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Computational Study on Hydroxybenzotriazoles as Reagents for Ester Hydrolysis

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1-Hydroxybenzotriazole (**1**) and several of its derivatives (**2**−**5**) demonstrate potent esterolytic activity toward activated esters such as *p*-nitrophenyl diphenyl phosphate (PNPDPP) and *p*-nitrophenyl hexanoate (PNPH) in cationic micelles at pH 8.2 and 25 °C. The deprotonated anionic forms of such reagents act as reactive species in the hydrolysis of ester. To rationalize the origin of their nucleophilic character, a detailed ab initio/DFT computational study has been performed on **1**−**5** along with additional hydroxybenzotriazole derivatives (**6**−**13**). The geometries of 1-hydroxybenzotriazoles (**1**−**13**) and their corresponding bases are discussed in detail. All calculations were carried out using different methods, i.e., restricted Hartree−Fock (RHF) and hybrid ab initio/DFT (B3LYP) using 6-31G* and 6-31+G* basis sets. Free energy of protonation ("fep") of the 1-hydroxybenzotriazoles (**1**−**13**), free energy of solvation ΔG_{aq}, and the corresponding pK_a values have been calculated. Solvation-free energies were calculated using density functional theory and the polarizable continuum model. In addition, to examine the reliability of calculated fep, benzaldehyde oxime (**14**) and 2-methyl propionaldehyde oxime (**15**) have been computed as reference systems using different methods and basis sets, the experimental feps of which are known. Our experimental finding shows that the compound **4** is the most effective catalyst for the hydrolytic cleavages of PNPDPP and PNPH. This has been predicted from our calculated fep, pK_a, and natural charge analysis results as well. In general, the introduction of electron-withdrawing substituents on 1-hydroxybenzotriazoles facilitates the lowering of pK_a and fep. As the pK_a values are lowered, a greater percentage of such hydroxybenzotriazoles remain in their deprotonated, anionic forms at pH 8.2. Since the anionic forms are nucleophilic, pK_a lowering should enhance their ester cleaving capacity. However, such substitution also decreases the charge density on the catalytically active oxido atom (O_7). Taking these two factors together, the derivatives are only modestly better nucleophiles in comparison to the parent 1-hydroxybenzotriazole. Interestingly, the introduction of electron-donating groups does not significantly enhance the charge accumulation on the oxido atom (O_7) of 1-hydroxybenzotriazoles.

Introduction

Many persistent chemicals such as paraoxon, parathion, and chemical warfare compounds such as VX or sarin, etc. (Chart 1), are hydrophobic phosphorus(V) esters or phosphorylating agents.[1] Such compounds are highly toxic to both target and nontargeted organisms.[1,2] Paraoxon and parathion, the phosphotriester-based pesticides, are most frequently responsible for the poisoning of agricultural field workers.[2a] Remediation of such contamination therefore continues to be a challenge for research groups. However, high toxicity of such compounds mandates that most research laboratories employ simulants instead of the actual compounds. For instance,

CHART 1

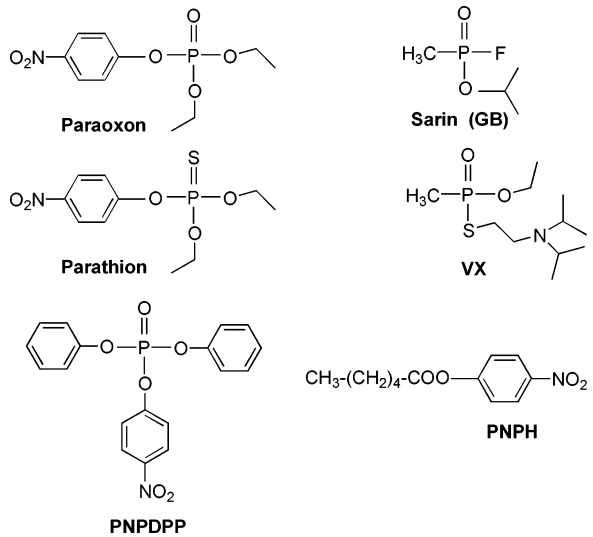

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TABLE 1. Kinetic Parameters for Micellar Esterolysis of PNPH and PNPDPP Mediated by Various HOBt Systems in CTABr Micelles[a]

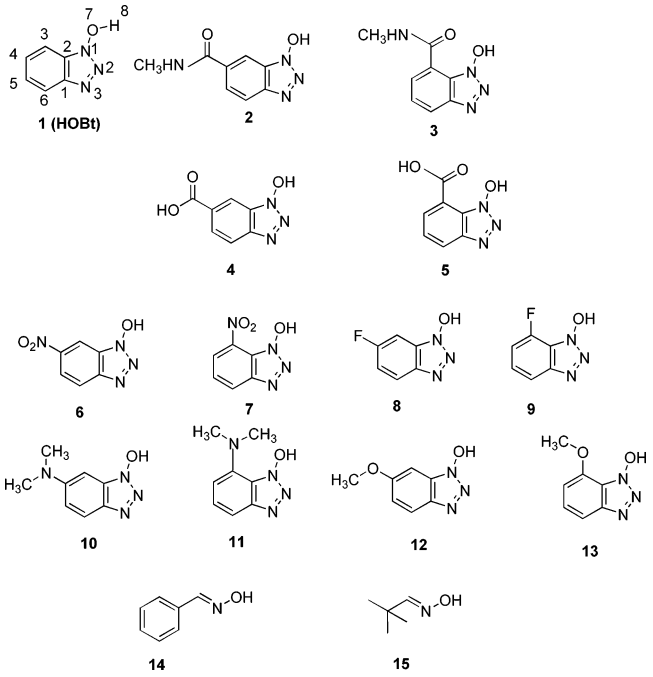
			PNPDPP		PNPH	
entry	catalyst	pK_a[b] [% of ionizaion]	$10^3\,k_\psi$, s^{-1}	k_{rel}[c]	$10^3\,k_\psi$, s^{-1}	k_{rel}[c]
1	none	-	0.04	1.0	0.09	1.0
2	1	7.0 [95.2]	3.21	80.2	5.35	59.4
3	2	6.5 [98.4]	4.52	113.0	5.76	64.0
4	3	6.7 [97.5]	4.28	107.0	5.69	63.2
5	4	6.5 [98.4]	5.36	134.0	6.61	73.4
6	5	6.7 [97.5]	4.75	118.8	6.02	66.9

