CROATICA CHEMICA ACTA
CCACAA, ISSN 0011-1643, e-ISSN 1334-417X
Croat. Chem. Acta **87** (4) (2014) 423–430.
http://dx.doi.org/10.5562/cca2487

Original Scientific Article

The Utility of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as a Hydrogen Bond Acceptor in the Design of Novel Superbasic Guanidines – A Computational Study†

Vjekoslav Štrukil,* Ivana Antol, and Zoran Glasovac*

Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička cesta 54, 10000 Zagreb, Croatia

RECEIVED JUNE 4, 2014; REVISED AUGUST 26, 2014; ACCEPTED SEPTEMBER 5, 2014

Abstract. New guanidine-derived superbases with **TBD**-functionalized alkyl side chains have been developed using a computational DFT approach. Exploiting the high hydrogen bond basicity of **TBD** allowed access to systems with strong charge-assisted intramolecular hydrogen bonds in the protonated state. The enhanced stability of such guanidines is mirrored in their gas-phase basicities, which cover the range from 1044−1168 kJ mol^{-1}, depending on the number of alkyl side chains, the type of alkyl spacer and the hydrogen-bonding pattern.

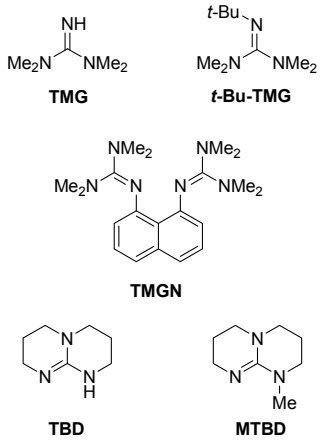
Keywords: guanidine, TBD, organic superbases, DFT, intramolecular hydrogen bond

INTRODUCTION

The past two decades have witnessed a growing interest in naturally occuring and synthetic guanidines.[1] The ubiquity of guanidine functionality in biological systems has guided research in bioorganic chemisty towards discovery and design of pharmacologically active guanidine compounds.[2] On the other hand, the symmetry of the guanidinium cation and its potential to form hydrogen bonds have been exploited in crystal engineering,[3a] supramolecular chemistry[3b] and especially organocatalysis.[4] Also, a number of guanidine derivatives, that are utilized as neutral organic superbases, are commercially available in the market (Scheme 1).

Among them, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (**TBD**) and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (**MTBD**) are frequently selected as base catalysts to promote Knovenagel,[5a] and Henry reactions,[5b] Michael addition,[5c] Wittig reaction,[5d] transesterification of vegetable oils[5e] etc. While **TBD** and **MTBD** are non chiral, the bicyclic scaffold can be functionalized to introduce chirality affording superbasic asymmetric catalysts.[6] In general, the catalytic activity of bicyclic guanidines originates from their ability to form strong hydrogen bonds in the protonated state with acceptor molecules. As such, a combination of their high basicity and directionality of hydrogen bonds makes **TBD** a suitable template for the development of novel organosuperbases.

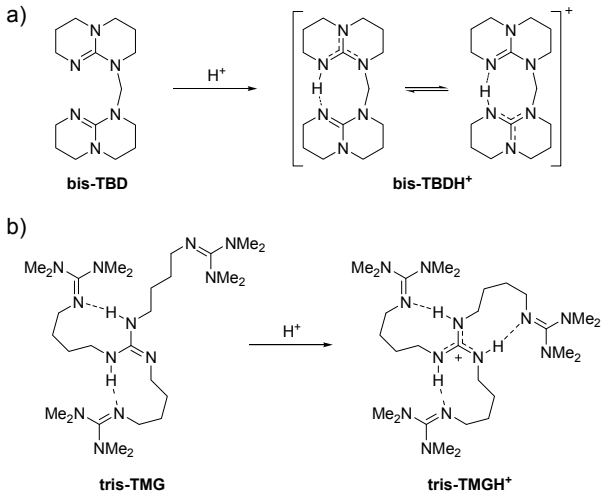
Recently, Coles *et al*. described the synthesis and basicity of bis(**TBD**)methane (bis-**TBD**, Scheme 2a).[7] The calculated proton affinity (PA) of 1132.2 kJ mol^{-1} and the measured pK_a value of 29.0 in acetonitrile reflect the cooperative effect between the two **TBD** units where the protonation of one unit induces a partial protonation in the second one through a strong intramolecular hydrogen bond (IMHB). The proton shuttles back and forth between the protonation sites in an almost barrierless process as evidenced by solid state CP-MAS ^{15}N NMR measurements and theoretical calculations.[7]



Scheme 1. Commercially available guanidine superbases.

† Dedicated to Dr. Mirjana Eckert-Maksić on the occasion of her 70th birthday.

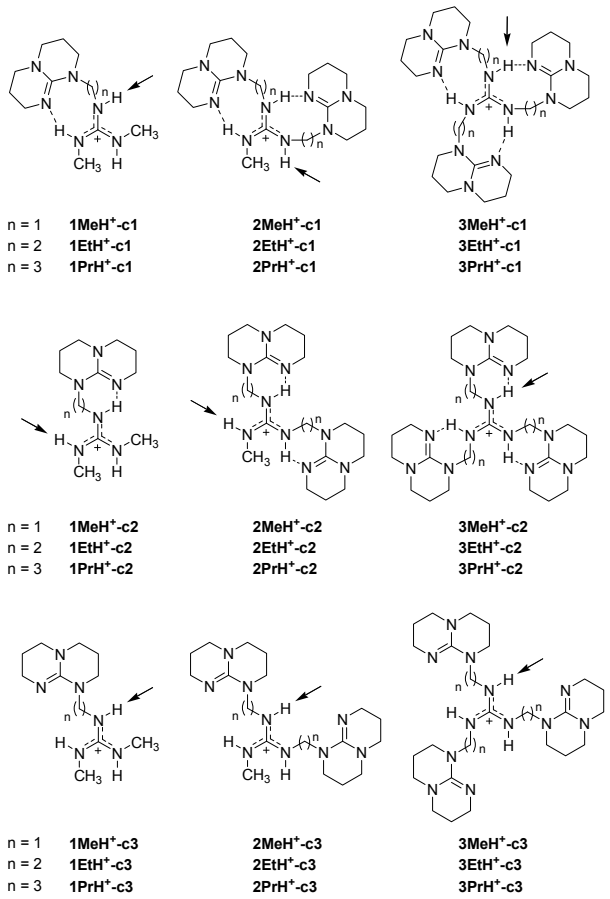
* Author to whom correspondence should be addressed. (E-mail: Vjekoslav.Strukil@irb.hr, Zoran.Glasovac@irb.hr)



