

Step Forward to Stronger Neutral Organic Superbases: Fused Troponimines

Kayvan Saadat, Ali Shiri,* and Borislav Kovačević

Cite This: *J. Org. Chem.* 2020, 85, 11375–11381

Read Online

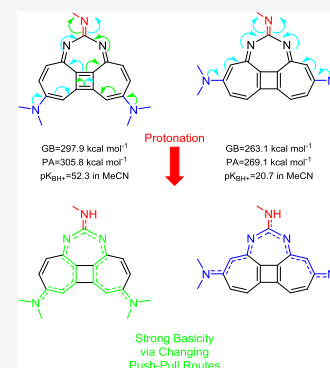
ACCESS |

Metrics & More

Article Recommendations

Supporting Information

ABSTRACT: In this study, using a computational approach, we are pursuing to find a proper answer about the possible application of fused TIs as superbases through the calculation and discussion of standard thermochemistry parameters, like gas-phase basicity (GB) and proton affinity (PA). In some studied cases, the role of aromaticity/antiaromaticity fluctuations supposed to be more important than mesomeric effects. In this sense, nucleus-independent chemical shift (NICS) and anisotropy of the induced current density (ACID) were utilized in this study to probe into the aromaticity-related parameters of the proposed molecules. Results revealed the highest GB/PA values for the molecules having cyclobutadiene in between two troponimines. Additional investigation was performed into the other candidates of cyclobutadiene-fused troponimines by substituting several electron donors along with the changing position of donors. Some novel superbases offered record-holding GB/PA values so that PA magnitudes higher than 300 kcal mol⁻¹ are now feasible for nonphosphorous neutral organic superbases (NOS).



INTRODUCTION

The deprotonation of the reactant is usually the most crucial step in many organic reactions,¹ which sometimes require very strong superbases. Neutral organic superbases (NOS) are organic molecules that have higher basicity than that of 1,8-bis(dimethylamino)naphthalene (DMAN) with gas basicity (GB) of 239 kcal mol⁻¹ and proton affinity (PA) of 245.3 kcal mol⁻¹.^{2,3} The NOS are commonly categorized into amidines,⁴ guanidines,^{5–7} phosphazenes,^{8,9} phosphines,^{10,11} aromatization-assisted cyclo-organic compounds like cyclopropenimines and troponimines,^{12–14} and compounds where above-mentioned subgroups are combined into one molecule, which are usually called hybrid superbases. Superbases, where basic substituents are brought into close proximity by substitution of aromatic backbone, are termed proton sponges. Examples are DMAN, 1,8-bis(hexamethyltriainophosphazenylnaphthalene (HMPN), 1,8-bis(methylidene(hexamethyltriaino)phosphorane)naphthalene (MHPN), 1,8-bis(tetramethylguanidino)naphthalene (TMGN), and 1,8-bis(bis(diisopropylamino)cyclopropeniminylnaphthalene (DACN).^{15–18}

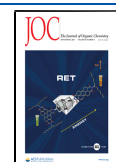
The development of NOS systems has been focused on the ability of the delocalization of protonation-induced positive charge and of the formation of intramolecular H-bond(s) in the conjugate acid.^{19,20} Efforts pursued to develop NOS with aromatic character upon protonation have lasted more than a decade.²¹ Cyclopropenimine (CPI) is an excellent example of this since it enables the delocalization of positive charge of protonated molecule in the smallest 2πe⁻ aromatic system.²² It is worth mentioning that bis-*N,N'*-(1,3-dialkyl-4,5-dimethyl-1H-imidazol-2(3H)-ylidene) guanidines (pK(BH⁺) of 24.9–

28.5 in tetrahydrofuran (THF))²³ and biscyclopropeniminylguanidine (pK(BH⁺) of 35.6 in THF) superbases as the most basic phosphorous-free NOS synthesized so far. In some recent theoretical studies, it was shown that in mixed CPI/guanidine systems where multiple intramolecular H-bonds (IMHB) stabilize conjugate acid PA values of up to 306.0 kcal mol⁻¹ could be achieved.^{12,24} Recently, we have demonstrated that troponimines (TI) possess the same capability as CPI, but resulting in higher GB/PA values.²⁵ It should be mentioned that NOS design was not limited to theoretical investigations only; however, many theoretically designed NOS have been synthesized and are nowadays being used as promoters of chemical reactions.^{26–34} Aromatization, therefore, is considered to be the main driving force in high-basicity trait of new NOS systems. Investigation on the possible role of the antiaromaticity character of some NOS candidates, however, still remained on the margin of NOS researchers' desk, and the current paper tries to shed light on this area.