[a] Conditions: 0.05 M pH 8.2 (tris-maleate) buffer, 25 ± 0.1 °C, [substrate] = 2.5×10^{-5} M, [catalyst] = 2.5×10^{-4} M, [CTABr] = 1×10^{-2} M, 1 vol-% CH_3CN. [b] Values in [ ] are % of ionization at pH 8.2. [c] $k_{rel} = k_\psi/k_{CTABr}$.

p-nitrophenyl diphenyl phosphate (PNPDPP) is a well-known standard simulant for studying the hydrolytic reactions of phosphotriesters.[3] Since PNPDPP is not water-soluble, aqueous micellar solutions are often employed as reaction media for the cleavage of such substrate esters.[3,4] Organic reactants are partitioned into the surfactant micelles by columbic and hydrophobic interactions, and the observed rate accelerations are largely due to the enhanced localization of the reactants and also of the typical physicochemical properties of micellar environment, which are considerably different from those of the bulk solvents.[4]

Chemical means of achieving efficient destruction of organophosphate esters remains an active area of much research. The current attention is focused on peroxides,[5] iodosoarene carboxylates,[6] 4-*N*,*N*-dialkylaminopyridines,[7] and metalloorganics[8] employed in cetyltrimethylammonium (CTA^+) micelles as media. 1-Hydroxybenzotriazole (**1**) is a potent α-effect O-nucleophile.[9] The α-nucleophiles are known to enhance the hydrolytic reaction rates of toxic organophosphate esters. When solubilized in cationic micellar solution, **1** and its derivatives, **2**−**5** prove to be effective catalysts for the cleavage of reactive phosphotriester and carboxylate esters. In this report, the hydrolytic cleavage reactions of PNPDPP and PNPH in cationic micellar media with **1** and its derivatives **2**−**5** have been presented. The experimental results (Table 1) suggest that **4** is the most effective catalyst among **1**−**5** studied herein.

CHART 2. Structures of 1-Hydroxybenzotriazole and Its Derivatives (1−13) along with the Oximes (14, 15)



To understand the origin of the catalytic activity of 1-hydroxybenzotriazoles in **1**−**5** and to find a more potent nucleophile from a series of novel hydroxybenzotriazole compounds for the esterolytic reactions, we have carried out a detailed ab initio and Becky3LYP density functional hybrid computational investigation on **1** and a series of its derivatives bearing different electron-donating and electron-withdrawing substituents, **2**−**13** (Chart 2). The fep, pK_a, and charge on the oxido atom (N−O^-) of the conjugate bases responsible for the hydrolytic cleavage reactions of PNPDPP and PNPH of these hydroxybenzotriazoles have been calculated, as they are fundamental to the understanding of their catalytic properties toward dephosphorylation or deacylation reactions.

However, the 1-hydroxybenzotriazoles have so far not received any theoretical attention, although simple calculations have been performed on certain triazoles. Fabian and Guimon et al. have performed semiempirical calculations[10] to examine and reproduce the tautomeric phenomena of traizole systems. Anders et al.[11] investigated the phenomena of tautomerism for benzotriazole and triazole systems using ab initio and semiempirical methods. The calculations performed by Anders et al. suggested that semiempirical methods are not adequate to handle these related triazole systems and high level calculations are required to reproduce the structural and reactivity trends. Computing benzotriazoles at very high levels of theory was prohibitively expensive in the 1990s, and Anders et al. calculated only simple traizole systems at a higher level (MP2/6-31+G*) to correlate with the experimental observations. Accordingly, we report here the structural, conformational aspects of 1-hydroxyben-

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TABLE 2. Free Energy of Protonation[a] Calculated for 14 and 15 Using Different Methods

method	14	15
RHF/6-31G*	377.6	389.7
RHF/6-31+G*	368.1	379.0
B3LYP/6-31G*	366.4	381.8
B3LYP/6-31+G*	353.7	366.3
MP2/6-31G*	367.5	381.4
MP2/6-31+G*	353.4	364.9

[a] Energies are in kcal/mole. Experimental proton affinity of **14** and **15** are 355.1 and 364.6, respectively.

zotriazole and its different electron-withdrawing/donating derivatives at ab initio Hartree−Fock and DFT-B3LYP levels.

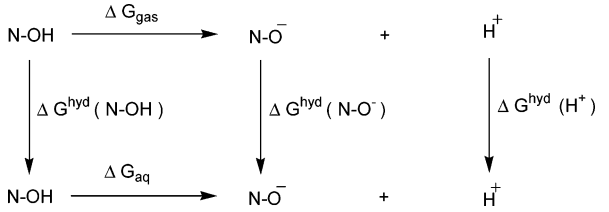
Computational Methods

All the ab initio Hartree−Fock and Becky3LYP density functional hybrid method[12] calculations reported in this work were performed using the Gaussian 98 suite program.[13] The stable conformers of 1-hydroxybenzotriazole derivatives (**2**−**13**) have been located and optimized at the level of restricted Hartree−Fock (RHF) and DFT (B3LYP) using the 6-31+G* basis set.[14] All structures were completely optimized without any symmetry constraints. For all systems studied, vibrational frequency calculations were carried out to confirm that they converged to true minima.

For the sake of simplicity, we define the deprotonation enthalpy of the neutral protonated forms of hydroxybenzotriazoles as free energy of protonation (fep) of the negatively charged species. Fep values were obtained by following Dewar's definition.[15] Essentially, we consider the cases as in the instances when we deal with isodesmic processes (e.g., ROH + MeO^- → RO^- + MeOH) and internal comparisons of the energy differences.[16]

To probe the relative validity of the basis sets and to evaluate the influence of electron correlation and diffuse functions, we calculated the free energy of protonation (N−OH → N−O^-) of two molecules, for instance, benzaldehyde oxime (**14**) and 2-methyl propionaldehyde oxime (**15**) (Chart 2) as references, whose experimental proton affinities are known. The results (Table 2) show that the electron correlation and diffuse functions are important to closely match with the experimental data. Results obtained employing B3LYP/6-31+G* and MP2/6-31+G* methods provide the best match with the experimental results, and accordingly we have chosen B3LYP/6-31+G* for further calculations. In addition this method requires less CPU time than the MP2 method. Natural charges calculated on the oxido (O_7) atom of N−O^- in the conjugate bases of **1**−**13** were calculated on the basis of the natural bond orbital (NBO) localization procedures developed by Weinhold et al.[17]

To calculate the pK_a values of molecules **1**−**13**, we have considered the thermodynamic cycle shown below.