Scheme 2. (a) bis-**TBD** molecule designed by Coles *et al*.[7] (b) Superbasic tris-**TMG** designed by Baric *et al*.[8]

In a paper by Barić *et al*.,[8] a series of superbasic heteroalkyl-substituted guanidines based on IMHB were modelled *in silico*. While the highest proton affinity (1227.2 kJ mol^{-1}) was achieved with phosphorus-containing (e.g. phosphazene) termini as IMHB acceptors in the side chains, tetramethylguanidinyl terminus in tris-**TMG** (Scheme 2b) also significantly increased the gas-phase basicity of the central guanidine subunit relative to its unfolded conformation. A combined effect of high intrinsic gas-phase basicity of alkyl-tetramethylguanidine and its pronounced propensity to form hydrogen bonds resulted in PA(tris-**TMG**) value of 1197.5 kJ mol^{-1} and the estimated pK_a 29.5 in MeCN.

High basicity of tris-**TMG** can be rationalised through hydrogen bond basicity expressed by the pK_{HB} value[9] (pK_{HB} = negative logarithm of the hydrogen bond association constant). For pentamethylguanidine (**PMG**), which is structurally equivalent to the alkyl-tetramethylguanidine fragment in tris-**TMG**, pK_{HB} amounts 3.16. Such high pK_{HB} value indicates strong internal solvation upon intramolecular hydrogen bond (IMHB) formation, particularly of the conjugate acid, and therefore a large increase in basicity with respect to the system without IMHB. The corresponding pK_{HB} value for **MTBD** is 3.48, indicating even stronger tendency for this compound to act as a hydrogen-bond acceptor with respet to **PMG**. Bearing this in mind, we continue our research on guanidine superbases[10] containing substituents capable of forming IMHB by reporting the design and computational investigation of a series of new tris-alkyl substituted guanidines **1**–**3** (Scheme 3). **TBD** molecules, which play the role of strong hydrogen bond acceptors as suggested by the high pK_{HB} value of **MTBD**, are appended at the termini of the side chains. Our main aim was to model a series



Scheme 3. Schematic representations of different conformations of alkyl-**TBD** substituted guanidines **1**–**3**. **c1** – intramolecular 1,3-hydrogen bonding, **c2** – intramolecular 1,1-hydrogen bonding, **c3** – unfolded forms (no intramolecular hydrogen bonds). The deprotonation sites are marked with an arrow.

of novel bases that will (a) approach the upper limit of the basicity scale and (b) to fill the region of GBs from 255 to 270 kcal mol^{-1} to increase the number of reference bases for future gas-phase measurements. This was achieved by varying the number and length of alkyl-substituents attached to the guanidine moiety using methylene (Me, n = 1), ethylene (Et, n = 2) and propylene (Pr, n = 3) spacers. The gas-phase basicities (GBs), pK_a in acetonitrile and the relative stabilities of 1,3- (**c1**) and 1,1- (**c2**) hydrogen-bonded structures, as well as the unfolded ones (**c3**), were estimated by DFT approach. Since **TBD** and the central guanidine subunit are of similar basicity, the preferred protonation site in **1**–**3** depends on the appropriate molecular conformation and the spacer length. In this paper we show for the first time that the actual protonation position can be tuned by intramolecular hydrogen bonding. Such a systematic approach enabled us to design the most basic phosphorus-free all-guanidine superbase **3Et-c2**, gas-

phase basicity of which is estimated to 1168 kJ mol^{-1} (PA = 1205.0 kJ mol^{-1}) and with pK_a as high as 33 pK_a units.

COMPUTATIONAL DETAILS

The geometry optimizations were carried out using the Gaussian09 suite of programs[11] employing the density functional theory hybrid functional B3LYP[12–15] in conjunction with the 6-31G(d) basis set. The minima on the Born-Oppenheimer potential energy surface were confirmed to be true minima by vibrational analyses. The resulting frequencies were also used to calculate zero-point energies, thermal corrections for enthalpies and entropies without any scaling or corrections for internal or hindered rotations. Refinement of the electronic energies was carried out by a single point calculations at B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) level of theory. Solvation energies in acetonitrile were calculated using IEFPCM/HF/6-31G(d)//B3LYP/ 6-31G(d) and IPCM/6-311+G(d,p)//B3LYP/6-31G(d) levels of theory which have been succesfully employed previously for similar types of bases.[10e,16] pK_a values were obtained using linear relationship between pK_a and $\Delta G^*(BH^+)_{a,sol}$ as described previously.[16] Geometries of the optimized structures were generated and visualized by MOLDEN 5.0.[17] All relative stabilities are expressed as the relative Gibbs energies. Both relative Gibbs energies and the gas-phase basicities are given in kJ mol^{-1}.

RESULTS AND DISCUSSION

In order to identify the most stable minima, three conformations of the neutral and protonated forms of trisubstituted guanidines **1**–**3** were optimized (Scheme 3). Conformation **c1** corresponds to 1,3-hydrogen bonding motif between the donor nitrogen atom in the substituent and the proton on the neighbouring nitrogen atom of the central guanidine subunit. This motif was found in the crystal structure of *N,N',N''-tris*-(3-dimethylaminopropyl)guanidinium hexafluorophosphate[18] and was also predicted to be the most stable in the 2-(2-pyridyl)ethyl substituted guanidine derivatives.[19] Next, the 1,1-hydrogen bonding motif, present in **c2** conformation, results from IMHB between the **TBD**-imino nitrogen atom and the proton located at the same nitrogen atom where the alkyl-**TBD** substituent is attached. Finally, the unfolded conformation **c3**, without any IMHB, was considered as well. Additionally, for each conjugate acid the structures protonated at the central guanidine and the **TBD** moiety were optimized.

The geometry optimization of the unfolded structures with methylene spacer proved to be a problematic case. The fully optimized minimum on the potential energy surface was found only in the case of neutral **1Me-c3** base. Attempts to fully optimize the geometries of its protonated form as well as of higher derivatives **2Me-c3** and **3Me-c3**, led to the formation of hydrogen bonded structures. On the other hand, the geometry optimization of the unfolded structures with ethylene and propylene spacers were successfully conducted.

Relative Stabilities

In the first part of the discussion we shall compare the relative stabilities of the conformers of neutral and protonated forms separately. In all cases, the 1,3-conformers were taken as a reference since this conformation has been previously found in a structurally similar compound.[18] The relative stabilities of all these structures are given in Table 1.

