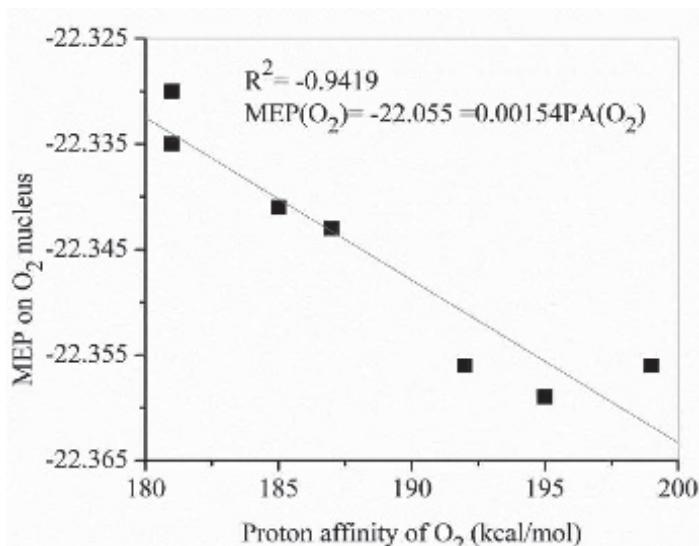


FIGURE 12.2 Linear relationships between the MEP on O₂ nucleus (in a.u.) and the proton affinity of O₂ (in kcal.mol) of the thiazolidine-2,4-dione derivatives.

12.3.3 ISORHODANINE

Table 12.7 displays the values of PAs, GB, and ΔH_{dep} of isorhodanine in gas phase and water (Scheme 5).

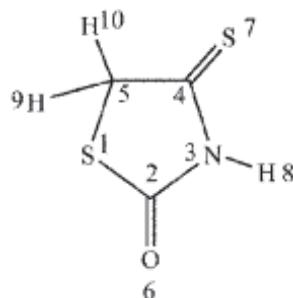
12.3.4 BENZAMIDE AND ITS DERIVATIVES

In this section, we introduce the results of the proton affinities and gas phase basicities of benzamide and its *m*- and *p*-(NH₂, -CH₃, OH, OCH₃, NO₂, CF₃, and Cl) derivatives in gas phase and in solution (Scheme 6). **Table 12.8** summarizes the calculated PAs and GBs [67], together with the available experimental value for all investigated species [22, 68].

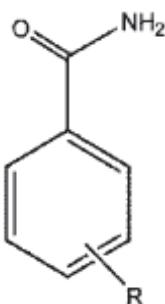
TABLE 12.7 Gas and Solvent Phase Proton Affinity, PA / kcal mol⁻¹, Gas-Phase Basicity, GB/kcal mol⁻¹, and the Enthalpy of Deprotonation, $\Delta H_{\text{dep}}/\text{kcal mol}^{-1}$, of Isorhodanine Obtained at B3LYP/6–11++(3df,2p)// B3LYP/6–11+(d,p) Level of Theory

	Gasphase			Water		
	PA	GB	DH _{dep}	PA	GB	DH _{dep}
S1	172.2	165.0	-	-43.3	-45.2	-
O6	190.1	184.6	-	-33.7	-32.5	-
N3	166.9	160.2	-	-53.3	-51.4	-
S7	194.4	187.9	-	-25.8	-22.7	-
N3-H8	-	-	324.2	-	-	554.8
C5-H2(3)	-	-	330.0	-	-	560.0

Results are taken from Ref. 29.



SCHEME 5 Isorhodanine.



SCHEME 6 Benzamide and its m- and p- derivatives.

A closer analysis of [Table 12.8](#) shows interesting linear relationships between the calculated PAs and GBs of the investigated benzamides and the available experimental ones ([Figure 12.3](#)), i.e., the PA (ΔH) in [Figure 12.3a](#) and the GB (ΔG) in [Figure 12.3b](#), with determination coefficients 0.9787 for PAs and 0.9782 for GBs, respectively. Therefore, linear correlations are derived between the calculated PA and GB and the corresponding experimental data as shown in [Figure 12.3](#). These results indicate, in agreement with previous studies, that the B3LYP method may be considered as a useful method to calculate the proton affinities and gas-phase basicities of the polyfunctional compounds.

Another topic that should be considered here is the electron densities at the O-H⁺ BCP, ρ_{BCP} , and their Laplacian, $\nabla^2 \rho$. These topological properties were evaluated at the B3LYP/6-311+G(d,p) level of theory by means of the AIM2000 approach. The values of ρ_{BCP} and $\nabla^2 \rho$ are included in [Table 12.7](#). As can be seen, the positive values of ρ_{BCP} and the negative value of $\nabla^2 \rho$ suggest that the O-H⁺ interaction have, in principle, a covalent character. Indeed, the ρ_{BCP} . Our results revealed an adequate relationship between the electron density at bcp of the O-H⁺, which results due to the protonation of the basic center (O atom) by the proton (H⁺) and the PA and/or GB ([Figure 12.4](#)). The correlation coefficient (R^2) is very close to 0.9. These results led us to conclude that the electron density at bcp can be used to estimate the PA and GB.