The thermodynamic cycle yields eq 1 in which the aqueous pK_a for the acid N−OH is given by

$$\Delta G_{aq} = \Delta G_{gas} + \Delta G^{hyd}(N{-}O^-) + \Delta G^{hyd}(H^+) - \Delta G^{hyd}(N{-}OH) \quad (1)$$

At a given temperature T, the pK_a is then given by

$$pK_a = \Delta G_{aq}/2.303\,RT \quad (2)$$

The gas phase fep is calculated at the same level of theory used for the calculation of solvation free energy. The free energy of solvation in water has been calculated using SCRF (self-consistent reaction field) methods using the polarized continuum model (PCM).[18−22] A dielectric constant (ϵ) of 78.39 (water) was used in the solvation calculations, at the B3LYP/6-31+G* level. The solvation-free energy of the proton taken from the experimental ΔG^{hyd} (H^+) is equal to −254 kcal/mol.[23]

Results and Discussion

Synthesis of 1-Hydroxybenzotrizoles (2−5). Derivatives of 1-hydroxybenzotriazole, **2** and **3**, have been synthesized following the procedure outlined in Scheme S1 (Supporting Information). First, 4-chloro-3-nitrobenzoic acid was converted to the corresponding acid chloride by refluxing in $SOCl_2$. Removal of excess $SOCl_2$ afforded 4-chloro-3-nitrobenzoyl chloride, which on reaction with *n*-tetradecylamine in the presence of Et_3N in dry THF gave the corresponding amide derivative, **7** (82%), as a yellow solid. This was then treated with ∼10-fold excess of hydrazine hydrate, and the mixture was refluxed in dry EtOH for 20 h to give **2** as a light yellow solid (60%). Compound **3**, the regioisomer of **2**, was synthesized start-

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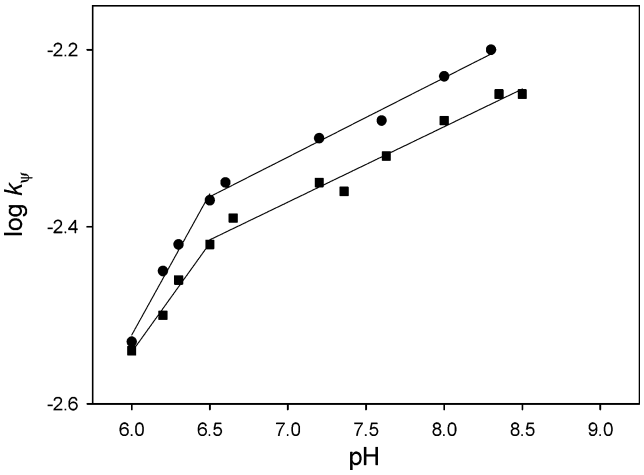

FIGURE 1. Observed rate constant k_ψ vs pH profiles for the comicellar cleavages of PNPDPP (2.5×10^{-5} M) by **2** (2.5×10^{-4} M) (■) and **4** (2.5×10^{-4} M) (●) in CTABr (1×10^{-2} M) micelles at pH 8.2.

ing from 3-chloro-2-nitrobenzoic acid employing a similar procedure as adopted for **2** (Scheme S1, Supporting Information). The corresponding 1-hydroxybenzotriazole carboxylic acids **4** and **5** were also synthesized to examine their efficacy as esterolytic agents in cationic micellar media. These were obtained upon treatment of 4-chloro-3-nitrobenzoic acid or 3-chloro-2-nitrobenzoic acid with a ~10-fold excess of hydrazine hydrate under refluxing conditions in dry EtOH for 15 h. Acidification of the respective reaction mixture gave **4** and **5** as white solids in 76 and ~55% yields, respectively. The final products and intermediates were characterized by IR, ^{1}H NMR, mass, and elemental analysis (Supporting Information).

pK_a Determination. It is known that the anion of hydroxybenzotriazole (N−O$^-$) acts as a reactive species in the hydrolysis of esters.[9] Therefore, the reactive species of **1**−**5** are the corresponding anionic forms N−O$^-$ in the hydrolysis of PNPH or PNPDPP. Consequently, the pK_a for the conversion of the N−OH to the N−O$^-$ form in each of **1**−**5** represents an important datum in all these cases. A pH−rate constant profile for the esterolytic cleavage of 2.5×10^{-5} M PNPDPP by 2.5×10^{-4} M reagent in host CTABr (cetyltrimethylammonium bromide) micelles (1×10^{-2} M) gave the apparent pK_a values for each reagent in 0.05 M tris-maleate buffer adjusted to appropriate pH.

Typically, the pseudo-first-order rate constants for PNPH or PNPDPP cleavages at 25 °C were determined at different pH values between 6.2 and 8.5 by following the release of the *p*-nitrophenoxide ion at 400 nm spectrophotometrically. In Figure 1, we present representative pH−rate constant profiles for the cleavage of 2.5×10^{-5} M PNPDPP by 2.5×10^{-4} M of **2** and **4** in micellar CTABr (1×10^{-2} M) and 0.05 M tris-maleate buffer at 25 °C. The plots of log k_ψ vs pH (Figure 1) gave discontinuities at pH 6.5 and 6.5, which were taken as systemic pK_a for **2** and **4**, respectively, under CTABr micellar conditions. A pK_a value of 7.4 for **1** in pure water has been reported.[24] Solubilization of **1** in micellar CTABr lowered the pK_a value to ~7.0. The pK_a values similarly determined for compounds **3**−**5** in CTABr micellar aggregates were 6.5 for **2**, 6.7 for **3**, 6.5 for **4**, and 6.7 for **5**.

