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Design of Superbasic Guanidines: The Role of Multiple Intramolecular Hydrogen Bonds

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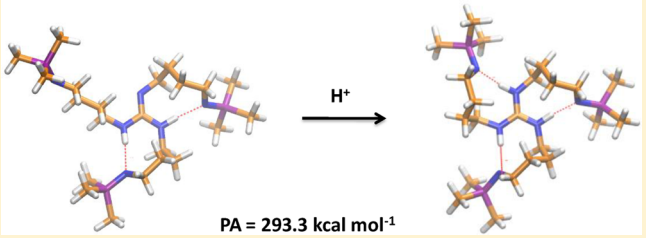
Supporting Information

ABSTRACT: New organic superbases have been designed using the concept of multiple intramolecular hydrogen bonds. Substituents capable of forming strong intramolecular H-bonds were selected on the basis of the energy of stabilization that occurs upon the formation of a complex between *N*,*N*′,*N*″-trimethylguanidine and small model molecules. The proton affinities and the corresponding pK_a values in acetonitrile of the new superbases are examined by Density Functional Theory (DFT). It is shown that *N*,*N*′,*N*″-substitution of guanidine with appropriate substituents results in new organic superbases with gas phase proton affinities between 286 and 293 kcal mol^{-1}, thus being 15 to 20 kcal mol^{-1} more basic than parental superbase *N*,*N*′,*N*″-tris[(3-dimethylamino)propyl]-guanidine (**tris-DMPG**), whereas estimated pK_a values in acetonitrile range between 29.5 and 33.2.



INTRODUCTION

For more than three decades, the design and preparation of new neutral organic bases has been a subject of considerable interest for many researchers. During this time several types of very strong neutral bases have been developed. These include Schwesinger's vinamidine[1,2] and phosphazene bases,[3] the proazaphosphatrane bases developed by Verkade,[4] and the proton sponges originally introduced by Alder's group[5,6] and later studied by Staab.[7] Modifications of Alder's 1,8-bis-(dimethylamino)naphthalene (DMAN) proton sponge where dimethylamino groups are replaced by more basic tetramethylguanidino, dimethylethyleneguanidino, and hexamethyltriamino-phosphazenyl groups, thus leading to more basic proton sponges, have been made by Sundermeyer's and our group.[8] Some authors studied different aliphatic and aromatic carriers of dymethylamino, tetramethylguanidino, and phosphazeno groups, mostly resulting with a very high basicity of newly designed proton sponges.[9−16] Utilizing supramolecular scaffolds containing pyridine subunits (i.e., azacalix[3]-2,6-pyridine), Maksić and co-workers designed extremely basic compounds with proton affinities up to 314 kcal mol^{-1}.[17−19] The same motif has been used by Uchida and co-workers[20] to design strong neutral superbases. Recently, Ganguly discovered a new class of carbene superbases with PAs in the gas phase up to 298 kcal mol^{-1}.[21] Present advances in the field of design and synthesis of organic superbases can be found in a two recently published review articles.[22,23]

Neutral organic superbases have a great practical importance due to the fact that they have some distinct advantages over their inorganic ionic counterparts. The latter exhibit some unfavorable features, such as low solubility in most organic solvents, pronounced sensitivity to the moisture and CO_2, and the production of hazardous waste. In contrast, strong neutral organic (super)bases permit milder reaction conditions and exhibit better solubility in organic solvents.

The importance of intramolecular hydrogen bonds and their contribution to the basicity of organic compounds in the design of strong organic bases has been shown in several experimental and theoretical works.[24−28] However, the previous studies were principally focused on molecules with a single hydrogen bond. Only recently has the presence of multiple intramolecular hydrogen bonds been recognized as an important factor that could be used in the design of strong organic bases.[29−31] In 2002 we computationally designed *N*,*N*′,*N*″-tris[(3-dimethylamino)propyl]-guanidine shown in Figure 1 (**tris-DMPG**), a system where guanidine was substituted by flexible 3-(dimethylamino)propyl chains capable of forming three intramolecular hydrogen bonds when protonated.[27] Our *ab*

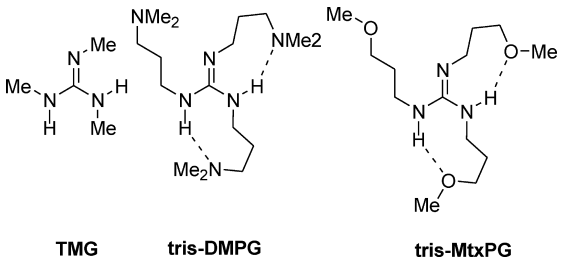


Figure 1. *N*,*N*′,*N*″-Trimethylguanidine (**TMG**), *N*,*N*′,*N*″-tris[(3-dimethylamino)propyl]-guanidine (**tris-DMPG**), and *N*,*N*′,*N*″-tris(3-metoxypropyl)-guanidine (**tris-MtxPG**).

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initio calculations predicted that the gas phase proton affinity (PA) of this compound was around 25 kcal mol^{-1} higher than the PA of *N*,*N*′,*N*″-trimethylguanidine (**TMG**, Figure 1), a molecule which served as a reference base, where intramolecular hydrogen bonds do not contribute to proton affinity.

Later, **tris-DMPG** was synthesized,[32] and the X-ray crystal structure revealed that protonated form of the molecule was indeed in possession of three intramolecular hydrogen bonds, as predicted by theoretical calculations. The calculated gas phase PA of this compound was found to be 273.2 kcal mol^{-1},[28] which is comparable to the basicity of *t*Bu-P2 phosphazene.[33] Eckert-Maksić and co-workers modified the original idea and synthethyzed *N*,*N*′,*N*″-tris(3-metoxypropyl)-guanidine (**tris-MtxPG** depicted in Figure 1) where all three dimethylamino-propyl groups on guanidine moiety are replaced with methoxypropyl chain.[34] However, the obtained proton affinity of **tris-MtxPG** (266.4 kcal mol^{-1}) is 6.8 kcal mol^{-1} lower than that of **tris-DMPG** base.