In continuation of our previous work on TIs, we raised the question of whether the basicity of fused TIs with different rings between troponimine moieties is high enough to enable the application of such designed molecules in organic chemistry. Therefore, synthetic routes for the fused types of such compounds should be addressed first to determine if their

Received: June 20, 2020

Published: July 31, 2020



synthesis is achievable or not. Reports are available on the synthesis of tropylium amines,^{35,36} troponimines, and their salts,^{37–39} 5-dibenzosuberone (A),⁴⁰ cycloheptadienes (B)^{41,42} (an antihistamine), and amitriptyline (C)⁴³ (an antidepressant agent). 6,7-Dihydro-5H-dicyclohepta[*b,d*]-pyrrole (D),⁴⁴ 1,7-dihydrobenzo-[1,2:4,5]dicycloheptene (E), and 1,11-dihydrobenzo-[1,2:4,5]dicycloheptene (F)⁴⁵ were also synthesized and identified properly (see Figure 1). Several

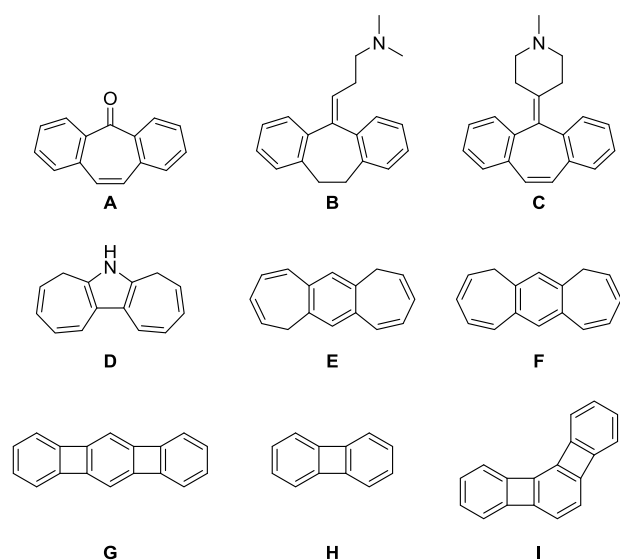


Figure 1. Examples of successfully synthesized fused cycloheptatrienes, cycloheptadienes, and biphenylenes.

seven-membered fused rings obtained by the Aza-Wittig-type reaction can be enumerated as an excellent strategy to introduce a carbon–nitrogen double bond on the cyclic system.⁴⁶ On the other hand, there are several examples of a successful synthesis of molecules where the four-membered ring is fused between two benzene rings (compounds G–I; Figure 1) as the main target^{47–51} or the side product.⁵² These examples especially could be useful to draw strategies for the possible synthesis of compound 4 in Figure 2.

With this synthetic background of fused seven-membered ring compounds, we proposed a set of fused TI molecules, differing from each other by the number and type of atoms in the middle of the two TI rings (Figure 2).

To the best of our knowledge, the only theoretical study on fused cycloheptatriene systems was the CPI-substituted 1-azaazulene, which was reported as the highest GB and PA for nonphosphorated substituted ones with 284.1 and 290.7 kcal mol⁻¹, respectively.⁵³

RESULTS AND DISCUSSION

GB and PA data of the most important bases studied here are presented in Figure 2. Initial results indicated that all proposed bases can be classified as superbases. Introducing dimethylamino groups (dma) to superbases resulted in an increase in basicity values ranging from 11.2 to 14.9 kcal mol⁻¹. For instance, GB and PA values of **1b** increase by 12.8 and 11.2 kcal mol⁻¹, respectively, upon implementation of two dimethylamino groups (dma) onto the C3 and C8 positions of **1a** superbase. Generally, most promising basicity values are obtained for **1b** and **2c** compounds. It should be noted that protonation of **2b** and **2c** occurs on the side TI ring and not in

the middle TI-imine. A few examples with lesser importance in terms of GB and PA are depicted in Figure S1.

Most of the studied NOS partially owe their superbasic property to the stabilization of the incorporated proton via intramolecular H-bonding. According to the electron density and Laplacian of H-bond BCPs, as well as E_{HB} calculated by eq 4 shown in the Computational Methodology section, effective H-bonding is confirmed for those structures where the suitable orientation of interacting moieties enable such interaction. Most of the bases show a range of 7.0–9.0 kcal mol⁻¹ of the H-bond strength (Table S3).