TABLE 12.8 Calculated Proton Affinities, PA and Gas-Phase Basicities, GB, in Gas Phase Calculated at B3LYP/6-311++G(d,p)//6-311++G(d,p) Level of Theory Together with the Available Experimental and Theoretical (ab initio and PM3 Semiempirical Level) of Benzamides and Its Derivatives

X	PA _{calc}	PA _{exp^a}	GB _{calc}	GB _{exp^a}	MEP(O)	NPA(O)	NPA(N)	ρ _{bp}	∇ ² p	δ ¹ H
<i>p</i> -OCH ₃	219.1	215.2	211.4	207.8	-22.409	-18.373	-1.634	-1.313	0.358	-2.56 7.1
<i>m</i> -OCH ₃	214.9	215.3	207.2	207.9	-22.406	-18.37	-1.645	-1.323	0.357	-2.56 7.6
<i>p</i> -OH	216.7	-	209	-	-22.407	-18.371	-1.644	-1.322	0.358	-2.56 7.1
<i>m</i> -OH	213.3	-	205.5	-	-22.404	-18.368	-1.653	-1.331	0.356	-2.56 7.6
<i>p</i> -NH ₂	223.6	221.6	216.1	214.4	-22.414	-18.378	-1.617	-1.295	0.358	-2.55 6.7
<i>m</i> -NH ₂	216.5	215.3	208.9	207.9	-22.405	-18.371	-1.64	-1.32	0.356	-2.54 7.5
<i>p</i> -CH ₃	217	215.3	209.4	207.9	-22.405	-18.378	-1.643	-1.322	0.356	-2.54 7.4
<i>m</i> -CH ₃	214.5	215.3	206	207.9	-22.404	-18.37	-1.647	-1.326	0.356	-2.54 7.5
H	208.4 ^a	213.2	204.9	205.8	-22.403	-18.367	-1.656	-1.334	0.355	-2.54 7.6
	212.6									
	224.5 ^b									
<i>p</i> -NO ₂	202.1	201.2	194.6	196.7	-22.381	-18.347	-1.732	-1.411	0.354	-2.54 8
	197.2 ^b									
<i>m</i> -NO ₂	203.1	204.3	195.3	196.7	-22.384	-18.35	-1.723	-1.4	0.354	-2.54 7.9
<i>p</i> -Cl	210.7	209.7	203	202.3	-22.394	-18.362	-1.681	-1.358	0.355	-2.54 7.5
<i>m</i> -Cl	208.9	209.7	201.1	202.3	-22.393	-18.361	-1.685	-1.363	0.356	-2.54 7.7
<i>p</i> -CF ₃	205.9	206.2	198.1	198.8	-22.39	-18.354	-1.706	-1.385	0.354	-2.54 7.8
<i>m</i> -CF ₃	206.4	206.7	198.9	199.8	-22.391	-18.355	-1.702	-1.38	0.355	-2.55 7.8

^aValues taken from Refs. [68, 69]. ^bValues taken from Ref. [69]. Results are taken from Ref. 22.

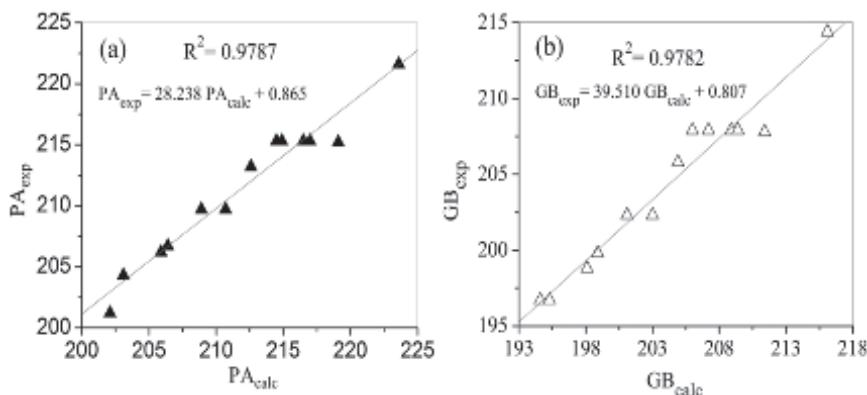


FIGURE 12.3 Linear relationships for (a) calculated proton affinity and the corresponding experimental data and (b) calculated gas-phase basicity and the corresponding experimental data.