Kinetic Studies in Micelles. Kinetics were performed under pseudo-first-order conditions, monitoring the appearance of *p*-nitrophenoxide at 400 nm, 0.05 M tris-maleate buffer, pH 8.2, at 25 ± 0.1 °C, using [substrate] = 2.5×10^{-5} M and [catalyst] = 2.5×10^{-4} M at different CTABr concentrations. The buffer solutions also contained 1.0 vol % CH_3CN. Pseudo-first-order rate constants, k_ψ, were spectrophotometrically determined for both substrate (PNPH and PNPDPP) cleavages at each combination of [CTABr]/[catalyst] by following the release of *p*-nitrophenoxide ion at 400 nm. The reproducibility of k_ψ was generally ±2% with all the catalytic formulations. Determination of full rate constant vs [CTABr] profiles for the cleavage reactions of PNPH and PNPDPP in micellar aggregates allowed assessment of the ester cleavage abilities of **1** to **5**. The plot of k_ψ vs [CTABr] gave maxima for all the catalysts at [CTABr] = 10 mM (data not shown).

The values of k_ψ for the cleavages of PNPDPP and PNPH by each catalyst at 10 mM [CTABr] are shown in Table 1. When the molar ratio of catalyst to CTABr was fixed at 1:40, we observed the best k_ψ values for each catalyst, **1**−**5**. The last column of Table 1 provides a comparison of the cleavage abilities of the all catalysts under pseudo-first-order conditions. The ratio k_ψ/k_{CTABr} reveals the catalytic capacities of these hydroxybenzotriazoles compared to background cleavage rates at identical pH and temperature in CTABr micelles alone. Data in Table 1 reveal that compounds **1**−**5** are reasonably effective reagents for the cleavage of both PNPDPP and PNPH and afford almost 2 orders of magnitude rate acceleration over CTABr alone.

Comicellar **4**/CTABr displayed the highest esterolytic activity among all the catalytic systems toward both PNPDPP and PNPH. Thus, **4**/CTABr cleaved PNPDPP 134 times faster than the same reaction in CTABr micelles alone. **5**/CTABr comicelles were the next most effective ester cleavage agent (Table 1). Incorporation of *n*-tetradecyl chain potentiates the kinetic efficiency in **2** or **3** over **1**. However, such enhancement in reactivity for the hydrolysis of both PNPDPP and PNPH by **2** or **3** over **1** was not enormous. To rationalize the origin of nucleophilicity in this type of reagent and to enable us to design more potent hydroxybenzotriazoles, we decided to perform detailed ab initio/DFT calculations on a large set of compounds bearing either electron-withdrawing or electron-donating substituents.

We also performed saturation kinetics experiments in CTABr comicelles at pH 8.2 and 25 °C for **1**−**5** with solutions containing increasing amounts of catalyst and CTABr with molar ratios relative to the catalyst of 30, 40, and 50, using PNPDPP as the substrate. Analysis of the curves by fitting the k_{obs} vs [catalyst] data using the Michaelis−Menten equation[8a] allows the estimation of the k_{lim}, that is, the rate constants expected for the substrate being fully incorporated into the micellar aggregates, K_b, is the apparent binding constant and second-order rate constants, k_2.

Data in Table S1 also reveal that **4** has higher k_{lim}, K_b, and k_2 values, which again suggests that indeed catalyst **4** has better catalytic activity among other catalysts in

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this series of molecules even in the fully bound form, i.e., where catalyst and substrates should be fully transferred to micellar aggregates. Hence, we assume that the higher catalytic activity of **4** is due to the higher nucleophilicity of the N−O⁻ of **4**, which arises from the higher natural charge on the oxido atom.

To examine the true catalytic activities of different **HOBt** derivatives, kinetic experiments were performed in the presence of excess substrate in CTABr micellar media. At pH 8.2 (0.05 M tris-maleate buffer, 25 °C, [**4**] = 2.5 μM, [CTABr] = 1 mM and 25-fold excess PNPH with respect to catalyst concentration), we observed a quantitative monoexponential release of *p*-nitrophenoxide ion (not shown). The catalytic effectiveness of **4** was still intact even after complete hydrolysis of 25-fold PNPH. This was also true for the cleavage of excess PNPDPP.

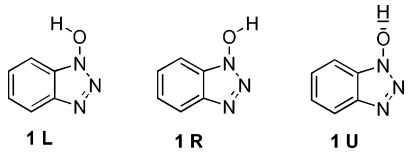
The hydroxybenzotriazoles are rapidly acylated or phosphorylated by PNPH or PNPDPP at pH 8.2 in micellar conditions. The resulting products do not, however, retain the acyl or phosphoryl groups. In fact, the acylated or phosphorylated hydroxybenzotriazoles rapidly deacylate in a second and even faster step, regenerating the parent hydroxybenzotriazoles. Therefore, the hydroxybenzotriazole reagents are not stoichiometric acyl transfer agents; they are true catalysts. The observed reactions are therefore purely hydrolytic reactions and not mere reactions between triazoles and phosphate esters.

Theoretical Calculations

Accounting for solvent effects computationally is a challenging task. Rate constants are sensitive to small free energy changes. Also, there are uncertainties in heats of formation from even high-level calculations, which apply to isolated molecules and do not of themselves provide evidence on structural effects on entropy. However, these concerns should not preclude computational studies in this direction. Especially with the development of statistical Monte Carlo and quantum mechanical methods, it is possible to gauge the role of solvents with reasonable accuracy.[25] Although continuum models may not be the best in analyzing reactions such as dephosphorylation, there is an advantage in using a continuum description in that it speeds up computation considerably with reasonable accuracy. Accordingly, we have herein attempted to understand the experimental results using quantum mechanical methods.