Calculating nucleus-independent chemical shift⁵⁴ on $\pm 1\text{Å}$ from the center of the rings, namely, NICS(1)_{zz} helps us to track the change in aromaticity of the proposed bases upon protonation. As expected, the cyclobutadiene rings in **1a** and **1b** reveal a high antiaromatic character for the free bases and become even more antiaromatic in the conjugated acids. NICS(1)_{zz} values are increased from about 43 to 50 ppm in both cases of cyclobutadiene rings. Such an increase in the antiaromatic character of cyclobutadiene ring, in **1a** for instance, comes with a relatively high PA of 279.5 kcal mol⁻¹ with respect to the other candidates in Figure 2. For **2a** compound, as the corresponding imine group is not located on the TI rings, the broad π -system can delocalize the positive charge throughout three fused rings and therefore show high aromaticity. The other considered bases demonstrate a slight to moderate decrease of NICS(1)_{zz} on the protonated TI ring while unprotonated TI moiety generally shows an increase in these values. The middle ring in most cases exhibits a decrease in aromaticity, with slight fluctuation. Full details of NICS(1)_{zz} values of the bases presented in Figure 2 are available in the Supporting Information (Table S1).

Thermodynamic properties of molecules presented in the first row in Figure 2 look promising for our goal of designing a new class of fused TI-NOS. Inspection of GB/PA values of **1a** and **1b** along with their NICS(1)_{zz} data raises a question of what level of tuning can be applied to **1b** and which values of basicity parameters can be achieved through this tuning. Therefore, we calculated the basicity of several modified fused TIs, where modification goes from placing CPI substituents on right position on TI rings to bridging of N atoms of TIs by the imino group. A new set of bases that we considered theoretically are presented in two lower rows of Figure 2, along with their GB and PA values.

To continue probing the basicity of **1a**, two TIs cyclized by a diazene moiety to yield a pyridazine ring at the bottom (**3a**). However, GB/PA values for **3a** drop by 13.2 kcal mol⁻¹, compared with GB/PA of **1a**. The main reason for such a decrease in basicity can be deduced from the electron-withdrawing effect of pyridazine's nitrogen. The absence of any electron donor in the π -system also leaves imine groups alone in the polarization of TIs. For **3b** compound, GB/PA decreases by 6.6/4.9 kcal mol⁻¹, indicating that the more suitable positions of DMA groups are 3- and 8- positions. On the contrary, compound **3c** showed an 8.2/9.5 kcal mol⁻¹ increase in GB/PA values with respect to those of **1b**. This proves the fact that adding two dma groups in conjugation with the existing dma groups moderately improves the basicity.

In the next phase, two imines of **1b** are cyclized by a C=NMe group to form **4a** (GB = 263.1 and PA=269.1 kcal mol⁻¹), which is associated with about 10 kcal mol⁻¹ decrease in GB/PA in comparison with **1b** analogue. On the other hand, **4c** shows an approximately 15 kcal mol⁻¹ increase in the GB/

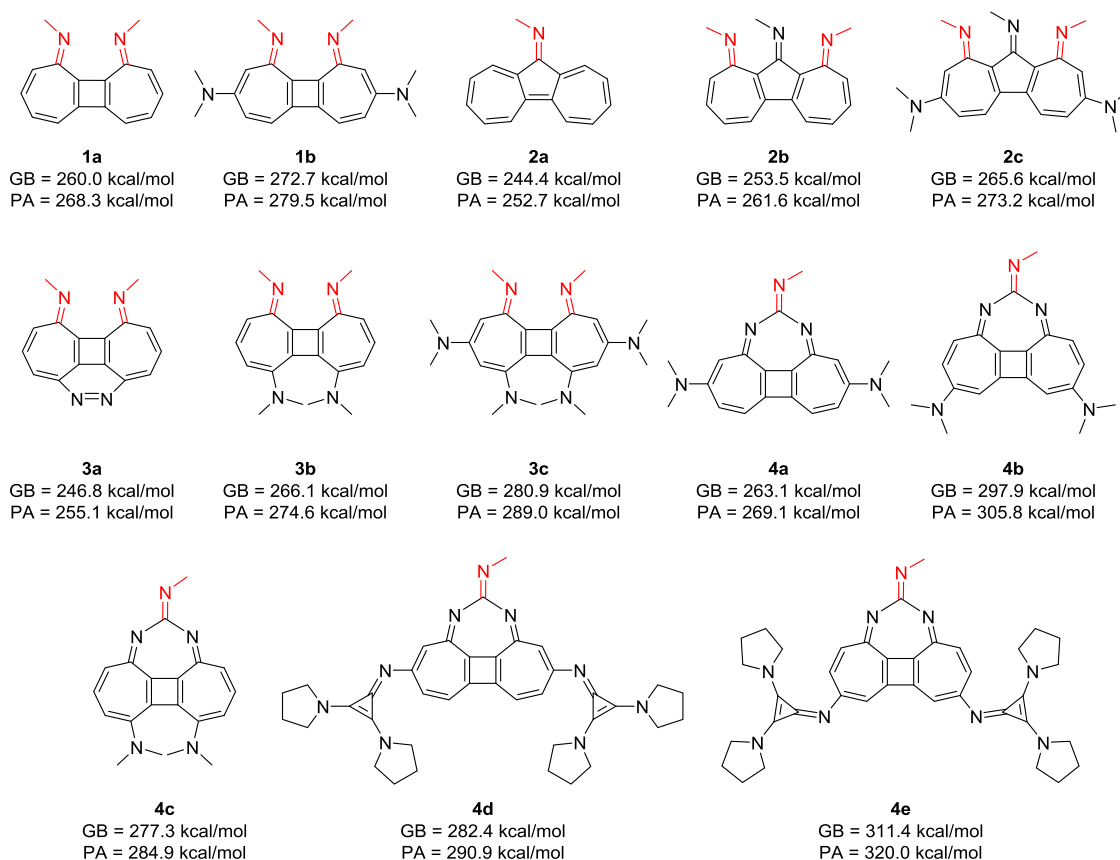
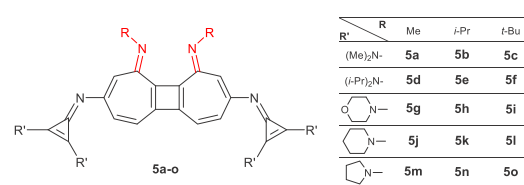