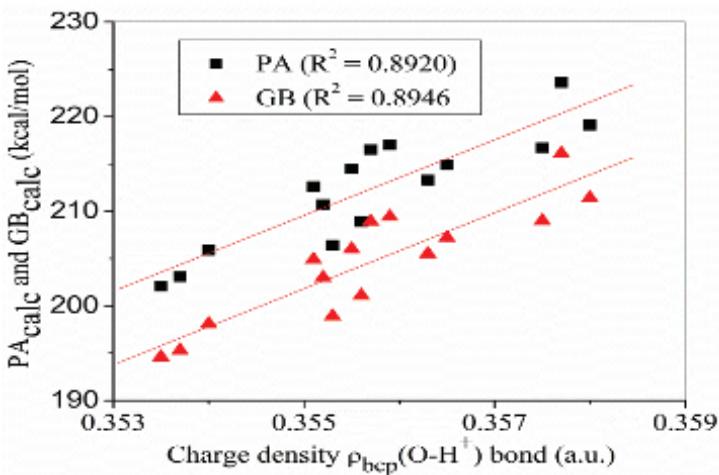


FIGURE 12.4 Linear correlation between the electron density at the bond critical point of the O-H⁺ bond (in a.u.) and the proton affinity and gas phase basicity (in kcal/mol) of m- and p-substituted benzamides.

A good linear relationship between the ¹H NMR chemical shift (δ^1H) in (ppm) and the PA and GB of the benzamides is shown in Figure 12.5. Good linear relationships are obtained with correlation coefficients of 0.9173 (PA vs. δ^1H) and 0.9201 (GB vs. δ^1H). In agreement with recent

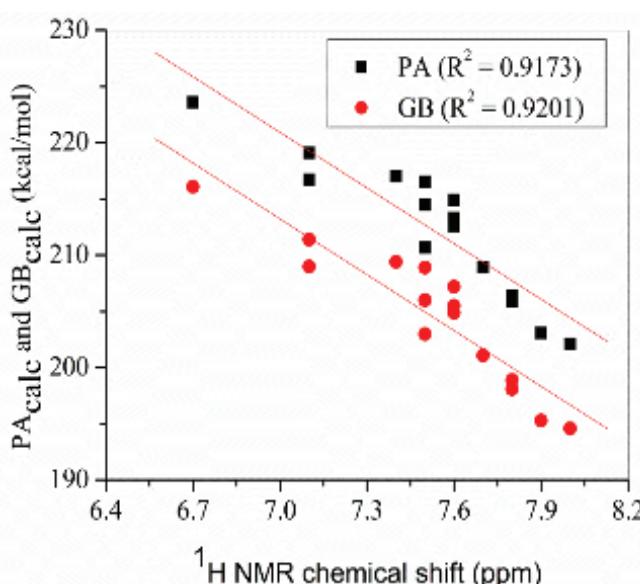


FIGURE 12.5 Linear correlation between the ^1H NMR of the incoming proton $\delta^1\text{H}$ (in ppm) and the proton affinity and gas phase basicity (in kcal/mol) of m- and p-substituted benzamides.

studies [62, 68, 70], these strong correlations permit us to conclude, among the abovementioned parameters, that the PA and GB of the species under probe can be estimated by other quantum descriptors such as MEP, NAVO, $\delta^1\text{H}$, and ρ_{bcp} .

Table 12.9 presents the protonation energy, $\Delta_{\text{prot}}E$, proton affinities, PA , Gibbs free energy of deprotonation, $\Delta_{\text{prot}}G$, and the base equilibrium constant, pK_b of *para*- and *meta*-substituted benzamides calculated at the B3LYP/6-311++G(2df,2p)//6-311++G(d,p) level of theory in solution (water), together with the available experimental pK_b . A closer look at Table 12.8 indicates that quantitative agreement between theory and experiment is poor for water. These pK_b values were calculated by using different techniques (see Ref. [71] and the references therein). Plot of pK_b (calc.) vs. pK_b (exp) exhibits qualitative agreement, with a correlation coefficient of 0.9728 (see Figure 12.6). If one assumes linear behavior, the fitted equation should be given by the expression given in Figure 12.6. However, these

TABLE 12.9 $\Delta_{\text{prot}} E$, PA, $\Delta_{\text{prot}} G$ and pK(B) of Para- and Meta-Substituted Benzamides Calculated at B3LYP/6–311++G(2df,2p)//6–311++G(d,p) Level of Theory in Solution (Water), Together with the Available Experimental pK_b Values