Ab Initio/DFT Results of 1-Hydroxybenzotriazoles (1−13). 1-Hydroxybenzotriazole and its derivatives **1**−**13** have been optimized at RHF/6-31+G* and B3LYP/6-31+G* levels of theory. To examine the most stable form of **1**−**13**, three different orientations for the N−OH bond have been considered for each molecule and optimized without any symmetry constraints (Scheme 1). For simplification of calculations and to economize CPU usage, long *n*-tetradecyl chains in **2** and **3** have been replaced with methyl group. RHF/6-31+G* and B3LYP/6-31+G* levels, in general, arrived at similar stable conformations for 1-hydroxybenzotriazole and its derivatives **1**−**13**. Most stable conformations predicted for **1**−**13**

SCHEME 1. Three Different Orientations of the N−OH Bond Considered for 1-Hydroxybenzotriazoles 1−13 Calculations



at B3LYP/6-31+G* levels and their conjugate bases are shown in Figure 2. In general, the **U**-type conformation (Scheme 1) was predicted to be the most stable conformation for 1-hydroxybenzotriazole, **1**, and its substituted derivatives **4**, **6**, **8**, **9**, **12**, and **13** by 0.3−0.6 kcal/mol in comparison to their corresponding **R**-type conformations. In these cases, **L**-type conformations have been found to be least stable. Interestingly, all three initial conformations for **2**, **3**, and **10** converged with the **U** type-conformations (Figure 2). In the case of **5**, **5L** and **5U** converged to the same conformation with intramolecular hydrogen bonding. These conformations have been found to be more stable than their corresponding **5R** conformation by 8.1 kcal/mol. A similar trend has been predicted for **7**. Conformations **7L** and **7U** have been found to be more stable than **7R** by 5.8 kcal/mol. **11L** is predicted to be a more stable conformation than the corresponding **11R** and **11U** conformations by 0.6 kcal/mol due to the favorable intramolecular hydrogen bonding. The preferred "**U**-type" orientation achieved by HOBt and their derivatives over **L**- and **R**-type structures is due to the lone-pair repulsions between the adjacent nitrogen and oxygen atoms. The −OH group orients perpendicular to the ring plane to minimize lone pair−lone pair repulsions, which otherwise would be larger in the other two forms.

The computed benzotriazole rings for **1**−**13** are predicted to be almost planar (torsional angle N1−N2−N3−C1) (Figure 2). Such planarity was also observed for triazole rings at the MP2/6-31+G* level.[11] The Hartree−Fock RHF/6-31+G* calculated bond lengths for **1**−**13** are generally shorter than the B3LYP/6-31+G* calculated bond lengths (Tables S2a and S2b, Supporting Information). However, the calculated internal bond angles and torsional angles are comparable at both levels of theory (Table S3a, S3b, and S4, Supporting Information). The influence of electron correlation on the structural parameters were also observed by Anders et al. while calculating the triazole ring systems.[11] The calculated bond lengths obtained for the triazole rings of benzotriazoles **1**−**13** at B3LYP/6-31+G* are found to be in good agreement with MP2/6-31+G*-calculated bond lengths for triazole rings reported by Anders et al. The only discrepancy observed was in the bond lengths of N_2-N_3. The bond lengths based on B3LYP/6-31+G* calculations are relatively shorter than the bond lengths obtained from MP2/6-31+G* calculations. It is interesting to note that the isolated (−N=N−) double bonds of the diazene is 1.26 Å, and B3LYP/6-31+G* as well as MP2/6-31+G* predict longer −N=N− bonds (1.30 and 1.34 Å, respectively) for benzotriazole and triazole rings than isolated diazene. A Cambridge-based crystallographic structural data search indicates that the N_2-N_3 bonds in triazole

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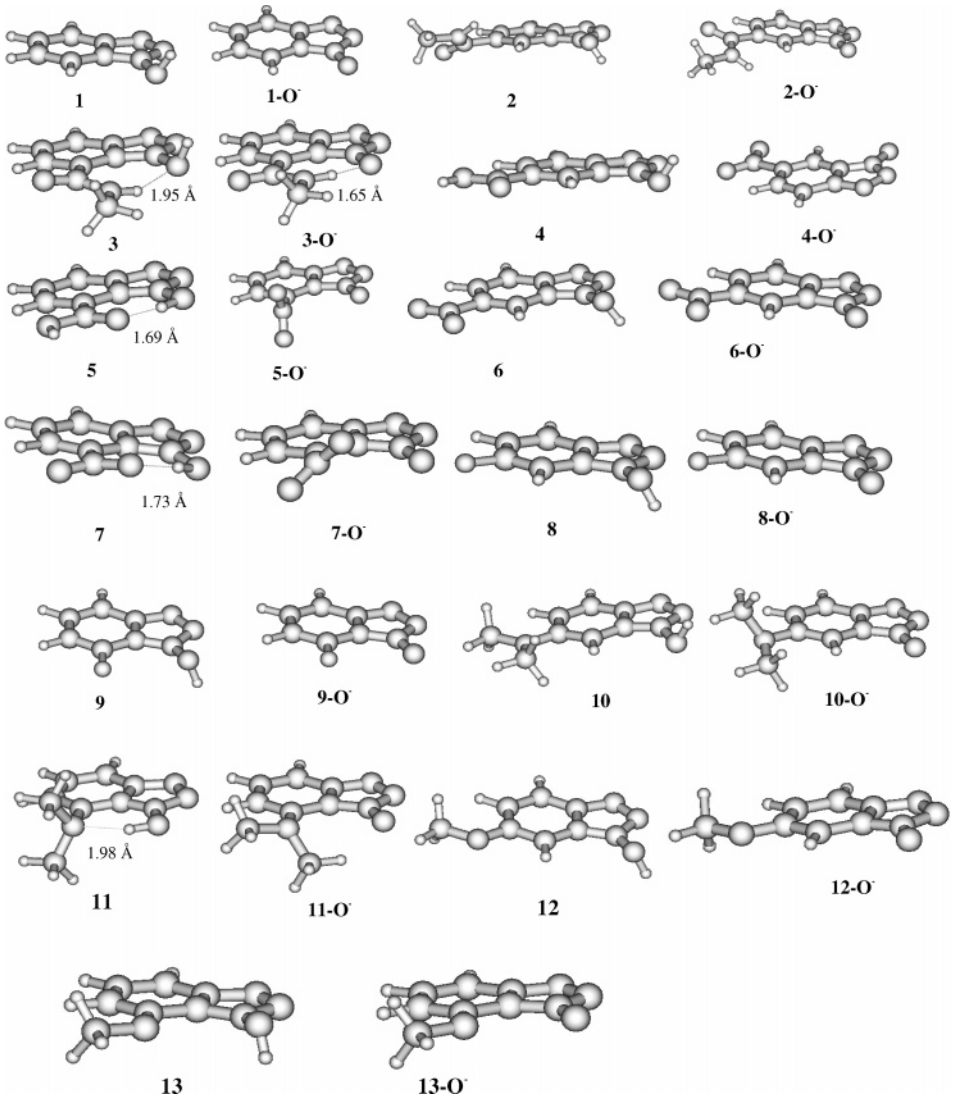