Figure 2. Gas basicity (GB) and proton affinity (PA) of the most promising superbase candidates calculated at M06-2X/def2TZVPP//M06-2X/def2SVP level of theory. The most basic sites are shown in red.

PA values (GB = 277.3 kcal mol⁻¹ and PA = 284.9 kcal mol⁻¹) in contrast to those of **4a**. Due to the antiaromatic properties observed in **1a** and **1b** bases, we decided to move dma groups to a new position (C4 and C7) in conjugation with cyclobutadiene ring to form **4b**. With this, pushing electrons in an alternative π -conjugated route enable us to track the antiaromaticity character of the cyclobutadiene and also basicity parameters. Unexpectedly, we obtained GB/PA values of 297.9 and 305.8 kcal mol⁻¹ for **4b**, respectively. Upon protonation, the cyclobutadiene moiety in **4b** is more squeezed than in **4a**. Influenced bond lengths are depicted in Figure S2 and available in the Supporting Information.

The hypothesis of altering the push–pull routes was tested again by substituting dma groups with bis(2,3-dipyrrolidin-1-yl)CPI. Compound **4d** (GB = 282.4 kcal mol⁻¹, PA = 290.9 kcal mol⁻¹) reveals a moderate improvement of ~10 kcal mol⁻¹ in GB/PA compared to **1b**. As expected, **4e** recorded GB of 311.4 kcal mol⁻¹ and PA of 320.0 kcal mol⁻¹, which push the limit of GB and PA for nonphosphorous aromatic-stabilized NOS. As long as the CPI's imine group can act as a plausible protonation site of **4e**, another calculation shows 277.5 and 285.0 kcal mol⁻¹ of GB and PA for CPI protonation, respectively. This demonstrates that the protonation mostly occurs on the imine of diazeno moiety of **4e**.

In a side study, we replaced dma groups with several CPI-based substitutions in **4a** to explore any systematic effects of various secondary amines of CPIs and alkyl groups of imines on the basicity. According to Figure 3, GB and PA values of **5a–o** bases obtained in the range of 280.5–291.3 and 287.6–300.5 kcal mol⁻¹, respectively, which is expressive of a high



Base	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	5m	5n	5o
GB	288.9	288.3	284.1	290.7	289.4	285.8	281.0	284.5	280.5	291.3	291.3	287.7	290.3	290.1	287.9
PA	297.6	297.6	294.3	298.1	297.4	293.6	287.6	292.3	288.1	297.9	298.1	294.5	300.2	300.5	297.6

Figure 3. Extended CPI-substituted **4a** NOS, gas basicity (GB), and proton affinity (PA) in kcal mol⁻¹ calculated at M06-2X/def2TZVPP//M06-2X/def2SVP level of theory.

electron-donor trait of the substituted secondary amines on CPIs. The highest values of GB/PA can be achieved when pyrrolidine and piperidine substituents are introduced in **5m–o** and **5j–l** bases, respectively. On the other hand, morpholino-CPI substituent shows the lowest basicity among the set of considerations. The effect of alkyl substituents on the imino groups on GB/PA values can be waived off; however, we could see some trends here. *t*-Bu group contributes least to the PA and GB values, although its inductive effect is higher than that of Me or *i*-Pr groups. However, its bulkiness induces steric problems, and repulsion between imino moieties, which reduce PA/GB values. Contribution of Me and *i*-Pr groups to GB/PA is very similar, although ordering of their contribution is not the same since GB involves entropic term too.