It is well-known that guanidines are generally very good catalysts for biodiesel production. There is a positive correlation between their basicity and the catalytic activity in trans-esterification reactions.[35] In this context, **tris-DMPG** has proven to be a superior catalyst compared to other guanidine type bases.[36] Consequently, the design of very basic guanidines is not just an intellectual challenge. Rather, it can be of great practical importance. In this paper we demonstrate that it is possible to design highly basic guanidines, with a proton affinity up to 293 kcal mol^{-1}, using the concept of multiple intramolecular hydrogen bonds.

COMPUTATIONAL METHODS

Calculations in gas phase are performed at the B3LYP/6-311+G-(2df,p)//B3LYP/6-31G(d) level of theory. All structures were confirmed to be energy minima on potential energy surface by computing their vibrational frequencies analytically. PA are calculated according to the equation

$$\mathrm{PA} = H^{298}(\mathrm{B}) - H^{298}(\mathrm{BH}^+) + (5/2)RT \quad (1)$$

where H^{298}(B) and H^{298}(BH$^+$) stand for the enthalpies at 298 K of the neutral and protonated base (B and BH$^+$, respectively) calculated at the B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) level of theory. The pK_a values in acetonitrile (MeCN) are estimated according to the procedure described in detail in the paper by Glasovac et al.,[37] which involves the application of eq 2 obtained by correlation between experimental data for pK_a values in MeCN and calculated basicities:

$$\mathrm{p}K_a = 0.545\Delta G'_{a,\mathrm{sol}}(\mathrm{BH}^+) - 133.5 \quad (2)$$

The term $\Delta G'_{a,\mathrm{sol}}$(BH$^+$) corresponds to the difference of Gibbs energies between product and reactants for the deprotonation reaction of a protonated base (BH$^+$) in solution. The Gibbs energy is calculated as the sum of electronic energy, the thermal correction to Gibbs energy, and the energy of solvation. The calculation of solvation energies are performed using isodensity polarizable continuum (IPCM) method at the B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) level of theory.

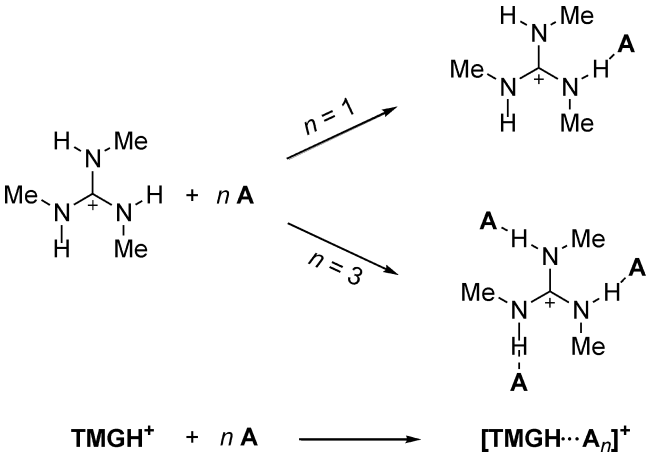
All computations were carried out using the Gaussian03[38] suite.

RESULTS AND DISCUSSION

Designing New Guanidine Superbases. To design highly basic guanidines using the concept of multiple intramolecular hydrogen bonds, it is necessary to find substituents for the guanidine moiety that are capable of forming intramolecular hydrogen bonds even stronger than those present in **tris-DMPG**. To simplify the process of designing the appropriate substitutents, we defined the substituent as a molecular fragment that consists of two parts: (1) a basic functional group, which serves as a hydrogen bond acceptor, and (2) an alkyl chain that links the hydrogen bond acceptor with the nitrogen atoms of the central guanidine moiety. For example, in case of **tris-DMPG**, the substitutent is built from the dimethyl amino group serving as a hydrogen bond acceptor and a propyl chain as the bridging group.

To find the appropriate basic functional groups, we calculated the energy of stabilization that occurs upon the formation of a complex between the protonated *N*,*N*′,*N*″-trimethylguanidine (**TMGH**$^+$) and a series of model molecules (**A**), as shown in Scheme 1. The molecules **A** provide models

Scheme 1



for the basic functional groups in substituents that will be involved in the putative superbases. Two types of complexations are examined: formation of a monocomplex, [**TMGH**···**A**]$^+$ (Scheme 1, n = 1, where n stands for number of molecules **A** in a complex) and formation of a tricomplex [**TMGH**···**A**$_3$]$^+$ (Scheme 1, n = 3). The conformational space of the monocomplexes has been meticulously examined, and the global minimum was found for each complex. The starting geometries of tricomplexes were obtained applying C_3 symmetry on optimized geometries of the monocomplexes. Namely, C_3 is the expected symmetry of the protonated form of newly designed superbases, as was the case in **tris-DMPG** and its methoxypropyl counterpart **tris-MtxPG**. The optimizations of tricomplexes were not constrained to any symmetry; however, the optimized structures still retained approximate C_3 symmetry.

The stabilization energy of the complexation reaction corresponds to the energy of intermolecular hydrogen bond(s). It is expressed as the enthalpy of formation of a mono- and tricomplex, respectively, at 298 K:

$$\Delta H^{298} = H^{298}([\mathbf{TMGH}\cdots\mathbf{A}_n]^+) - (H^{298}(\mathbf{TMGH}^+) + nH^{298}(\mathbf{A})) \quad (3)$$

We proposed that the greater stability of a complex would lead to a stronger superbase and, additionally, that the differences between the PA values of new superbases and **TMG** (Figure 1) could be similar to the absolute values of the enthalpy of complexation for tricomplexes.