The values were found to depend on the spacer length. Thus, for methylene spacer, the 1,3-conformer is preferred for both neutral and protonated forms, while in the case of propylene spacer the 1,1-conformers were found to be the most stable structures. With an ethylene spacer, the neutral and protonated forms show different preference for intramolecular hydrogen bonding. Whereas the formation of a larger ring (1,3-hydrogen bonding) is energetically favourable in neutral bases, the 1,1-hydrogen bonding motif is preferred in their conjugate acids, irrespectively of the protonation site. The calculated relative stabilities of these isomers also show that the unfolded structures are not the most stable structures in neither of considered three isomers although our calculations predict that for the propylene derivatives, unfolded structures of the neutral bases are more stable than the "1,3" conformers.

Gas-phase Basicity

Although different conformers of the neutral and protonated species proved to be the lowest energy minima, the gas-phase basicities were calculated using the neutral base and its conjugate acid in the same conformation. The results obtained in this way provide an insight into dependence of the basicity on the size of the ring formed upon closure of IMHB. The GB values of all considered conformers for compounds **1**–**3** are compared in Table 2. The modelled **3Et-c2** and **3Pr-c1** guanidines, with their GB values above 1155 kJ mol^{-1} belong to the most basic neutral non-phosphorus all-guanidine bases and their gas-phase basicity is comparable to recently published bis-imidazolydene guanidine derivatives[20] and aforementioned bis-**TBD**.[7] Together with the analogues bearing 4-dimethylaminopyridine[21] or **TMG** subunit,[8] our compounds approach the region of the GB values where a spontaneous proton transfer from superacids[22] could be

Table 1. The relative stabilities of different conformers (**c1**, **c2** and **c3**) for mono- (**1**), bis- (**2**) and tris- (**3**) **TBD**-substituted guanidines in their neutral and protonated states depending on the spacer length (Me, Et and Pr)

	G_{rel} / kJ mol^{-1}								
	Me, n = 1			Et, n = 2			Pr, n = 3		
	neut	p1[(a)]	p2[(a)]	neut	p1	p2	neut	p1	p2
1									
c1	0.0	0.0	−9.1	0.0	0.0	−10.1	0.0	0.0	−9.2
c2	3.4	33.4	−0.4	0.6	−3.3	−18.3	−11.4	−0.9	−12.6
c3	-	-	-	4.2	35.0	10.7	−6.5	35.7	15.4
2									
c1	0.0	0.0	0.6	0.0	0.0	15.1	0.0	0.0	15.4
c2	16.3	50.6	40.2	3.7	−3.1	3.3	−19.9	−12.0	−2.9
c3	-	-	-	14.0	65.4	55.3	−18.7	44.3	39.1
3									
c1	0.0	0.0	18.4	0.0	0.0	21.1	0.0	0.0	31.5
c2	11.6	68.1	63.0	7.7	−4.0	15.0	−25.9	−22.7	−1.8
c3	-	-	-	19.5	82.6	66.3	−23.3	50.9	58.5

[(a)] p1 and p2 relate to the protonation at imino nitrogen atom of the central guanidine or **TBD** subunit, respectively.

Table 2. The gas phase basicities of **c1**, **c2** and **c3** conformers for mono- (**1**), bis- (**2**) and tris- (**3**) **TBD**-substituted guanidines depending on the spacer length (Me, Et and Pr)

	$GB_{gu}(B)$[(a)] / kJ mol^{-1}			$GB_{TBD}(B)$[(a)] / kJ mol^{-1}			$\Delta GB(B)$[(b)] / kJ mol^{-1}		
B	Me	Et	Pr	Me	Et	Pr	Me	Et	Pr
1									
c1	1074	1074	1084	1083	1084	1093	9	10	9
c2	1044	1078	1073	1078	1093	1085	34	15	12
c3	(-)	1043	1041	(-)	1068	1062	(-)	25	21
2									
c1	1110	1121	1128	1110	1106	1112	0	−15	−16
c2	1076	1128	1120	1086	1121	1111	10	−7	−9
c3	(-)	1069	1065	(-)	1079	1070	(-)	10	5
3									
c1	1158	1156	1157	1140	1135	1126	−18	−21	−31
c2	1102	1168	1155	1107	1149	1135	5	−19	−20
c3	(-)	1093	1085	(-)	1088	1077	(-)	−5	−8

[(a)] GB_{gu} and GB_{TBD} relate to the gas-phase basicity of the imino nitrogen atom located in the central guanidine and **TBD** subunits, respectively.
[(b)] $\Delta GB(B) = GB_{TBD}(B) - GB_{gu}(B)$

achieved. Additionally, bis-substituted derivatives **2** fall in the borderline region of the currently measured GBs for organic bases and are desirable for future extension of the experimental GB scale.

However, in the protonated forms of **1**–**3** we observed a competition between the two basic imino nitrogen atoms: one located in the central guanidine subunit and the second one in **TBD** moiety, as shown in Figure 1. We decided to explore how protonation at these basic sites depends on the structure of the base with particular emphasis on the influence of the spacer length which determines the ring size formed by IMHB.

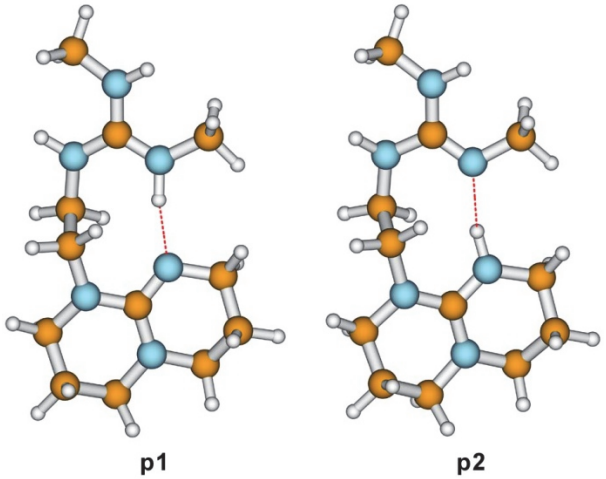
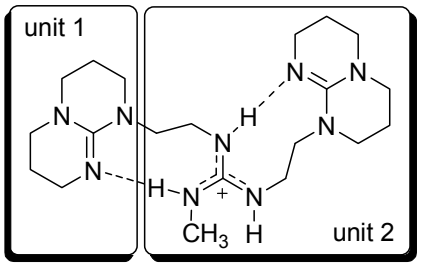


Figure 1. Protonation of the central guanidine imino nitrogen atom (**p1**) and the **TBD**-imino nitrogen atom (**p2**) in 1EtH$^+$-**c1**.