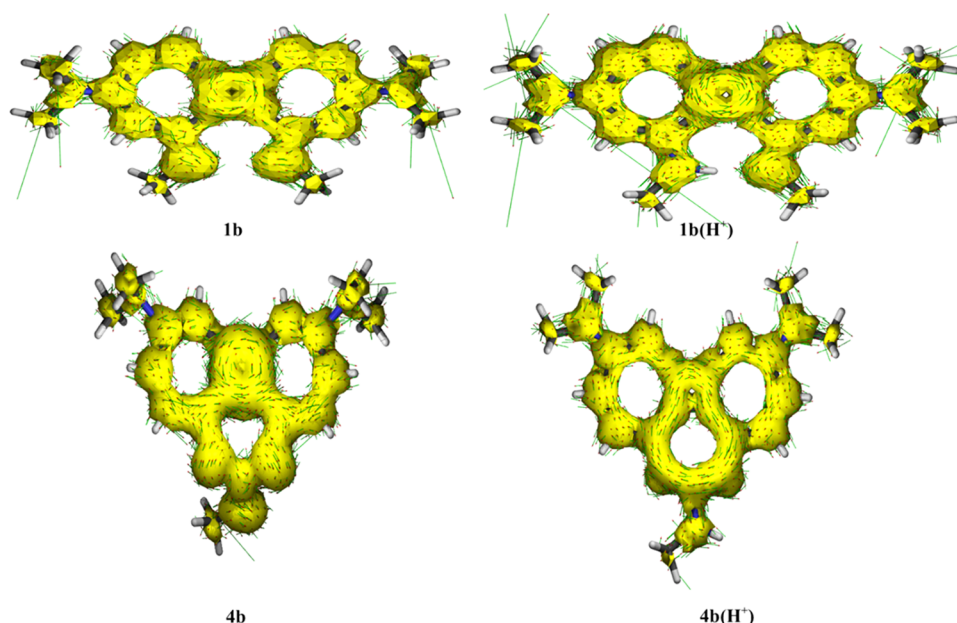


Figure 4. ACID plots of 1a and 13 bases and their conjugated acids.

The data obtained from NICS(1)_{zz} calculation show that 5a–o, 3b, and 3c bases display similar trends to those observed previously for 1a and 1b. The only additional point is that CPI rings (in 5a–o bases) exhibit lower NICS(1)_{zz} values after protonation of bases. It should be mentioned also that the aromaticity of the pyridazine ring remains almost unchanged in the base 3a. We can see a moderate aromatization of TI rings in the 4b, although they are still antiaromatic. In this regard, NICS(1)_{zz} values are calculated for the cyclobutadiene ring of 4b by 110.7 and 131.5 ppm for ± 1 Å above and behind the center of the ring. NICS(1)_{zz} values are highly decreased by 64.5 and 85.3 ppm after protonation of 4b and antiaromaticity transferred to the diazeno-TI upstream ring. Substantial ring current of 1a cyclobutadiene and more accumulation of such current could be seen in anisotropy of the induced current density⁵⁵ (ACID) plots presented in Figure 4. For 4b, however, the ring current changing is much considerable from cyclobutadiene to diazeno ring upon protonation. The modulation in the magnitude of cyclobutadiene ring antiaromaticity, soothing this character by the alternating ring current to adjacent rings in certain bases and its relevance to calculated high basicity, is emphasized again as a key finding of the presented study. Quantitatively calculated NICS(1)_{zz} data of important bases of Figures 2 and 3 are available in the Supporting Information (Tables S4–S6).

The case of molecular weight is a significant point in the current theoretical study since a low-molecular-weight base is mostly preferred in practical application.⁵⁶ Without any experiment data in hand, however, we can not reach to such level of reliance on how much our proposed superbase can be stable in real laboratory conditions or how many synthetic steps are needed to prepare them. Therefore, if such a hypothesis is made, in which our proposed bases have the desirable stability, we can address Schwesinger's P4-*t*-Bu⁵⁷ with GB = 287.7 kcal mol⁻¹ (according to a theoretical assessment of Leito et al.⁵⁶), which is a commercially available poly-(aminophosphazenic) superbase. Nevertheless, the main disadvantage of such a superbase is the problem of high molecular weight (M_w (P4-*t*-Bu) = 633.73 g mol⁻¹). The

strongest NOS in the current report, 4e (M_w = 623.81 g mol⁻¹) has an approximate molecular weight of P4-*t*-Bu, however, with much higher basicity. Base 4b (M_w = 331.42 g mol⁻¹) also has a similar magnitude of GB/PA with respect of P4-*t*-Bu, but in almost half of P4-*t*-Bu's molecular weight.