A set of 13 neutral model molecules **A** (Figure 2) that could play the role of strong hydrogen bond acceptors in mono-

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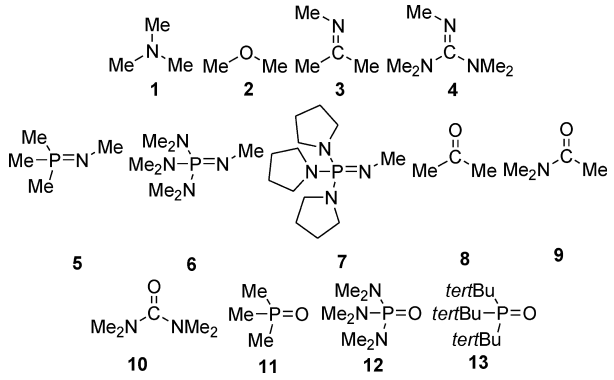

Figure 2. Molecules **A** that served as H-bond acceptors in complexes $[\mathbf{TMGH{\cdots}A}]^+$ and $[\mathbf{TMGH{\cdots}A_3}]^+$.

$[\mathbf{TMGH{\cdots}A}]^+$ and tricomplexes $[\mathbf{TMGH{\cdots}A_3}]^+$ were examined. Molecules **1** (trimethyl amine) and **2** (dimethyl ether) served as a reference, since they represent a model for the hydrogen bond acceptor involved in a previously studied **tris-DMPG** and **tris-MtxPG** superbases (Figure 1).

Enthalpies of complexation were calculated according to eq 3, and results are presented in Table 1. The data from Table 1

Table 1. Enthalpies of Complexations (kcal mol^{-1}) for Mono- and Tri-complexes (Scheme 1)

molecule **A**	ΔH^{298} (mono-)	ΔH^{298} (tri-)
1	−9.0	−23.4
2	−9.8	−26.0
3	−15.3	−38.3
4	−17.3	−40.6
5	−21.4	−49.8
6	−19.9	−43.9
7	−22.8	−48.2
8	−13.1	−33.2
9	−17.8	−44.1
10	−18.1	−44.1
11	−21.2	−52.0
12	−21.0	−50.4
13	−20.6	−49.4

reveal that molecules **3**−**13** form H-bonds with $\mathbf{TMGH}^+$ that are **much** stronger than those in the reference molecules **1** and **2**. To improve efficiency and to reduce computational cost, we selected only the most promising hydrogen bond acceptors (i.e., basic functional groups) for further consideration, so the value of $\Delta H^{298} = -40$ kcal mol^{-1} for a tricomplex was applied as a treshold. Therefore, molecules **3** and **8** were omitted from the set of candidates for the design of new superbases.

After suitable hydrogen bond acceptors were selected, the next step was to find the best possible linker (alkyl chain) that would bind hydrogen bond acceptors with the central guanidine moiety in such a way to obtain a favorable steric arrangement of substituents in new molecules. Namely, we assume that in tricomplexes the hydrogen bond acceptors achieved optimal arrangement around athe central guanidine, resulting in the strongest H-bond for a given model molecule. Accordingly, in the new superbases, the alkyl chain that serves as a linker between the hydrogen bond acceptor and the central guanidine is selected in a way to preserve the maximum possible strength of H-bonds. In other words, in new superbases we tried to ensure the least possible perturbation of the orientation and distance of H-bond acceptors from the model tricomplexes. Therefore, different conformations and lengths of alkyl chain were examined, and the optimal length and conformation was determined for each new superbase. Nine new superbases are schematically presented in Figure 3

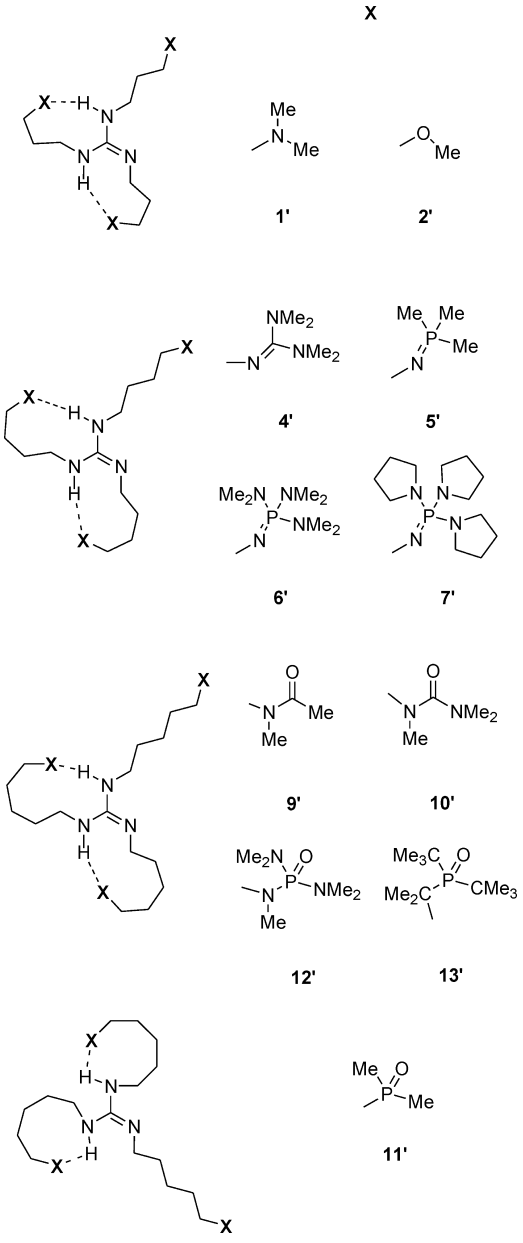

Figure 3. Schematic representation of designed substituted guanidines capable of forming multiple intramolecular hydrogen bonds.

denoted as **4′**, **5′**, **6′**, **7′**, **9′**, **10′**, **11′**, **12′**, and **13′**, where substituents **X** were derived from model molecules **4**, **5**, **6**, **7**, **9**, **10**, **11**, **12**, and **13** (shown in Figure 2), respectively. Molecules **1′** (**tris-DMPG**) and **2′** (**tris-MtxPG**) are given for comparison.