As expected, the calculated gas-phase basicities of the hydrogen bonded conformers are significantly higher than of the unfolded ones. The formation of IMHB in mono-**TBD**-substituted derivatives **1** leads to an increase in GBs of both basic sites by 16−43 kJ mol^{-1} depending on the conformation and the protonation site (**p1** or **p2**). Generally, the effect is more pronounced for the central guanidine subunit than for the **TBD** part of the molecule although the **TBD** imino nitrogen atom remains to be the most basic position (Tables 1 and 2). The GBs become more strongly affected by introducing the second and the third substituent capable of forming IMHB. The increase in GBs with respect to **c3** conformers is in the range 27−63 kJ mol^{-1} and 47−75 kJ mol^{-1} for **2** and **3** derivatives, respectively. Also, the preferred protonation site in **2** and **3** series is changed in comparison with the basicity trend in **1**. For example, on going from **1Et-c1** to **2Et-c1** conformer, the increase in GB_{gu} amounts 47 kJ mol^{-1}, while GB_{TBD} rises by 22 kJ mol^{-1}. These changes are sufficient to make the guanidine imino nitrogen atom the most basic position in the molecule. This could be rationalized by dividing **2EtH$^+$-c1** structure into two fragments separated by the ethyl spacer (Scheme 4).

The first fragment is **TBD** (unit 1) while the second fragment is guanidine containing one hydrogen-bonded **TBD**-substituent (unit 2). The latter fragment has the same structure as compound **1** and, if considered separately, unit 2 is more basic than **TBD** alone. Therefore, the switch in the preferred protonation site for hydrogen bonded structures on going from **1** to **2** series is not surprising.

The length of the spacer also affects the order of GBs for the two hydrogen bonded conformers. Comparison of the relative energies of **c1** and **c2** conformers with ethylene spacer shows that higher GB



Scheme 4. The structure of 2EtH$^+$-**c1** divided into **TBD** part (unit 1) and mono-**TBD**-substituted guanidine fragment (unit 2).

of the 1,1-hydrogen-bonded structure **c2** is a consequence of two effects: destabilization of the neutral form and stabilization of the protonated form with respect to the 1,3-conformer (Table 1). However, this is not the case in **c1** and **c2** conformers with a propyl spacer where **c2** is more stable, whether neutral or protonated structures are compared. Consequently, GB values of these two conformers are very similar. It is interesting to note that the switch from ethyl to propyl slightly attenuated the basicity what could be ascribed to the larger change in G_{rel} for neutral molecules than for the protonated structures upon spacer elongation.

Estimation of the GB for 1Pr and 3Pr Derivatives

Recently, we have found that the calculated GBs correlate well with combination of pK_{HB} and σ^{4B} parameters indicating possible usage of pK_{HB} as a general experimental descriptor of the molecular properties for the systems with intramolecular hydrogen bonds in their structure.[21] This could be beneficial for further improvement of quantitive structure/property relationship (QSPR) approaches. The equations obtained for a series of *N'*-substituted *N,N''*-dimethylguanidines and *N,N',N''-tris*-substituted guanidines (n = 17), structurally analogous to series **1** and **3**, are

$$GB_{est}(\mathbf{1}) = 8.02 \times pK_{HB} + 1.00 \times \sigma^{4B} + 1039.6 \quad (R^2 = 0.975) \tag{1}$$

$$GB_{est}(\mathbf{3}) = 24.24 \times pK_{HB} + 1.99 \times \sigma^{4B} + 1063.0 \quad (R^2 = 0.956) \tag{2}$$

where σ^{4B} is the difference in Gibbs energies between the unfolded conformer of the base in question and *N'*-propyl-*N,N''*-dimethylguanidine (Eq. 1) or *N,N',N''*-tripropylguanidine (Eq. 2). pK_{HB} is a tabulated value[9] characteristic for the hydrogen bond accepting group - **TBD** in our case. For **1Pr** the estimated GB amounts 1085 kJ mol^{-1} what is in an excellent agreement with

the directly calculated GB value of **c1** conformer (1084 kJ mol^{-1}, Table 2). For **3Pr**, GB_{est} amounts 1182 kJ mol^{-1} and it deviates from the calculated GB by 25 kJ mol^{-1} (Table 2). It has been shown earlier that r^2 value for Eq. 2 is significantly lower than for Eq. 1 and these new results confirm the necessity for its improvement.

Unfolded Derivatives

The preferential protonation at the **TBD** unit was also found in the unfolded conformer **c3** of **1** and **2** series. The effect of substituent replacement can be assessed in the same way as for the hydrogen bonded conformers **c1** and **c2**. In the case of **1Et-c3**, the increase in basicity of 27 and 30 kJ mol^{-1} was achieved for guanidine and **TBD** moieties, if compared with the GB values of isolated *N,N',N''*-trimethylguanidine (1016 kJ mol^{-1}) and **MTBD** (1038 kJ mol^{-1}).[19] These values could also be considered as a result of the replacement of one methyl group located on trimethylguanidine or **MTBD** with either **TBD**-ethyl or dimethylguanidine-ethyl subunit, respectively. The replacement of the second and third methyl groups located at the guanidine moiety with **TBD**-ethyl groups enhances the basicity of the guanidine part by 26 and 24 kJ mol^{-1}, respectively, while the basicity of the **TBD** subunit rises by ca 10 kJ mol^{-1} per additional **TBD**-ethyl substituent added. It appears that the step-by-step substituent change increases GB_{gu} in approximately additive manner.

On the other hand, the introduction of the second and third substituent contributes to the GB_{TBD} significantly lower than the first one. This is expected since the three-fold structural change occurs quite apart from the **TBD** subunit. Slightly smaller changes leading to the same general trend were also found for structures with the propyl spacer. Although the effect of the substituent change on the GB_{gu} is almost two-fold lower than in hydrogen bonded conformers, it is still large enough to change the preferential protonation site, but only when three alkyl-**TBD** groups are attached to the central guanidine moiety.