The last discussion reflects the calculated pK(BH⁺) of the presented NOS. In this study, we calculated the pK(BH⁺) of all bases both in MeCN and THF solvent by utilizing eq 3 in the Computational Methodology section. It appears that some bases, for example, 4b and 4e, show unusually high pK(BH⁺) values of 52.3 and 49.5, respectively, in MeCN; however, we should take obtained numbers with care since they are results of linear extrapolation against solvated reference superbase, and the accuracy of pK(BH⁺) calculated in this way is lower than the accuracy of the calculated PA/GB values. Calculated pK(BH⁺) data from Tables S1 and S2 have only such merit of direct comparison within the set of current calculation and any further conclusion must be associated with experimental measurements if some of the bases presented herein are to be successfully synthesized.

CONCLUSIONS

Neutral organic superbases (NOS) play an important role in organic synthesis. Designing an efficient NOS like cyclopropeneimine-derived (CPI) bases leads to a new generation of NOS that could find many beneficial applications in synthesis. In this study, several fused troponimine (fTI) molecules are considered to be the candidates of NOS. Among them, base 1b shows high GB/PA values with exceptional high antiaromaticity characteristics, and by modification of substituents and their position, we introduce hyperbases 4b (GB = 297.9 kcal mol⁻¹ and PA = 305.8 kcal mol⁻¹) and 4e (GB = 311.4 kcal mol⁻¹ and PA = 320.0 kcal mol⁻¹). Such thermodynamic data for 4e hit the GB/PA records for nonphosphorous aromatic-stabilized NOS with TI ring in the main structure. Also, base 4b is proposed as the most economical base of this study since it has a higher GB value compared with Schwesinger's P4-*t*-Bu superbase by almost halved molecular weight. This study also shows that the

aromaticity is not the only parameter involved in determining fused molecules that serve as NOS or not. Still, the changes in aromaticity will influence superbasicity behavior, substantially.

Computational Methodology. Geometry, of all structures and their corresponding conjugated acids, were optimized without any symmetry constraint at M06-2X/def2SVP level.^{58,59} Wavefunction stability⁶⁰ and frequency (at 298 K) calculations on optimized structures have been performed to ensure the stability of the closed-shell wavefunction of the system, and its location in the minimum on potential energy surface. Single-point calculations, both in the gas phase and in solution utilizing the SMD method,⁶¹ were done consequently at M06-2X/def2TZVPP//M06-2X/def2SVP to obtain GB, PA, and pK(BH⁺). GB and PA were calculated as follows

$$PA = -\Delta H = H(B) - H(BH^+) + (5/2)RT \quad (1)$$

$$GB = -\Delta G = G(B) - G(BH^+) + G(H^+) \quad (2)$$

where “H” is the enthalpy, “G” is the Gibbs free energy, and B and BH⁺ are the free base and its conjugate acid, respectively. We take into account that G(H⁺) = -6.29 kcal mol⁻¹ (at 298 K/gas phase).⁶²

To evaluate pK(BH⁺) values, we used the following equation,⁶³ where “A” is a reference base with experimentally known pK(AH⁺) and which possesses values of pK(BH⁺) close to that of the investigated compounds. Applying acetonitrile as the solvent phase and considering 1,2-diisopropylamino-cycloprop-1-ene(*t*-butyl)imine (DAC) as the reference base with experimental pK(AH⁺) = 26.9 in MeCN,⁶⁴ and a recently developed phosphazeny phosphine NOS ((**dma**)P₃P) base with pK(AH⁺) = 34.9 in THF¹¹ were chosen as the reference bases for pK(BH⁺) calculation in MeCN and THF, respectively.

$$\begin{aligned} pK(BH^+) = pK(AH^+) + [G_{\text{gas}}(B) - G_{\text{gas}}(A) \\ - G_{\text{gas}}(BH^+) + G_{\text{gas}}(AH^+) + \Delta G_{\text{solv.}}(B) \\ - \Delta G_{\text{solv.}}(A) - \Delta G_{\text{solv.}}(BH^+) \\ + \Delta G_{\text{solv.}}(AH^+)]/2.303RT \quad (3) \end{aligned}$$