For new molecules **4′**, **5′**, **6′**, and **7′**, the optimal alkyl chain was found to be butyl. For the remainder of the molecules the pentyl chain was preferred. It should be noted here that one of the -CH_2 groups in the alkyl chain is always derived from one of the methyl groups present in the model molecules **A**. In superbases **4′**, **5′**, **6′**, and **7′**, the intramolecular H-bond takes

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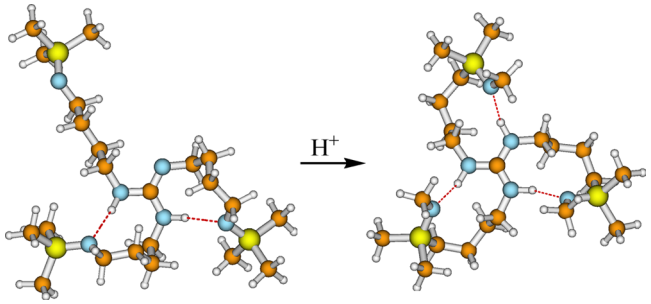
place between the imino nitrogen of the substituent and hydrogen covalently bound to the guanidine moiety. In the remaining superbases, the atom that accepts the H-bond is the oxygen linked to carbon (in **9′** and **10′**) or to phosphorus (in **11′**, **12′**, and **13′**). There are two ways in which intramolecular H-bonds in guanidines can be formed. In the first, the substituent linked to the N atom of the guanidine moiety interacts with the hydrogen atom covalently bound to N′ atom, as in **tris-DMPG** depicted in Figure 1. The second form arises when the substituent forms a H-bond with the hydrogen covalently bound to the same nitrogen atom. For all superbases except for the molecule **11′** the first arrangement was found to be more favorable.

It was found that **tris-DMPG** in its neutral form possesses two intramolecular hydrogen bonds, although much weaker than in the protonated form.[27] Consequently, we assumed that superbases **4′**−**13′** in their neutral form also possess two intramolecular H-bonds. In a proces of exploring conformational space of neutral bases, we retained the orientation of two substituents (heteroalkyl side chains) that allows formation of two intramolecular H-bonds in the same way as in protonated form. Only the conformation of the third substituent, the one that is not engaged in creation of an intramolecular H-bond in the neutral form of the superbase, has been explored. We found that in the majority of molecules the third substituent has an extended zigzag form. Typical arrangement of heteroalkyl side chains around central guanidine moiety in neutral and protonated superbase is shown in Scheme 2, using the superbase **5′** as an example.

Scheme 2



Proton Affinity and pK_a Values of Newly Designed Superbases. The PA values are calculated according to eq 1 as explained in the theoretical section. The accuracy of the applied theoretical model for gas phase PA calculations has been recently tested[28] with some substituted guanidines and amines exhibiting intramolecular hydrogen bonds in neutral and protonated forms. It turns out that the applied theoretical model gives results that are in relatively good agreement with the experimentally observed values. However, accurate determination of the pK_a values still represents a challenging problem for computational chemistry. In papers previously published by our group, we have been using the approach where theoretically calculated PA values in solvent (acetonitrile) are correlated with experimentally determined pK_a values.[8,11,17,18,33,39] The obtained correlation was successfully utilized in calculation of some newly designed compounds. However, Glasovac et al.[37] showed that, for the molecules where intramolecular hydrogen bonding significantly contributes to the PA, better results are obtained if GB (instead of PA) in solvent is correlated with pK_a. For a series of guanidines substituted with heteroalkyl side chains the agreement between the theoretical and experimental values were within 1 pK_a unit, with a deviation of only 0.5 for **tris-DMPG** base. The results of PA and pK_a calculations for superbases **1**−**13** are presented in Table 2.

Table 2. Gas Phase Proton Affinities (PA, in kcal mol^{-1}) and pK_a Values in Acetonitrile of Superbases Shown in Figure 3

molecule **A′**	PA	pK_a
1′	273.2[a]	27.7[b]
2′	266.4[a]	26.5[b]
4′	286.2	29.5
5′	293.3	32.3
6′	289.3	30.6
7′	293.1	32.0
9′	286.3	29.5
10′	287.5	30.8
11′	287.6	33.2
12′	286.4	28.1
13′	289.5	30.4

[a]PA value from ref 28. [b]pK_a value from ref 37.

Superbases **5′**, **6′**, **7′**, and **13′** with PA values between 289.3 and 293.3 kcal mol^{-1}, exhibit gas phase proton affinities higher than that of *t*Bu-P3 phosphazene (PA = 288.8 kcal mol^{-1}).[33] The rest of the newly designed superbases (**4′**, **9′**, **10′**, **11′**, and **12′**) are slightly less basic than *t*Bu-P3 phosphazene, having PA values within a narrow range from 286.2 to 287.6 kcal mol^{-1}. Superbases with PA values higher than in *t*Bu-P3 phoshpazene are those with phosphine imide based substituents as H-bond acceptors (**5′**, **6′**, and **7′**) and one of the molecules with phosphine oxide (**13′**). The strongest new superbase is molecule **5′**, containing *P*,*P*,*P*-trimethyl-phosphine imide based substituent.

The calculated pK_a values are in the range from 29.5 to 33.2, being 5 to 9 orders of magnitude lower than the pK_a of *t*Bu-P3 phosphazene. The reason for such a striking difference between proton affinity in the gas phase and the basicity in solution lies in the fact that superbases **4′**−**13′** are already internally solvated due to the presence of intramolecular H-bonds, and therefore, the effect of external solvation is diminished. As a consequence, the energy of solvation is less pronounced compared to the bases where such internal solvation does not exist (i.e., phosphazenes).

Estimation of the Influence of H-Bonds on PA Using the Enthalpies of Complexation. Based on the data from Table 1, the expected influence of intramolecular H-bonds strength to the PA of the new superbases is remarkable. In that context, it is illustrative to compare the PA values of new superbases with the proton affinity of *N*,*N*′,*N*″-trimethylguanidine (**TMG,** Figure 1) where no intramolecular H-bonds are present. Computed at the same level of theory, the PA of **TMG** is 249.9 kcal mol^{-1}, which is roughly 40 kcal mol^{-1} lower than the PA of **5′**, **6′**, **7′**, and **13′**. If the presence of alkyl chains in the substituent could be neglected, the stabilization that occurs due to the formation of three intramolecular H-bonds in the superbases should be proportionate to the enthalpy of complexation in tricomplexes. Thus, if the strength of **inter**molecular H-bonds present in tricomplexes is related to the strength of **intra**molecular H-bonds in superbases, it may be useful to compare the enthalpies of complexation with the difference in PA values between **TMG** and new superbases.