FIGURE 2. Most stable conformations for **1**−**13** and their conjugated bases at the B3LYP/6-31+G* level of theory. Hydrogen bonding distances are in Å.

moieties are 1.29−1.31 Å.[26] Therefore, the elongation of N_2-N_3 bond appears to be slightly longer at the MP2 level. The most significant changes are found for the $N-O^-$ bonds in the conjugate bases **1**−**13**, which are much shorter than the normal N−OH bonds (Tables S2a and S2b). Such shortening can arise from the influence of an anomeric effect, which originates due to the interaction of an oxygen (O_7^-) with a σ^* bond orbital of the N_1-C_2 ring bonds. The high-level ab initio calculations performed for the anomeric charged species have shown similar shortening in anomeric bonds.[27] The N_2-N_3 bonds are found to be elongated in conjugate bases **1**−**13** in comparison to their corresponding acids at both RHF/6-31+G* and B3LYP/6-31+G* levels of theory (Tables S2a and S2b). Such elongation of N_2-N_3 bonds in the conjugate base forms of **1**−**13** in comparison to N_2-N_3 bonds in the corresponding acids could be the result of electrostatic repulsions between N_1,N_3 centers. Natural charge analyses at B3LYP/6-31+G* levels suggest that the N_1,N_3 centers carry more negative charge in the conjugate bases than their corresponding acids.

The RHF/6-31+G* and B3LYP/6-31+G* calculated results show that the $-C(O)NHCH_3$ attached to 1-hydroxybenzotriazole ring at 4-position **2** deviates from planarity in the case of both the acid and its conjugate base due to the steric interaction between the amide N−H and the neighboring benzene hydrogen. Disrupted conjugation has been observed for the conjugate base **10** in which the *N*,*N*-dimethyl group deviates significantly from the ring planarity. However, its corresponding acid shows that the *N*,*N*-dimethyl group lie in the plane of the ring (Figure 2). Other substituents attached at 4-positions of the 1-hydroxybenzotriazole rings prefer to lie in the plane of the ring for extended conjugation. However, the orientation of the substitutents at the 3-position of 1-hydroxybenzotriazole rings in acids and their conjugate bases depend on the hydrogen bonding and repulsive electrostatic interactions with the neighboring N−OH group (Figure 2).

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TABLE 3. Calculated Free Energy of Protonation and pK_a Values for 1−13 at B3LYP/6-31+G* Levels

	free energy of protonation[a]	pK_a[b]
1	323.1	5.81
2	316.3	5.47
3	307.9	3.64
4	314.5	5.32
5	327.4	6.42
6	307.5	4.70
7	319.8	5.26
8	319.9	5.40
9	320.7	5.18
10	327.3	6.48
11	324.1	5.86
12	325.2	6.61
13	326.6	5.19

[a] Energies are in kcal/mole. [b] Calculated in water by using dielectric constant (∈) of the solvent 78.39.

Free Energy of Protonation. Free energy of protonation (fep) calculated for 1-hydroxybenzotriazole and its derivatives **1**−**13** (monoanionic forms) at the B3LYP/6-31+G* level is shown in Table 3. We have calculated the fep at the RHF/6-31+G* level also. Hartree−Fock-calculated feps are found to be relatively higher than the ones calculated using B3LYP (data not shown). However, the trends predicted with electron-withdrawing and electron-donating substituents of 1-hydroxybenzotriazoles are quite similar in both the cases. (The possibility of free energy of dideprotonation (i.e., via deprotonation of the carboxylic acid group to form dianion) was also examined for **4** and **5**, and the values were 711.2 and 730.0 kcal/mol for **4** and **5**, respectively. However, for direct comparison with **1** and other related systems **2**−**13**, we have only discussed monoanionic deprotonation in the text. The relative feps for dianionic forms for **4** and **5** follow a trend similar to that obtained for monoanionic forms).

In general, electron-withdrawing substituents show lower fep in comparison to parent 1-hydroxybenzotriazole, **1**, with an exception of **5**, which shows a relatively higher fep. Calculations at B3LYP/6-31+G* and RHF/6-31+G* levels show that the substituents attached at different positions in 1-hydroxybenzotriazoles have an influence on the fep. The predicted fep for **3** has been found to be ∼10 kcal/mol lower than the fep calculated for its regioisomer, **2**. Such a lowering in fep for **3** may be understood by examining the geometries of the acid and its conjugate base (Figure 2). The most stable form of **3** calculated at both levels of theory shows that the N−OH hydrogen is not involved in the intramolecular hydrogen bonding and hence is free for deprotonation. The O−H oxygen in this geometry, being an acceptor, facilitates the deprotonation of the −OH proton. Further, upon deprotonation, the conjugate base **3** should be stabilized due to the strong hydrogen bonding (N−H...$^-O_7$), and hence the fep of **3** would be expected to be lower than that of the regioisomer, **2**.

The calculated fep for **5** has been found to be the highest among the series of hydroxybenzotriazoles bearing electron-withdrawing groups, i.e., **2**−**9**. The calculated geometry suggests that the N−OH hydrogen in **5** is intramolecularly hydrogen bonded with the carboxyl oxygen, less available for deprotonation, and the corresponding conjugate base formed will be less stable due to the repulsive electrostatic interactions between N−O$^-$ and the neighboring carboxyl group, which will contribute to enhance the fep for **5** (Figure 2). Feps calculated for hydroxybenzotriazoles bearing electron-donating groups (*N*,*N*-dimethyl and methoxy groups) **10**−**13** are either comparable to the parent 1-hydroxybenzotriazole **1** or slightly higher than the latter (Table 3). Results of the fep calculations suggest that the deprotonation (N−OH → N−O$^-$) is more facilitated in the case of compounds with electron-withdrawing groups.