Calculation of nucleus-independent chemical shift⁵⁴ (NICS) index for aromaticity of ±1 Å above and below the ring's geometry center was performed by Multiwfn software⁶⁵ and by utilizing wavefunction provided from M06-2X/def2SVP optimized geometries. Isotropic tensors for NICS calculation were computed and extracted via NMR calculations with gauge-independent atomic orbital (GIAO) method⁶⁶ at WP04⁶⁷/Def2TZVPP//M06-2X/def2SVP in the gas phase. Anisotropy of the induced current density (ACID)⁵⁵ plots was calculated and depicted by AICD 2.0.0 suite⁵⁵ at M06-2X/def2SVP level and using a continuous set of gauge transformations (CSGT) method.⁶⁸

The energies of H-bonding of each conjugated acids were calculated by modified Espinosa equation,⁶⁹ in which $E_{\text{HB}}(\rho^{\text{BCP}})$ and ρ^{BCP} represent the H-bonding associated with -NH-N- moiety of the conjugated acid and density of electron in such bonding critical points (BCP) calculated by AIMAll suite⁷⁰ at M06-2X/def2SVP (eq 4).

$$E_{\text{HB}}(\rho^{\text{BCP}}) = 191.4\rho^{\text{BCP}} - 1.78 \quad (4)$$

All geometry optimization, frequency calculation, solvation energies, and NMR calculations were done by Gaussian 09 package.⁷¹

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.0c01466>.

pK(BH⁺) (in MeCN and THF) and NICS(1)_{zz} values and H-bonding BCPs of proposed bases, two figures of other NOS candidates with their corresponded GB/PA values and bonding lengths of **4a** and **4b**, Cartesian coordination for geometrically optimized bases and relative conjugated acids, their SCF, zero-point corrected energies, and other calculated thermochemistry parameters (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Ali Shiri – Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, 91775-1436 Mashhad, Iran; orcid.org/0000-0003-2987-3166; Email: alishiri@um.ac.ir

Authors

Kayvan Saadat – Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, 91775-1436 Mashhad, Iran; orcid.org/0000-0003-1912-8875

Borislav Kovačević – Group for Computational Life Science, Division of Chemistry, Ruder Boskovic Institute, 10000 Zagreb, Croatia

Complete contact information is available at: <https://pubs.acs.org/10.1021/acs.joc.0c01466>

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the Research Council of Ferdowsi University of Mashhad (3/44506) and the HPC Center of the Ferdowsi University of Mashhad for performing the computations.

■ REFERENCES

- (1) Ishikawa, T. General Aspects of Organosuperbases. In *Superbases for Organic Synthesis*; Wiley Online Library, 2009; pp 1–7.
- (2) Alder, R. W.; Bowman, P. S.; Steele, W. R. S.; Winterman, D. R. The Remarkable Basicity of 1, 8-Bis (Dimethylamino) Naphthalene. *Chem. Commun.* **1968**, 723–724.
- (3) Decouzon, M.; Gal, J.-F.; Maria, P.-C.; Raczyńska, E. D. Superbases in the Gas Phase: Amidine and Guanidine Derivatives with Proton Affinities Larger than 1000 KJ Mol⁻¹. *Rapid Commun. Mass Spectrom.* **1993**, 7, 599–602.
- (4) Raczyńska, E. D.; Laurence, C.; Nicolet, P. Hydrogen Bonding Basicity of Amidines. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1491–1494.
- (5) Schwesinger, R.; Mißfeldt, M.; Peters, K.; von Schnering, H. G. Novel, Very Strongly Basic, Pentacyclic “Proton Sponges” with Vinamidine Structure. *Angew. Chem., Int. Ed.* **1987**, 26, 1165–1167.
- (6) Raczyńska, E. D.; Cyrański, M. K.; Gutowski, M.; Rak, J.; Gal, J.-F.; Maria, P.-C.; Darowska, M.; Duczmal, K. Consequences of Proton Transfer in Guanidine. *J. Phys. Org. Chem.* **2003**, 16, 91–106.
- (7) Barić, D.; Dragičević, I.; Kovačević, B. Design of Superbasic Guanidines: The Role of Multiple Intramolecular Hydrogen Bonds. *J. Org. Chem.* **2013**, 78, 4075–4082.