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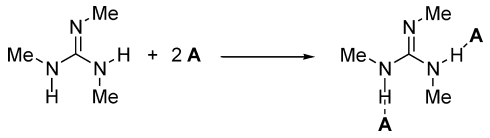
However, as already mentioned, the neutral form of guanidines substituted with three heteroalkyl side chains possesses two intramolecular H-bonds (Figure 3). Although these H-bonds are much weaker than those in the protonated forms,[27,28] they cannot be neglected due to the influence they make to the stability of the neutral form of superbases. Therefore, the expected PAs of new superbases are related to the energy of complexation of tricomplexes **corrected** for the value of the enthalpy of complexation of dicomplexes formed between neutral **TMG** and two model molecules **A**, according to the reaction shown in Scheme 3.

Scheme 3



The corresponding enthalpies of formation of dicomplexes are given by eq 4:

$$\Delta H^{298}(\text{di-}) = H^{298}([\mathbf{TMG}\cdots\mathbf{A}_2]) - (H^{298}(\mathbf{TMG}) + 2H^{298}(\mathbf{A})) \quad (4)$$

Their values are represented in Table 3. Molecules **3** and **8** are omitted, since they were not used for the design of new superbases. The corrected enthalpies of complexation are obtained as differences between the enthalpies of complexation of tri- and dicomplexes and are denoted as $\Delta\Delta H^{298}$ (Table 3). They are compared with the increase of PAs of new superbases (ΔPA(I)) calculated as a difference between the PA of a given superbase and that of trimethylguanidine, **TMG**.

Table 3. Comparison of the Enthalpies of Complexation with the Difference of PA between Superbases 1′−13′ and TMG, in kcal mol^{-1}

A	ΔH^{298} (di-)	$\Delta\Delta H^{298}$	ΔPA(I)	ΔPA(I) − $\lvert\Delta\Delta H^{298}\rvert$
1	−1.7	−21.7	23.3	1.6
2	−2.6	−23.4	16.5	−6.9
4	−4.3	−36.1	36.3	0.2
5	−6.7	−43.1	43.4	0.3
6	−4.5	−39.4	39.4	0.0
7	−5.6	−43.6	43.2	−0.4
9	−4.7	−39.4	36.4	−3.0
10	−4.9	−39.2	37.6	−1.6
11	−8.1	−43.9	37.7	−6.2
12	−5.6	−44.8	36.5	−8.3
13	−6.0	−43.4	39.6	−3.8

For the reference superbase **tris-DMPG** (**1′**) the agreement between the increase of PA (ΔPA(I)) and the corrected enthalpy of complexation ($\Delta\Delta H^{298}$) is good. The difference is only 1.6 kcal mol^{-1}. For the molecules **4**, **5**, **6**, **7**, and **10** similar or even better consistency is achieved, since the differences between the $\Delta\Delta H^{298}$ and the obtained increase in PA of new superbases do not exceed the value of 1.6 kcal mol^{-1}. Significant deviations are found for the molecules **2**, **11**, and **12**. Molecules **9** and **13** also show notable disagreement between ΔPA(I) and $\Delta\Delta H^{298}$, although less pronounced compared to former examples.

The molecule **2** is used as a model for *N*,*N*′,*N*″-tris(3-metoxypropyl)-guanidine (**tris-MtxPG**, Figure 1). As mentioned above, Eckert-Maksić and co-workers found that methoxypropyl as a substituent on the guanidine moiety has lower contribution to the PA than the dimethyaminopropyl chain.[28,34] The PA of superbase **tris-MtxPG** was found to be 6.8 kcal mol^{-1} lower than the PA of **tris-DMPG**. However, the complexation energies presented in Tables 1 and 3 show that molecule **2** (dimethyl ether), as a model for methoxy substituent, has complexation enthalpy slightly higher than that of molecule **1** (trimethyl amine) used as a model for **tris-DMPG** superbase. The reason for a lower PA of **tris-MtxPG** could be an inappropriate length of the alkyl chain that serves as a linker. Therefore, we tested different lengths of alkyl chain and found that propyl is not long enough to ensure the least perturbation of arrangement between the methoxy group and the guanidinium cation that was obtained in tricomplexes. The proton affinities of superbases depicted in Figure 4, where either the butyl (**2′-butyl**) or the pentyl (**2′-pentyl**) chain is engaged as a linker between the metoxy group and the guanidine moiety, are found to be 272.8 and 271.7 kcal mol^{-1}, respectively. The PA values of **2′-butyl** and **2′-pentyl** are now more consistent with corrected enthalpy of complexation in tricomplex.

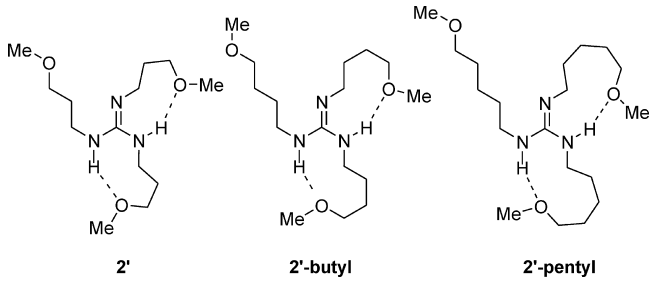


Figure 4. Schematic representation of *N*,*N*′,*N*″-tris(3-metoxypropyl)-guanidine (**2′**), *N*,*N*′,*N*″-tris(3-metoxybutyl)-guanidine (**2′-butyl**), and *N*,*N*′,*N*″-tris(3-metoxypentyl)-guanidine (**2′-pentyl**).