The experimentally determined pK_a values for **2**−**5** in miceller media show that the electron-withdrawing substituents on 1-hydroxybenzotriazoles have lower pK_a values than that of the parent 1-hydroxybenzotriazole, **1**. These data are in general in agreement with our calculated free energy of protonation (Table 3). However, calculating the pK_a for these 1-hydroxybenzotriazole systems would allow a better comparison with our experimentally observed results. Since the experimental results are not available for other 1-hydroxybenzotriazole derivatives **6**−**13**, it will be interesting to predict the pK_a for these systems, as it is an important factor for predicting the catalytic activities toward dephosphorylation or deacylation reactions in cationic micellar media. The trends projected from calculations will be useful for understanding the catalytic activity of theoretically examined systems **6**−**13**; in particular, the electron-donating-substituted 1-hydroxybenzotriazoles **10**−**13**.

Calculated pK_a. The prediction of absolute pK_a from first principle theory remains extraordinarily difficult, in part because of the difficulty in computing accurate gas-phase deprotonation free energies and also because of the large magnitude of solvent effects for charged species.[28] Typical accuracies in the computed quantities are rarely better than 2−5 kcal/mol, which results in absolute errors of possibly a few log units in pK_a, a disappointing result given the accuracy possible from experimental measurements (when such measurements can be made). Fortunately, trends in pK_a values for similar compounds suggest more accurate predictions,[28b,e−g,29] although rationalizing differences in some simple series, e.g., the methylated amines, continue to be challenging.[28,30] Efforts have been put forward to predict the absolute pK_a for systems of particular interest by developing new parameters and by fitting the computational results with experimental ones using linear regression analysis.[31]

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In this study, we compare the trends of pK_a calculated for 1-hydroxybenzotriazoles **1**−**13** using the thermodynamic cycle mentioned in the computational methodology section. We wanted to compare computed pK_a values of **1**−**5** with our experimental pK_a results for these compounds in micellar solutions. We also sought to examine the pK_a for those systems (**6**−**13**), which could not be studied experimentally. This is because several of these are difficult to synthesize and, when feasible, may be prepared only in very poor yields.[32] Therefore, we directed our efforts in the direction of comparing trends observed from calculations even if it was not possible to examine the absolute pK_a for **6**−**13**. Polarizable continuum model (PCM) as a solvation model has been used to calculate the free energy of hydration. Most theoretical approaches differ concerning solvation treatment in calculating pK_a. Several solvation models exist, each having its strengths and weaknesses. Some of the discrete solvation methods used in pK_a calculations include free energy perturbation simulations in explicit water[33] and the Langevin dipole method.[34] On the other hand, the commonly used continuum models are based on the Born model,[35] the Poisson−Boltzmann (PB) equation,[31a,c] and various implementations of the polarizable continuum model (PCM).[36,28f] The advantage of continuum models over discrete methods is that the solvent reaction field may be incorporated into the quantum mechanical Hamiltonian, and thus an accurate description of the solvated solute may be achieved.

The computed pK_a values for **1**−**13** at the B3LYP/6-31+G* level are shown in Table 3. Examining the pK_a values for **1**−**5**, it appears that the calculated values are in general shifted ∼1 unit lower than the experimentally observed values (Table 1). The 1-hydroxybenzotriazoles **2**−**9** with electron-withdrawing substituents show lower pK_a values than the parent 1-hydroxybenzotriazole, in agreement with the available experimental observations. The apparent discrepancy in the calculated pK_a shifts for **3** and **5** may be due to the fact that, in aqueous solution, intervening water molecules will attenuate the intramolecular hydrogen bonding in the gas-phase structures. Thus, the conformations predicted in the gas phase may not be the same in the solution, and hence the calculated pK_a values differ significantly from the experimentally determined values. The conformational effects on pK_a have been observed in several other cases.[37] Further, it should be noted that the experimental pK_a values were obtained in water (miceller) media, and hence the compared experimental and calculated pK_a values are not derived under similar reaction conditions. Comparing the calculated pK_a for the hydroxybenzotriazoles bearing electron-donating groups, **10**−**12**, it appears that the pK_a values are generally higher than for the parent system, **1**, although the calculated pK_a shows a lower value for compound **13** (Table 3). The calculated and observed pK_a data suggest that the 1-hydroxybenzotriazoles bearing electron-withdrawing substituents can facilitate the formation of ionized N−O^- species. This in turn can help the acceleration of the hydrolysis rates of PNPDPP and PNPH in comparison to **1**. However, the nucleophilicity of the conjugate bases is another important factor, which contributes significantly to determining the catalytic strengths of these compounds.

TABLE 4. Calculated Natural Charges on O_7 for Conjugate Base (1−13) at B3LYP/6-31+G* Level

Conjugate base	B3LYP/6-31+G*
1−O^-	−0.647
2−O^-	−0.629
3−O^-	−0.644
4−O^-	−0.609[a] (−0.675)[b]
5−O^-	−0.615[a] (−0.626)[b]
6−O^-	−0.585
7−O^-	−0.592
8−O^-	−0.647
9−O^-	−0.623
10−O^-	−0.652
11−O^-	−0.643
12−O^-	−0.652
13−O^-	−0.626

[a] Charge on the Oxido atom of carboxylic acid form. [b] Charge on Oxido atom of di-deprotonated (carboxylated) form.