Basicity in Acetonitrile

To investigate the potential usage of **TBD**-containing guanidine derivatives as bases or basic catalysts we calculated their pK_a values in acetonitrile. For this purpose, only the most stable conformers of neutral or protonated form of each base were considered. More precisely, in the case of methylene and propylene spacers, **c1** and **c3** conformations of base and its conjugated acid were used. Only in the case of ethylene spacer (n = 2) **c1** conformation was taken for neutral and **c2** conformation for protonated form. For **1Me**–**1Pr** series, protonation on the **TBD** subunit was assumed

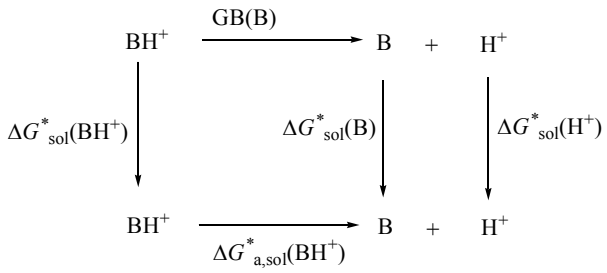


Figure 2. Thermodynamic cycle used for calculation of the solution phase Gibbs energy of deprotonation ($\Delta G^*_{a,sol}(\mathbf{BH}^+)$) of the bases investigated in this work.

while for other two series, protonation at the central guanidine moiety was found to be the most probable. Additionally, pK_a of bis-**TBDH**$^+$ and tris-**DMAPAH**$^+$ (tris-**DMAPAH**$^+$ = *N,N',N''-tris-(*3 di-methylaminopropyl)guanidinium cation) was also calculated at the same level of theory and compared with compounds studied in this work.

In pK_a calculation, a thermodynamic cycle was used as described previously[23] (Figure 2) which draws the relation between the gas-phase basicity of base **B** and the Gibbs energy of deprotonation of its conjugate acid **BH**$^+$ [$\Delta(G^*_{a,sol}(\mathbf{BH}^+)$].

Absolute pK_a(**BH**$^+$) in solution is calculated using Eq. 3:

$$\mathrm{p}K_a(\mathbf{BH}^+) = \frac{\Delta G^*_{a,sol}\left(\mathbf{BH}^+\right)}{2.303 \times RT} \tag{3}$$

or, after several simple mathematical operations described in Ref. 16:

$$\mathrm{p}K_a\left(\mathbf{BH}^+\right) = a \times \left(\Delta G'_{a,sol}\left(\mathbf{BH}^+\right)\right) + b \tag{4}$$

where

$$\begin{aligned}\Delta G'_{a,sol}\left(\mathbf{BH}^+\right) = {} & G^\circ_{gas}\left(\mathbf{B}\right) - G^\circ_{gas}\left(\mathbf{BH}^+\right) \\ & + \Delta G^\circ_{sol}\left(\mathbf{B}\right) - \Delta G^\circ_{sol}\left(\mathbf{BH}^+\right)\end{aligned} \tag{5}$$

while paramers a and b were obtained from the linear regression between the experimentally measured pK_a's and calculated $\Delta G'_{a,sol}(\mathbf{BH}^+)$ for a set of 57 various nitrogen bases. In this way, $G_{sol}(H^+)$ needs not to be known as it is hidden in the intercept of linear function given in Eq. 4. The results are listed in Table 3.

Calculated pK_a's for bis-**TBDH**$^+$ and tris-**DMAPAH**$^+$ derivatives as reference compounds indicate that the approach using IPCM solvation model

Table 3. The gas phase basicities of mono- (**1**), bis- (**2**) and tris- (**3**) **TBD**-substituted guanidines and their pK_a values in acetonitrile depending on the spacer length (Me, Et and Pr)

	conformation used[a]			IEF-PCM[b]				IPCM[c]			
B	n	p	proton at	$\frac{GB(\mathbf{B})}{kJ\ mol^{-1}}$	$\frac{\Delta(\Delta G°)_{sol}}{kJ\ mol^{-1}}$	$\frac{\Delta G°_{a,\,sol}{}^{(d)}}{kJ\ mol^{-1}}$	pK_a[d]	$\frac{\Delta(\Delta G°)_{sol}}{kJ\ mol^{-1}}$	$\frac{\Delta G°_{a,\,sol}{}^{(d)}}{kJ\ mol^{-1}}$	pK_a[d]
1										
Me	c1	c1	TBD	1083	−136.0	1246	28.1	−131.8	1242	28.2
Et	c1	c2	TBD	1092	−124.2	1243	27.7	−122.4	1241	28.1
Pr	c2	c2	TBD	1085	−124.8	1236	26.7	−121.7	1233	27.1
2										
Me	c1	c1	gu	1110	−108.7	1245	28.0	−107.1	1244	28.5
Et	c1	c2	gu	1124	−93.8	1244	27.8	−92.1	1242	28.3
Pr	c2	c2	gu	1120	−95.4	1242	27.5	−90.1	1236	27.5
3										
Me	c1	c1	gu	1158	−88.0	1273	32.0	−94.6	1279	33.1
Et	c1	c2	gu	1160	−71.6	1258	29.9	−74.5	1261	30.7
Pr	c2	c2	gu	1155	−58.7	1240	27.3	−69.9	1252	29.5
bis-**TBDH**$^+$				1096	−136.6	1258	30.0 (29.0)[e]	−126.7	1249	29.1 (29.0)[e]
tris-**DMAPA**[e]				1098	−111.5	1235	26.6 (27.2)[e]	−111.7	1236	27.5 (27.2)[e]

[a] the most stable conformers of neutral and protonated structures were used for calculation of GB and pK_a; n – neutral, p – protonated, with protonation occurring either at **TBD** (1Me–1Pr) or central guanidine subunit (gu, series **2** and **3**).
[b] pK_a = 0.14627 × $\Delta G°_{a,sol}$(**BH**$^+$) − 154.1. Linear function between pK_a and $\Delta G°_{a,sol}$(**BH**$^+$) was obtained from correlation between the experimental and calculated pK_a's for 57 nitrogen bases in the same way as in Ref. 16.
[c] pK_a = 0.13026 × $\Delta G°_{a,sol}$(**BH**$^+$) − 133.5. Linear function was taken from the reference 16 and switched to kJ mol^{-1}.
[d] relates to the properties of the conjugate acid (**BH**$^+$).
[e] experimental pK_a values taken from the references 7b (bis-**TBDH**$^+$) and 10c (tris-**DMAPAH**$^+$).

gives better agreement with the experimental data than the IEFPCM approach. Therefore, we consider IPCM results for compounds **1MeH**$^+$–**3PrH**$^+$ as more reliable. The obtained pK_a values for all bases cover the range from 27 to 33 pK_a units with **3MeH**$^+$**-c1** derivative being more basic than bis-**TBDH**$^+$ and tris-**DMAPAH**$^+$ by ca. 4 and 6 pK_a units, respectively. In contrast to the gas-phase, methylene spacer was found to be optimal for maximizing the pK_a values in acetonitrile, irrespectively of the number of intramolecular hydrogen bonds. The reason for this lies in an increased overall solvation contribution ($\Delta(\Delta G°)_{sol}$ in derivatives with methylene spacer which overcomes their slightly lower GB. The pK_as of derivatives with one and two **TBD**-spacer substituents (**1MeH**$^+$**–2PrH**$^+$) fall in between the values obtained for the two reference compounds. Based on these results one can expect that all investigated derivatives are indeed strong bases in the gas-phase and solution. However, the basicity in protic solvents could be somewhat attenuated by intermolecular hydrogen bonding with solvent molecules since it depends on the presence of IMHB.