The agreement between the increase of proton affinity (ΔPA(I)) and the corrected enthalpies of tricomplexation ($\Delta\Delta H^{298}$) for most of the molecules presented here is remarkably good, as stated above. However, it is not immediately clear why molecules **9′**, **11′**, **12′**, and **13′** do not follow this trend. It should not be forgotten that the presence of alkyl chain in the superbases is completely neglected in this analysis. The question arises as to whether this approach really offer a realistic quantitative estimation of the PA increase due to a presence of intramolecular hydrogen bonds? To answer this question, we decided to investigate other possible contributions to the PA of superbases **4′**−**13′** in more detail.

Estimation of Intramolecular H-Bond Strength in Newly Designed Superbases by Comparison of Folded and Unfolded Conformers. One of the approaches for estimating hydrogen bond strength and its influence on the proton affinities of substituted guanidines utilized previously[27] is to compare the difference in PA of the fully extended (unfolded) conformer of superbase where no H-bonds are present (Figure 5) with the folded conformer that has all intramolecular H-bonds intact (Figure 3).

The proton affinities of unfolded conformers are presented in Table 4 along with the differences in PAs (marked as ΔPA(II)) between folded and unfolded conformers. Comparison of

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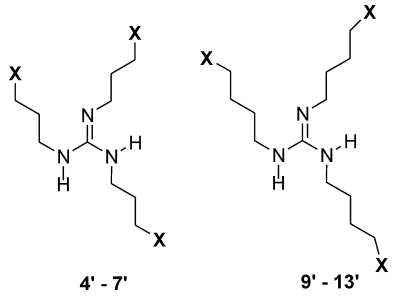

Figure 5. Schematic representation of unfolded conformers of superbases **4′**−**13′**.

Table 4. Proton Affinities of Unfolded Conformers of Newly Designed Superbases A′ (kcal mol^{-1}) Together with the Contributions ΔPA(II) and ΔPA(III)[a]

A′	PA (unfolded)	ΔPA(II)	ΔPA(III)
4′	265.2	21.0	8.6
5′	269.7	23.6	13.1
6′	269.4	19.9	12.8
7′	271.6	21.5	15.0
9′	246.7	39.6	−10.7
10′	252.9	34.6	−4.5
11′	256.1	31.5	−1.3
12′	260.9	25.5	3.5
13′	257.5	32.0	0.1

[a]ΔPA(II) corresponds to the difference between the PAs of folded and unfolded conformers, and ΔPA(III) is the difference between unfolded superbases and guanidines substituted with corresponding alkyl chains only.

ΔPA(II) values with corrected enthalpies of complexation ($\Delta\Delta H^{298}$) from Table 3 shows a relatively good agreement for the molecules **9′**, **10′**, **11′** and **13′**. Surprisingly, in superbases **4′**, **5′**, **6′**, **7′** and **12′** this approach for estimating H-bond contribution to the PA gives much smaller values than when the approach through enthalpies of complexation. The estimated strength of the H-bonds is now 20−27 kcal mol^{-1}, whereas enthalpies of complexation suggest that H-bonds contribute between 36 and 44 kcal mol^{-1} to the PA. It can be concluded that some effect(s) other than H-bonds may contribute to the PA of new superbases. One of them is certainly the positive inductive effect of alkyl chains present in the superbases, which has not previously been accounted for. The other, which could be more important, is the electron-donating or accepting nature of functional group **X**. We may therefore postulate that the difference in PA between superbases **4′**−**13′** and **TMG** (ΔPA(I) in Table 3) can be divided into these three contributions: (1) the influence of intramolecular H-bonds, (2) the inductive effect of alkyl groups, and (3) the inductive effect of functional groups **X**. The first contribution, denoted as ΔPA(II), is calculated as a difference between the PA of the folded and unfolded conformers of the relevant superbases, as presented in Table 4. The second term, the contribution of the inductive effect of alkyl chains, is obtained as a difference in PA values of guanidine that was *N*,*N*′,*N*″-tris-substituted by butyl and pentyl chain and PA of **TMG**. Proton affinities of tris-butyl-guanidine and tris-pentyl-guanidine are 256.6 and 257.4 kcal mol^{-1}, respectively, as shown in Figure 6. These values are 6.7 and 7.5 kcal mol^{-1} higher than PA of **TMG**. Finally, the third contribution, the inductive effect of functional groups **X** to

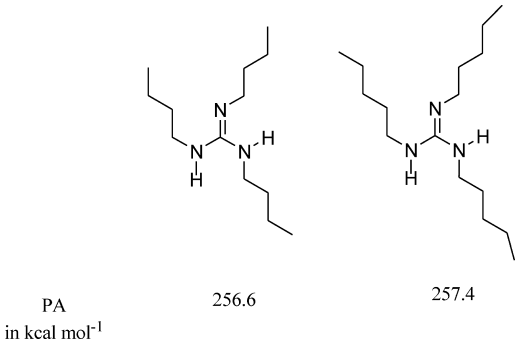

Figure 6. Schematic representation of guanidine's trisubstituted with butyl and pentyl chains and their PA.

PA of the newly designed superbases, may be estimated as a difference in PA between unfolded superbases and guanidines that are tris-substituted with only the corresponding alkyl chains. Namely, the alkyl chain is butyl for superbases **4′**−**7′** and pentyl for superbases **9′**−**13′**, as depicted in Figure 6. The obtained values are denoted as ΔPA(III) and presented in Table 4.

The values of ΔPA(III) are positive for superbases **4′**−**7′**, being between 8 and 15 kcal mol^{-1}. Since these numbers represent the increase of PA due to the presence of functional group **X** at the end of the unfolded alkyl chain, their positive value means that **X** has a strong positive inductive effect, donating electrons trough the alkyl chain toward central guanidine moiety. The inductive effect leads to a higher basicity of the molecule. However, at the same time it decreases the H-bond accepting ability of **X** due to the electron transfer from **X** toward the central guanidine moiety. Consequently, in superbases **4′**−**7′** the **intra**molecular H-bonds are actually weaker than the **inter**molecular bonds in the corresponding tricomplexes, despite the good agreement between ΔPA(I) and $\Delta\Delta H^{228}$ values obtained in modeling H-bond contribution to the PA using enthalpies of complexation. Values of $\Delta\Delta H^{298}$ from Table 3 are in good agreement with ΔPA(I) for these molecules due to an interplay of contributions described above that probably have same magnitude but opposite sign. Nevertheless, the values of enthalpy of complexation ($\Delta\Delta H^{298}$) still represent reliable guidance during the process of finding the appropriate substituents in this type of superbases.