X	PA	$\Delta_{\text{prot}} G$	pK _b	pK _b (experimental)		
				*	*	**
<i>p</i> -OCH ₃	-15.1	-13.7	-10	-	-	-
<i>m</i> -OCH ₃	-17.6	-16.2	-11.8	-	-	-
<i>p</i> -OH	-15.7	-14.7	-10.7	-	-	-
<i>m</i> -OH	-17.8	-16.4	-12	-	-	-
<i>p</i> -NH ₂	-12.4	-10.8	-7.8	-	-	-
<i>m</i> -NH ₂	-16.6	-15.4	-11.2	-	-	-
<i>p</i> -CH ₃	-16.4	-15.4	-11.2	1.46	1.44	1.67 ^a
<i>m</i> -CH ₃	-17.3	-16.7	-12.2	1.33	1.37	1.76 ^a
H	-17.3	-15.9	-11.6	1.4	1.43	1.54 ^c , 1.45 ^c , 1.54f, 1.38 ^c , 1.65 ^d , 1.74 ^a , 1.45 ^b ,
<i>p</i> -NO ₂	-21.5	-20.5	-14.9	2.36	2.28	2.70 ^a , 2.13 ^d
<i>m</i> -NO ₂	-21.1	-20.1	-14.6	2.04	2.01	2.42 ^a
<i>p</i> -Cl	-18.3	-16.9	-12.3	1.6	1.66	1.97 ^a
<i>m</i> -Cl	-19.3	-18.3	-13.3	1.63	1.65	2.09 ^a
<i>p</i> -CF ₃	-20	-18.9	-13.8	-	-	-
<i>m</i> -CF ₃	-19.8	-19.1	-13.9	-	-	-

(*) Values are taken from Ref.[72]; (**) values are taken from Refs ((a):[73], (b):[74], (c):[75], (d):[76], (e):[77], and (f): [78].

All values are in kcal/mol.

Results are taken from Ref. 22.

values of the correlation coefficients R are not representatives of a true linear relation (for which $R \geq 0.99$), but they are indicative of a quasi linear correlation. According to our results, although the quantitative comparison with experimental methods is poor, one can conclude that the computation of the proton free enthalpy in solution with high accuracy is fundamental in solvation study if reliable experimental data are not available (Table 12.9).

12.4 CONCLUSION

In this chapter, we have introduced the calculation of the proton affinities (PA), gas phase basicities (GB), deprotonation energies (ΔH_{dep}), and

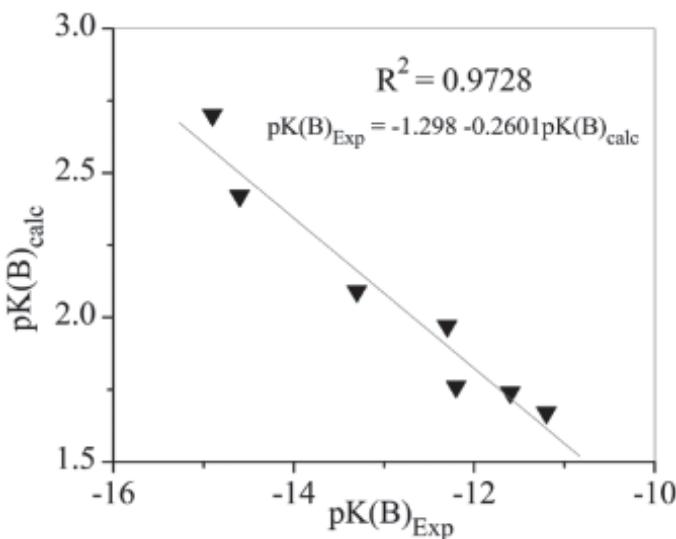


FIGURE 12.6 Linear correlation between the experimental PK_b (experimental) and theoretical PK_b values. (Reprinted with permission from Safi, Z., & Omar, S. Proton affinity and molecular basicity of m- and p-substituted benzamides in gas phase and in solution: A theoretical study. Chemical Physics Letters, 601–602, pp. 321–330. © 2014 Elsevier.)

some quantum descriptors such as molecular electrostatic potential on the nuclei, natural valence orbital energies, ${}^1\text{H}$ NMR chemical shifts, and electron density at bond critical points of some polyfunctional compounds in the framework of density functional theory (DFT) using the famous B3LYP at different basis sets. The obtained results were compared with the available experimental data. A good agreement between the calculated and the experimental data was obtained. Finally, our findings led us to conclude that the DFT method is as effective as ab initio to calculate the PA, GB, and ΔH_{dep} .

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A generous allocation of computational time at the Scientific Computational Center (CCC) of the Universidad Autónoma de Madrid (Spain) acknowledged the University of Marburg (Germany).

KEYWORDS

- **B3LYP**
- **benzamide**
- **density functional theory**
- **gas-phase basicity**
- **hydantoin**
- **isorhodanine**
- **proton affinity**

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