CONCLUSION

By utilizing the concept of basicity increase through the formation of IMHB, and the high propensity of **TBD** to participate in hydrogen bonding as an acceptor, we successfully designed novel guanidine superbases with the estimated GB values of 1044−1168 kJ mol^{-1}. Optimization of the structural parameters such as the number of alkyl side chains (1, 2 or 3), the type of alkyl spacer (Me, Et or Pr) and the hydrogen-bonding pattern (1,3- and 1,1-motif), revealed **3Et-c2** as one of the most basic phosphorus-free guanidine superbase reported so far. In acetonitrile solution, the predicted pK_a values span from 27−33 units with **3MeH**$^+$**-c1** as the strongest base. Additionally, the preferred protonation site (**TBD**- or central guanidine imino nitrogen) depends on the number of alkyl substituents and the spacer length. We hope these results will foster further theoretical investigations in the field of neutral organic superbases, as well as encourage experimental chemists to develop synthetic routes to these compounds and explore their potential application as organocatalysts.

Supplementary Materials. – Supporting information to the paper is enclosed to the electronic version of the article. A list of electronic energies, zero-point vibrational and Gibbs free energy corrections is provided. The Cartesian coordiantes of the optimized geometries are available from authors upon request. These data can be found on the website of *Croatica Chemica Acta* (http://public.carnet.hr/ccacaa).

Acknowledgements. The authors are grateful for the financial support of the Ministry of Science, Education and Sport of Croatia (Grant No. 098-0982933-2920). The calculations were performed on the Isabella cluster (isabella.srce.hr) at the University of Zagreb Computing Center (SRCE).

REFERENCES

1. R. G. S. Berlinck, A. E. Trindade-Silva, and M. F. C. Santos, *Nat. Prod. Rep.* **29** (2012) 1382−1406 and references therein.
2. F. Sączewski and Ł. Balewski, *Expert Opin. Ther. Pat.* (2013) 965−995.
3. (a) K. T. Holman, A. M. Pivovar, J. A. Swift, and M. D. Ward, *Acc. Chem. Res.* **34** (2001) 107−118; (b) P. Blondeau, M. Segura, R. Pérez-Fernández, and J. de Mendoza, *Chem. Soc. Rev.* **36** (2007) 198−210.
4. P. Selig, *Synthesis* **45** (2013) 703−718.
5. (a) Y. V. Subba Rao, D. E. De Vos, and P. A. Jacobs, *Angew. Chem. Int. Ed.* **36** (1997) 2661−2663; (b) D. Simoni, R. Rondanin, M. Morini, R. Baruchello, and F. P. Invidiata, *Tetrahedron Lett.* **41** (2000) 1607−1610; (c) W. Ye, J. Xu, C. -T. Tan, and C. -H. Tan, *Tetrahedron Lett.* **46** (2005) 6875−6878; (d) D. Simoni, M. Rossi, R. Rondanin, A. Mazzali, R. Baruchello, C. Malagutti, M. Roberti, and F. P. Invidiata, *Org. Lett.* **2** (2000) 3765−3768; (e) U. Schuchardt, R. M. Vargas, and G. Gelbard, *J. Mol. Cat. A: Chem.* **99** (1995) 65−70.
6. D. Leow and C. -H. Tan, *Synlett* **21** (2010) 1589−1605.
7. (a) S. H. Oakley, M. P. Coles, and P. B. Hitchcock, *Inorg. Chem.* **43** (2004) 7564−7566; (b) M. P. Coles, P. J. Aragón-Sáez, S. H. Oakley, P. B. Hitchcock, M. G. Davidson, Z. B. Maksić, R. Vianello, I. Leito, I. Kaljurand, and D. C. Apperley, *J. Am. Chem. Soc.* **131** (2009) 16858−16868.
8. D. Barić, I. Dragičević, and B. Kovačević, *J. Org. Chem.* **78** (2013) 4075−4082.
9. C. Laurence and J. -F. Gal, *Lewis Basicity and Affinity Scales: Data and Measurement*, John Wiley & Sons Ltd, Chichester UK, 2010, p. 137.
10. (a) B. Kovačević, Z. Glasovac, and Z. B. Maksić, *J. Phys. Org. Chem.* **15** (2002) 765−774; (b) Z. Glasovac, V. Štrukil, M. Eckert-Maksić, D. Schröder, M. Kaczorowska, and H. Schwarz, *Int. J. Mass Spec.* **270** (2008) 39−46; (c) M. Eckert-Maksić, Z. Glasovac, P. Trošelj, A. Kütt, T. Rodima, I. Koppel, and I. A. Koppel, *Eur. J. Org. Chem.* **11** (2008) 5176−5184; (d) V. Štrukil, Z. Glasovac, I. Đilović, D. Matković-Čalogović, L. Šuman, M. Kralj, and M. Eckert-Maksić, *Eur. J. Org. Chem.* **15** (2012) 6785−6797; (e) Z. Glasovac, P. Trošelj, I. Jušinski, D. Margetić, and M. Eckert-Maksić, *Synlett* **24** (2013) 2540−2544; (f) V. Štrukil, E. Lekšić, E. Meštrović, and M. Eckert-Maksić, *Austr. J. Chem.* **67** (2014) 1129−1133.
11. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, *Gaussian09 rev D.01*, Gaussian, Inc., Wallingford CT, 2013.
12. A. D. Becke, *J. Chem. Phys*. **98** (1993) 5648−5652.
13. C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B* **37** (1988) 785−789.
14. B. Miehlich, A. Savin, H. Stoll, and H. Preuss, *Chem. Phys. Lett*. **157** (1989) 200−206.
15. P. J. Stephens, F. J. Devlin, C. F. Chabalowski, and M. J. Frisch, *J. Phys. Chem.* **98** (1994) 11623−11627.
16. Z. Glasovac, M. Eckert-Maksić, Z. B. Maksić, *New J. Chem.* **33** (2009) 588−597.
17. G. Schaftenaar and J. H. Nordik, *J. Comput.-Aided Mol. Design* **14** (2000) 123−134.
18. Z. Glasovac, B. Kovačević, E. Meštrović, and M. Eckert-Maksić, *Tetrahedron Lett*. **46** (2005) 8733−8736.
19. Z. Glasovac, F. Pavošević, V. Štrukil, M. Eckert-Maksić, M. Schlangen, and R. Kretschmer, *Int. J. Mass Spec.* **354−355** (2013) 113−122.
20. K. Vazdar, R. Kunetskiy, J. Saame, K. Kaupmees, I. Leito, and U. Jahn, *Angew. Chem. Int. Ed.* **53** (2014) 1435−1438.
21. Z. Glasovac and M. Eckert-Maksić, *Austr. J. Chem.* **67** (2014) 1056−1062.
22. (a) Z. B. Maksić, B. Kovačević, and R. Vianello, *Chem. Rev.* **112** (2012) 5240−5270. (b) E. D. Raczynska, J. -F. Gal, P. -C. Maria, and M. Szelag, *Croat. Chem. Acta* **82** (2009) 87−103.
23. For a review of the thermodynamic cycles used in calculations of the solvation energies and pKa values see: J. Ho and M. L. Coote, *Theor. Chem. Acc*. **125** (2010) 3−21.