The inductive effect, but with opposite sign, is the cause for relatively large negative ΔPA(III) value for superbase **9′**. In this molecule, the *N*-methyl acetamide substituent acts as an electron acceptor. This enables relatively good preservation of the H-bond strength obtained in the tricomplex. However, at the same time, it significantly decreases the basicity of the molecule when H-bonds are not present, as can be seen from the PA value of the unfolded conformer. It is interesting that the negative inductive effect of the functional group **X** (ΔPA(III) of −10.7 kcal mol^{-1}) is partially canceled out by the positive inductive effect of the pentyl chain, being 7.5 kcal mol^{-1}, resulting in an additional increase in basicity that was already achieved due to the presence of strong intramolecular bonds. A similar situation is apparent for the superbase **10′**, but with a smaller negative inductive effect of **X** (ΔPA(III) of −4.5 kcal mol^{-1}) and consequently a weaker preservation of H-bond strength compared to the tricomplex.

The PA values for molecules **11′**, **12′**, and **13′** are between 286 and 289 kcal mol^{-1}, whereas the stabilization energy based

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on intermolecular H-bondings in tricomplexes is estimated to be ∼44 kcal mol^{-1}. If the stabilization that occurs due to the presence of H-bonds was completely preserved, the resulting proton affinities would reach almost 295 kcal mol^{-1}. We have already established that part of that stabilization may be lost due to the inductive effect of **X** (ΔPA(III)) when the electrons from **X** are withdrawn toward guanidine moiety, thus diminishing the H-bond accepting ability of **X**. However, the inductive effect of **X** is negligible in this case, so it cannot cause the weakening of H-bonds. As in all other cases, different lengths and conformations of alkyl chains were explored; however, such high values of PA were not achieved. The exact reason for this discrepancy is not entirely clear. However, it could be attributed to an unfavorable interaction between the substituent **X** and the alkyl chain. The atom of phosphorus in superbases **11′**, **12′**, and **13′** is linked to the sp^3 atom (nitrogen or carbon) that binds **X** with an alkyl chain. In molecules **5′**, **6′**, and **7′** with higher PA, phosphorus is bound to the sp^2 atom of nitrogen that links **X** with alkyl chain. Different hybridization of the linker atom results in different steric arrangement, since the linker atom in superbases **11′**, **12′**, and **13′** already binds methyl groups that can cause steric clashes with the alkyl chain and induce strain in the heteroalkyl substituent. The strain is more pronounced in the protonated form of these molecules, where additional pseudoring is created due to formation of the third intramolecular H-bond. Increased strain in the protonated form thus leads to a lower PA value.

CONCLUSIONS

A step-by-step approach in designing new superbasic guanidines with heteroalkyl side chains able to form intramolecular H-bonds is presented. This approach consists of two steps: (1) finding a strong H-bond acceptor by calculating the enthalpy of complexation between the central guanidine moiety (**TMG**) and basic molecules that can serve as molecular fragments with strong H-bond ability and (2) finding the optimal length of alkyl chain that connects central guanidine with basic molecular fragment in a way to preserve the ideal orientation of the basic molecular fragments around the central guanidine. This approach proved very efficient since we were able to find substituted guanidines that are far more basic than the parental **tris-DMPG** in the gas phase as well as in acetonitrile. The obtained gas phase proton affinities vary between 286.2 and 293.3 kcal mol^{-1}, while the pK_a values range from 29.5 to 33.2. Using this approach we found that when a methoxy group serves as the basic molecular fragment, as in the previously synthesized **tris-MtxPG**, the propyl chain is not long enough to achieve maximal PA. Replacing the propyl chain with a butyl or pentyl bridge increases the PA of the resulting molecules by ∼6 kcal mol^{-1}. A more detailed analysis of various effects that may influence PA of heteroalkyl-substituted guanidines revealed that not only do intramolecular hydrogen bonds play an important role but the inductive effect of the molecular fragment at the end of alkyl chain and alkyl chain itself also have a significant influence on PA.

The new superbases studied herein are the most basic guanidines designed so far. As these compounds should be synthetically accessible, we look forward to their preparation and application in an experimental setting.

ASSOCIATED CONTENT

Supporting Information

Cartesian coordinates, number of imaginary frequencies and thermal corrections to enthalpy for optimized structures of neutral and protonated form of superbases **2′-butyl**, **2′-pentyl**, **4′**, **5′**, **6′**, **7′**, **9′**, **10′**, **11′**, **12′**, and **13′** calculated at the B3LYP/6-31G(d) level of theory. Energies of these superbases calculated at the B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) level of theory. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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DEDICATION

This paper is dedicated to the memory of the late Professor Zvonimir Maksić.