Natural Charges Calculated for Oxido Atoms (O_7). Since N−O^- is the nucleophile in the hydrolytic reactions of PNPDPP and PNPH, the charge on the oxido atom (O_7) will give an idea of nucleophilicity of these conjugate bases (for the numbering of the atoms see Chart 2). To ascertain the relative charges on the oxido atom (O_7) for **1**−**13**, natural population analysis was performed. Relative natural charges calculated at the B3LYP/6-31+G* level for the conjugate bases of **1**−**13** on the oxido atoms are shown (Table 4). Natural charges obtained from the NBO calculations show that the oxido atom (O_7) carries comparable or slightly less charge for electron-withdrawing-substituted 1-hydroxybenzotriazoles **2**−**9** than the parent molecule **1** (−0.647). Therefore, the relative nucleophilicity should not be significantly different from **1** in these cases. However, the available experimental kinetic data for **1**−**5** indicate that molecule **4** has considerably better catalytic activity than that of other molecules studied (Table 1). Since **4** and **5** possessed a −CO_2H group, one might expect that the carboxylic O−H residue must also get deprotonated at pH 8.2 in cationic micellar solution and can influence the overall distribution of electrons within the molecule. The dideprotonated form of **4** and **5** will also help to associate with cationic micellar interfaces more tightly, making them effective catalysts. Therefore, we considered the dideprotonated form of **4** and **5** for the calculations and compared the computed N−O^- oxygen charges. The relative oxido charge calculated at B3LYP/6-31+G* for the dideprotonated form of **4** (−0.675) was found to be larger than that for the monodeprotonated form (−0.609) and apparently higher in the series. However, such enhancement in the charge of the oxido atom for dideprotonated form **5** (−0.626) was not observed (Table 4). The

(32) Indeed, we attempted to synthesize the alkoxy derivatives of 1-hydroxybenzotriazole in our laboratory. However, the yields of these compounds were extremely poor (<1−2%) and the literature procedures were not found to be reproducible in our hands.

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experimental kinetic data support this result that **5** has lower catalytic activity than its regioisomeric form **4**.

The natural charges calculated for the hydroxybenzotriazoles with electron-donating groups **10**−**13** do not show any significant enhancement of charges on the oxido atom (O_7) in comparison to the parent system **1** (Table 4). The B3LYP/6-31+G* level-calculated natural charges on oxido atom in conjugate bases of **1**, **10**, **11**, **12**, and **13** are −0.647, −0.652, −0.643, −0.652, and −0.626, respectively. Therefore, the predicted rates of hydrolytic cleavage reactions of PNPDPP and PNPH seem to be comparable or slightly higher with the electron-donating groups.

By examining the electronic structure, pK_a values, fep, and the nucleophilicity of reactive N−O$^-$ oxido atoms, the ab initio/DFT results provide a rationale for understanding the catalytic potential of 1-hydroxybenzotriazole derivatives as nucleophiles in the hydrolytic cleavage reactions of PNPDPP and PNPH. The available experimental results show that compound **4** has greater catalytic activity in the series studied herein. The calculated results predict lower fep and pK_a values for **4** than for the parent system **1**, in agreement with our experimental observations. The natural charge calculated for the oxido atom (O_7) in the dideprotonated form of **4** supports the above kinetic experimental data and explains why it is more nucleophilic than other derivatives examined in this study. Furthermore, the calculated results predict that the incorporation of electron-donating substituents on to 1-hydroxybenzotriazole (**10**−**13**) would not enhance the catalytic activity significantly. Since the present methods of synthesis of compounds such as **10** or **12** are inefficient in view of their very low yield, the calculated results may be used to predict their catalytic effectiveness. However, as the predicted nucleophilicity values of N−O$^-$ are not enhanced appreciably, the present investigation strongly suggests that undertaking alternative or elaborative synthetic routes to compounds such as **10**−**13** may not be practical.

The theoretical work presented herein is important, and it is possible to isolate the factors that affect deprotonation and reactivity in water. Whether these conclusions are directly applicable to reactions in cationic micelles is, however, another question. It is possible that the rate differences in Table 1, for example, could be due to transfer effects and not inherent reactivities. While the hydrophobic substrate esters should be completely in the micelles, this is probably not so for all the hydroxybenzotriazoles. The relatively small effect on introduction of the tetradecyl group suggests that here transfer effects are not large, but nor are the rate effects in Table 1. Therefore, the experimental conclusions may be qualitative.

Conclusion

To examine the catalytic acitivity of a series of 1-hydroxybenzotriazoles, **1**−**13**, bearing electron-withdrawing and electron-donating substituents for the hydrolytic cleavages of PNPDPP and PNPH, a detailed computational study has been performed at ab initio and hybrid-DFT levels of theory. Most stable conformations of **1**−**13** and their conjugate bases have been predicted. The calculated geometries on the basis of B3LYP/6-31+G* were found to be in good agreement with the earlier calculations by Anders et al.[11] and the available crystal structure results.[11] The fep and pK_a values calculated for hydroxybenzotriazoles bearing electron-withdrawing groups were generally found to be lower than for the parent 1-hydroxybenzotriazole, **1**. However, the corresponding compounds with electron-donating groups show higher fep and pK_a. The experimentally measured pK_a values for **2**−**5** show that the electron-withdrawing groups lower the pK_a in comparison to **1**. This is in agreement with our calculated results. The natural charge calculated at the B3LYP/6-31+G* level for the oxido atom of N−O$^-$ for **2**−**5** shows that the monoanionic forms carry comparable or slightly less charge than the N−O$^-$ of **1**. However, the natural charge calculated for the dideprotonated form of **4** on N−O$^-$ is higher in the series and supports the experimental observation that **4** is a better catalyst for the hydrolytic cleavages of PNPDPP and PNPH. Fep and pK_a values were predicted to be higher, in general, for the hydroxybenzotriazoles having electron-donating substituents in comparison to the parent system **1**. This suggests that the deprotonation will be less facile in these cases. Comparing the natural charge calculated on the oxido atom (O_7) for electron-donating **10**−**13**, it appears that they are comparable to the charge calculated for the oxido atom of N−O$^-$ in **1**. This in turn predicts that the incorporation of electron-donating substituents into 1-hydroxybenzotriazole may provide similar or slightly better catalytic strength in them in comparison to **1**. Herein we have made available a substantial amount of data, viz., energies, geometrical parameters, and properties such as fep, pK_a, charges on the nucleophilic species. The full discussion of such a large body of information is too space demanding. However, we believe that these will be useful for many research groups.

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Supporting Information Available: Synthetic scheme of **2**−**5** and characterization of compounds, geometry parameters (bond lengths, bond angles, and torsion angles) of **1**−**13** and their conjugate bases, total energies of **1**−**13** and their conjugate bases, Cartesian coordinates of fullly optimized geometries of **1**−**13** and their conjugate bases, and kinetic and thermodynamic parameters for the cleavage of PNPDPP by **1**−**5** with CTABr micelles. This material is available free of charge via the Internet at http://pubs.acs.org.

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