Supplementary Material

The utility of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as a hydrogen bond acceptor in the design of novel superbasic guanidines – A computational study

Vjekoslav Štrukil, Ivana Antol and Zoran Glasovac**

Division of Organic Chemistry and Biochemistry

Ruđer Bošković Institute

Bijenička cesta 54, 10000 Zagreb, Croatia

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Table S1. Energies of the conformers and proton affinities (PA) of the two most basic sites in the investigated guanidine derivatives with methylene spacer calculated using B3LYP/6–311+G(2df,p) //B3LYP/6-31G(d) level of theory[a,b]

conformers[c]	E_{el}	E_{ZPV}	H_{corr}	G_{corr}	H	G	PA_{gv}	PA_{TBD}
1Et-c1	–761.16486	0.34894	0.36720	0.30331	–760.79766	–760.86155	1104	1111
1Et-c1 (p1)	–761.59653	0.36198	0.38069	0.31579	–761.21584	–761.28075		
1Et-c1 (p2)	–761.59956	0.36203	0.38102	0.31533	–761.21854	–761.28423		
1Et-c2	–761.16153	0.34826	0.36676	0.30128	–760.79476	–760.86024	1077	1111
1Et-c2 (p1)	–761.58417	0.36269	0.38139	0.31615	–761.20278	–761.26802		
1Et-c2 (p2)	–761.59753	0.36311	0.38185	0.31664	–761.21568	–761.28090		
2Et-c1	–1198.92653	0.53676	0.56341	0.47879	–1198.36311	–1198.44774	1144	1141
2Et-c1 (p1)	–1199.37380	0.55058	0.57733	0.49317	–1198.79647	–1198.88063		
2Et-c1 (p2)	–1199.37275	0.55041	0.57730	0.49236	–1198.79545	–1198.88039		
2Et-c2	–1198.92060	0.53674	0.56336	0.47906	–1198.35724	–1198.44154	1109	1118
2Et-c2 (p1)	–1199.35498	0.55112	0.57776	0.49363	–1198.77722	–1198.86136		
2Et-c2 (p2)	–1199.35845	0.55096	0.57779	0.49312	–1198.78066	–1198.86533		
3Et-c1	–1636.68112	0.72449	0.75960	0.65533	–1635.92152	–1636.02579	1191	1172
3Et-c1 (p1)	–1637.14676	0.73887	0.77392	0.66977	–1636.37283	–1636.47698		
3Et-c1 (p2)	–1637.13892	0.73849	0.77351	0.66896	–1636.36541	–1636.46996		
3Et-c2	–1636.67309	0.72353	0.75897	0.65172	–1635.91412	–1636.02136	1141	1147
3Et-c2 (p1)	–1637.12058	0.73895	0.77407	0.66953	–1636.34651	–1636.45105		
3Et-c2 (p2)	–1637.12291	0.73918	0.77438	0.66991	–1636.34853	–1636.45299		
TriMG[d]	–323.40202	0.16052	0.17054	0.12735	–323.23148	–323.27467	1046	
TriMGH$^+$	–323.81254	0.17458	0.18517	0.14072	–323.62737	–323.67182		

[a] PA values are given in kJ mol^{-1} while electronic energies (E_{el}), zero-point vibrational corrections (E_{ZPV}), thermal corrections to enthalpies (H_{corr}), corrections to Gibbs energies (G_{corr}), enthalpies(H_{tot}) and Gibbs free energies (G_{tot}) are given in Hartrees (H).

[b] **c3** conformers of the protonated bases with methylene spacers converged to the hydrogen bonded forms and they were not used in this work.

[c] **p1** label indicates protonation at guanidine imino nitrogen, while **p2** indicates protonation at TBD subunit.

[d] **TriMG** = *N,N′,N″*-trimethylguanidine

Table S2. Energies of the conformers and proton affinities (PA) of the two most basic sites in the investigated guanidine derivatives with ethylene spacer calculated using B3LYP/6-311+G(2df,p) //B3LYP/6-31G(d) level of theory[(a)]