REFERENCES

(1) Schwesinger, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1164−1165.
(2) Schwesinger, R.; Missfeldt, M.; Peters, K.; von Schnering, H. G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1165−1167.
(3) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1167−1169. Schwesinger, R. *Nachr. Chem., Tech. Lab.* **1990**, *38*, 1214−1226. Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435−2454. Schwesinger, R.; et al. *Liebigs Ann.* **1996**, 1055−1081. Kaljurand, I.; Rodima, T.; Leito, I.; Koppel, I. A.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 6202−6208.
(4) Verkade, J. G. *Acc. Chem. Res.* **1993**, *26*, 483−489. Verkade, J. G. *Coord. Chem. Rev.* **1994**, *137*, 233−295. Wroblewski, A. E.; Pinkas, J.; Verkade, J. G. *Main Group Chem.* **1995**, *1*, 69−79. Verkade, J. G. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1621−1631. Verkade, J. G. *New Aspects Phosphorus Chem. II (Top. Curr. Chem.)* **2003**, *223*, 1−44. Verkade, J. G.; Kisanga, P. B. *Aldrichimica Acta* **2004**, *37*, 3−14.
(5) Alder, R. W.; Bowman, P. S.; Steele, W. R. S.; Winterman, D. R. *Chem. Commun.* **1968**, 723−724.
(6) Alder, R. W. *Chem. Rev.* **1989**, *89*, 1215−1223.
(7) Staab, H. A.; Saupe, T. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 865−879. Barth, T.; Krieger, C.; Neugebauer, F. A.; Staab, H. A. *Angew. Chem.* **1991**, *103*, 1006−1008.
(8) Kovačević, B.; Maksić, Z. B. *Chem.—Eur. J.* **2002**, *8*, 1694−1702. Raab, V.; Kipke, J.; Gschwind, R. M.; Sundermeyer, J. *Chem.—Eur. J.* **2002**, *8*, 1682−1693. Raab, V.; Harms, K.; Sundermeyer, J.; Kovačević, B.; Maksić, Z. B. *J. Org. Chem.* **2003**, *68*, 8790−8797. Raab, V.; Gautchenova, K.; Merkoulov, A.; Harms, K.; Sundermeyer, J.; Kovačević, B.; Maksić, Z. B. *J. Am. Chem. Soc.* **2005**, *127*, 15738−15743.
(9) Alder, R. W. *J. Am. Chem. Soc.* **2005**, *127*, 7924−7931.
(10) Singh, A.; Chakraborty, S.; Ganguly, B. *Eur. J. Org. Chem.* **2006**, 4938−4942.
(11) Kovačević, B.; Maksić, Z. B.; Vianello, R.; Primorac, M. *New J. Chem.* **2002**, *26*, 1329−1334.
(12) Singh, A.; Ganguly, B. *New J. Chem.* **2008**, *32*, 210−213.

(13) Margetić, D.; Ishikawa, T.; Kumamoto, T. *Eur. J. Org. Chem.* **2010**, 6563−6572. Margetić, D.; Trošelj, P.; Ishikawa, T.; Kumamoto, T. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1055−1057.
(14) Singh, A.; Ganguly, B. *Eur. J. Org. Chem.* **2007**, 420−422.
(15) Singh, A.; Ganguly, B. *New J. Chem.* **2009**, *33*, 583−587.
(16) Ganguly, B.; Koley, D.; Thiel, W. *Tetrahedron* **2007**, *63*, 7970−7976.
(17) Despotović, I.; Kovačević, B.; Maksić, Z. B. *New J. Chem.* **2007**, *31*, 447−457.
(18) Despotović, I.; Kovačević, B.; Maksić, Z. B. *Org. Lett.* **2007**, *9*, 1101−1104.
(19) Despotović, I.; Kovačević, B.; Maksić, Z. B. *Org. Lett.* **2007**, *9*, 4709−4712.
(20) Uchida, N.; Kuwabara, J.; Taketoshi, A.; Kanbara, T. *J. Org. Chem.* **2012**, *77*, 10631−10637.
(21) Lo, R.; Singh, A.; Kesharwani, M. K.; Ganguly, B. *Chem. Commun.* **2012**, *48*, 5865−5867.
(22) Ishikawa, T. *Superbases for Organic Synthesys: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; Wiley: New York, 2009.
(23) Maksić, Z. B.; Kovačević, B.; Vianello, R. *Chem. Rev.* **2012**, *112*, 5240−5270.
(24) Raczynska, E. D.; Maria, P.-C.; Gal, J. F.; Decouzon, M. *J. Phys. Org .Chem.* **1994**, *7*, 725−733.
(25) Maksić, Z. B.; Kovačević, B. *J. Phys. Chem. A* **1999**, *103*, 6678−6684.
(26) Raczynska, E. D.; Maria, P. C.; Gal, J. F.; Decouzon, M. *J. Org. Chem.* **1992**, *57*, 5730−5735.
(27) Kovačević, B.; Glasovac, Z.; Maksić, Z. B. *J. Phys. Org. Chem.* **2002**, *15*, 765−774.
(28) Glasovac, Z.; Štrukil, V.; Eckert-Maksić, M.; Schröder, D.; Kaczorowska, M.; Schwarz, H. *Int. J. Mass Spectrom.* **2008**, *270*, 39−46.
(29) Tian, Z. T.; Fattahi, A.; Lis, L.; Kass, S. R. *Croat. Chem. Acta* **2009**, *82*, 41−45.
(30) Bachrach, S. M.; Wilbanks, C. C. *J. Org. Chem.* **2010**, *75*, 2651−2660.
(31) Bachrach, S. M. *Org. Lett.* **2012**, *14*, 5598−5601.
(32) Glasovac, Z.; Kovačević, B.; Meštrović, E.; Eckert-Maksić, M. *Tetrahedron Lett.* **2005**, *46*, 8733−8736.
(33) Kovačević, B.; Barić, D.; Maksić, Z. B. *New J. Chem.* **2004**, *28*, 284−288.
(34) Eckert Maksić, M.; Glasovac, Z.; Trošelj, P.; Kutt, A.; Rodima, T.; Koppel, I.; Koppel, I. A. *Eur. J. Org. Chem.* **2008**, *30*, 5176−5184.
(35) Schuchardt, U.; Serchelia, R.; Vargas, R. M. *J. Braz. Chem. Soc.* **1998**, *9*, 199−210.
(36) Glasovac, Z.; Eckert-Maksić M. EP Patent 1786763(A1), 2007.
(37) Glasovac, Z.; Eckert-Maksić, M.; Maksić, Z. *New J. Chem.* **2009**, *33*, 588−597.
(38) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A. *Gaussian 03*, Revision D.02; Gaussian, Inc.: Wallingford, CT, 2004.
(39) Kovačević, B.; Maksić, Z. B. *Org. Lett.* **2001**, *3*, 1523−1526.