conformers[(b)]	E_{el}	E_{ZPV}	H_{corr}	G_{corr}	H	G	PA_{gv}	PA_{TBD}
1Et-c1	–800.48614	0.37800	0.39743	0.33104	–800.08871	–800.15509	1106	1115
1Et-c1 (p1)	–800.91898	0.39176	0.41153	0.34480	–800.50745	–800.57418		
1Et-c1 (p2)	–800.92268	0.39195	0.41182	0.34465	–800.51086	–800.57804		
1Et-c2	–800.48391	0.37698	0.39658	0.32906	–800.08733	–800.15485	1109	1126
1Et-c2 (p1)	–800.91790	0.39067	0.41071	0.34246	–800.50719	–800.57545		
1Et-c2 (p2)	–800.92511	0.39158	0.41146	0.34396	–800.51365	–800.58116		
1Et-c3	–800.48038	0.37647	0.39652	0.32689	–800.08386	–800.15349	1075	1098
1Et-c3 (p1)	–800.90236	0.39102	0.41142	0.34151	–800.49094	–800.56085		
1Et-c3 (p2)	–800.91108	0.39110	0.41156	0.34098	–800.49952	–800.57010		
2Et-c1	–1277.56807	0.59459	0.62382	0.53319	–1276.94425	–1277.03488	1156	1140
2Et-c1 (p1)	–1278.02054	0.60908	0.63831	0.54878	–1277.38223	–1277.47176		
2Et-c1 (p2)	–1278.01458	0.60915	0.63839	0.54856	–1277.37619	–1277.46602		
2Et-c2	–1277.56352	0.59298	0.62261	0.53006	–1276.94091	–1277.03346	1160	1155
2Et-c2 (p1)	–1278.01734	0.60737	0.63705	0.54441	–1277.38029	–1277.47293		
2Et-c2 (p2)	–1278.01598	0.60780	0.63732	0.54548	–1277.37866	–1277.47050		
2Et-c3	–1277.55623	0.59259	0.62258	0.52670	–1276.93364	–1277.02953	1104	1111
2Et-c3 (p1)	–1277.98909	0.60707	0.63748	0.54225	–1277.35161	–1277.44684		
2Et-c3 (p2)	–1277.99245	0.60731	0.63782	0.54176	–1277.35463	–1277.45070		
3Et-c1	–1754.64659	0.81048	0.84967	0.73382	–1753.79692	–1753.91276	1200	1175
3Et-c1 (p1)	–1755.11695	0.82653	0.86529	0.75396	–1754.25166	–1754.36299		
3Et-c1 (p2)	–1755.10668	0.82591	0.86475	0.75172	–1754.24193	–1754.35495		
3Et-c2	–1754.64019	0.80888	0.84853	0.73037	–1753.79165	–1753.90982	1205	1186
3Et-c2 (p1)	–1755.11163	0.82398	0.86342	0.74710	–1754.24821	–1754.36453		
3Et-c2 (p2)	–1755.10411	0.82380	0.86318	0.74683	–1754.24092	–1754.35728		
3Et-c3	–1754.63476	0.80884	0.84874	0.72943	–1753.78603	–1753.90533	1126	1111
3Et-c3 (p1)	–1755.07619	0.82363	0.86383	0.74467	–1754.21236	–1754.33152		
3Et-c3 (p2)	–1755.07031	0.82307	0.86365	0.74062	–1754.20666	–1754.32969		

[(a)] PA values are given in kJ mol^{-1} while electronic energies (E_{el}), zero-point vibrational corrections (E_{ZPV}), thermal corrections to enthalpies (H_{corr}), corrections to Gibbs energies (G_{corr}), enthalpies(H_{tot}) and Gibbs free energies (G_{tot}) are given in Hartrees (H).

[(b)] p1 label indicates protonation at guanidine imino nitrogen, while p2 indicates protonation at TBD subunit.

Table S3. Energies of the conformers and proton affinities (PA) of the two most basic sites in the investigated guanidine derivatives with propylene spacer calculated using B3LYP/6-311+G(2df,p) //B3LYP/6-31G(d) level of theory[(a)]

conformers[(b)]	E_{el}	E_{ZPV}	H_{corr}	G_{corr}	H	G	PA_{gv}	PA_{TBD}
1Pr-c1	–839.80639	0.40645	0.42717	0.35706	–839.37922	–839.44933	1115	1124
1Pr-c1 (p1)	–840.24292	0.42014	0.44132	0.37083	–839.80159	–839.87209		
1Pr-c1 (p2)	–840.24670	0.42053	0.44174	0.37110	–839.80496	–839.87560		
1Pr-c2	–839.81044	0.40629	0.42707	0.35679	–839.38337	–839.45366	1104	1117
1Pr-c2 (p1)	–840.24279	0.42018	0.44137	0.37036	–839.80142	–839.87243		
1Pr-c2 (p2)	–840.24866	0.42113	0.44211	0.37178	–839.80654	–839.87688		
1Pr-c3	–839.80559	0.40531	0.42665	0.35377	–839.37894	–839.45182	1072	1091
1Pr-c3 (p1)	–840.22595	0.41936	0.44125	0.36747	–839.78470	–839.85848		
1Pr-c3 (p2)	–840.23378	0.41972	0.44162	0.36756	–839.79216	–839.86622		
2Pr-c1	–1356.20830	0.65200	0.68365	0.58705	–1355.52465	–1355.62125	1162	1145
2Pr-c1 (p1)	–1356.66349	0.66690	0.69858	0.60272	–1355.96491	–1356.06078		
2Pr-c1 (p2)	–1356.65666	0.66662	0.69841	0.60177	–1355.95825	–1356.05489		
2Pr-c2	–1356.21604	0.65182	0.68342	0.58723	–1355.53262	–1355.62882	1153	1144
2Pr-c2 (p1)	–1356.66776	0.66647	0.69825	0.60241	–1355.96951	–1356.06536		
2Pr-c2 (p2)	–1356.66432	0.66661	0.69833	0.60243	–1355.96599	–1356.06189		
2Pr-c3	–1356.20930	0.65003	0.68265	0.58094	–1355.52664	–1355.62836	1093	1099
2Pr-c3 (p1)	–1356.63805	0.66412	0.69737	0.59416	–1355.94068	–1356.04389		
2Pr-c3 (p2)	–1356.64073	0.66454	0.69769	0.59483	–1355.94304	–1356.04590		
3Pr-c1	–1872.61110	0.89686	0.93984	0.81578	–1871.67126	–1871.79531	1195	1166
3Pr-c1 (p1)	–1873.07985	0.91320	0.95578	0.83375	–1872.12407	–1872.24609		
3Pr-c1 (p2)	–1873.06790	0.91255	0.95506	0.83380	–1872.11284	–1872.23410		
3Pr-c2	–1872.61794	0.89585	0.93915	0.81330	–1871.67879	–1871.80465	1199	1175
3Pr-c2 (p1)	–1873.08832	0.91257	0.95506	0.83356	–1872.13326	–1872.25476		
3Pr-c2 (p2)	–1873.07856	0.91207	0.95462	0.83179	–1872.12394	–1872.24677		
3Pr-c3	–1872.61108	0.89423	0.93843	0.80745	–1871.67265	–1871.80363	1115	1105
3Pr-c3 (p1)	–1873.04858	0.90883	0.95353	0.82186	–1872.09505	–1872.22672		
3Pr-c3 (p2)	–1873.04477	0.90902	0.95369	0.82098	–1872.09108	–1872.22380		

[(a)] PA values are given in kJ mol^{-1} while electronic energies (E_{el}), zero-point vibrational corrections (E_{ZPV}), thermal corrections to enthalpies (H_{corr}), corrections to Gibbs energies (G_{corr}), enthalpies(H_{tot}) and Gibbs free energies (G_{tot}) are given in Hartrees (H).

[(b)] **p1** label indicates protonation at guanidine imino nitrogen, while **p2** indicates protonation at TBD subunit.