- (8) Schwesinger, R. Extremely Strong, Non-Ionic Bases: Syntheses and Applications. *Chimia* **1985**, *39*, 269–272.
- (9) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H. Extremely Strong, Uncharged Auxiliary Bases; Monomeric and Polymer-Supported Polyaminophosphazenes (P2–P5). *Liebigs Ann.* **2006**, *1996*, 1055–1081.
- (10) Verkade, J. G.; Kisanga, P. B. Recent Applications of Proazaphosphatranes in Organic Synthesis. *Aldrichim. Acta* **2005**, *36*, 3–14.
- (11) Ullrich, S.; Kovačević, B.; Xie, X.; Sundermeyer, J. Phosphazanyl Phosphines: The Most Electron-Rich Uncharged Phosphorus Brønsted and Lewis Bases. *Angew. Chem., Int. Ed.* **2019**, *58*, 10335–10339.
- (12) Barić, D.; Kovačević, B. Towards the Strongest Neutral Organic Superbases. *Croat. Chem. Acta* **2014**, *87*, 459–464.
- (13) Barić, D.; Kovačević, B. Cyclopropenimine as Pincer Ligand and Strong Electron Donor in Proton Sponges. *J. Phys. Org. Chem.* **2016**, *29*, 750–758.
- (14) Kovačević, B.; Liebman, J. F.; Maksić, Z. B. “Nibbering’s C7H7N”: An Ab Initio Study of the Structure and Electronic Properties of Benzaldimine and Its Protonated Ion. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1544–1548.
- (15) Raab, V.; Gauchenova, E.; Merkoulou, A.; Harms, K.; Sundermeyer, J.; Kovačević, B.; Maksić, Z. B. 1, 8-Bis (Hexamethyl-triaminophosphazanyl) Naphthalene, HMPN: A Superbasic Bisphosphazene “Proton Sponge”. *J. Am. Chem. Soc.* **2005**, *127*, 15738–15743.
- (16) Raab, V.; Kipke, J.; Gschwind, R. M.; Sundermeyer, J. 1,8-Bis (Tetramethylguanidino) Naphthalene (TMGN): A New, Superbasic and Kinetically Active “Proton Sponge”. *Chem. - Eur. J.* **2002**, *8*, 1682–1693.
- (17) Belding, L.; Dudding, T. Synthesis and Theoretical Investigation of a 1,8-Bis(Bis(Diisopropylamino)Cyclopropeniminyl)-Naphthalene Proton Sponge Derivative. *Chem. - Eur. J.* **2014**, *20*, 1032–1037.
- (18) Kögel, J. F.; Margetić, D.; Xie, X.; Finger, L. H.; Sundermeyer, J. A Phosphorus Bisylide: Exploring a New Class of Superbases with Two Interacting Carbon Atoms as Basicity Centers. *Angew. Chem., Int. Ed.* **2017**, *56*, 3090–3093.
- (19) Bachrach, S. M.; Wilbanks, C. C. Using the Pyridine and Quinuclidine Scaffolds for Superbases: A DFT Study. *J. Org. Chem.* **2010**, *75*, 2651–2660.
- (20) Bachrach, S. M. Extended Hydrogen Bond Network Enabled Superbases. *Org. Lett.* **2012**, *14*, 5598–5601.
- (21) Maksić, Z. B.; Kovačević, B. Spatial and Electronic Structure of Highly Basic Organic Molecules: Cyclopropenimines and Some Related Systems. *J. Phys. Chem. A* **1999**, *103*, 6678–6684.
- (22) Barić, D.; Kovačević, B. Designing a next Generation of Proton Sponges: Cyclopropeniminophosphazenes as the Strongest Pincer Ligands. *Tetrahedron Lett.* **2016**, *57*, 442–445.
- (23) Vazdar, K.; Kunetskiy, R.; Saame, J.; Kaupmees, K.; Leito, I.; Jahn, U. Very Strong Organosuperbases Formed by Combining Imidazole and Guanidine Bases: Synthesis, Structure, and Basicity. *Angew. Chem., Int. Ed.* **2014**, *53*, 1435–1438.
- (24) Barić, D.; Dragičević, I.; Kovačević, B. Cyclopropenimine as a Hydrogen Bond Acceptor - Towards the Strongest Non-Phosphorus Superbases. *Tetrahedron* **2014**, *70*, 8571–8576.
- (25) Saadat, K.; Shiri, A.; Kovačević, B. Substituted Troponimines: When Aromatization of the Conjugate Acid Leads to Very Strong Neutral Organic Superbases. *New J. Chem.* **2018**, *42*, 14568–14575.
- (26) Bandar, J. S.; Lambert, T. H. Enantioselective Brønsted Base Catalysis with Chiral Cyclopropenimines. *J. Am. Chem. Soc.* **2012**, *134*, 5552–5555.
- (27) Stukenbroeker, T. S.; Bandar, J. S.; Zhang, X.; Lambert, T. H.; Waymouth, R. M. Cyclopropenimine Superbases: Competitive Initiation Processes in Lactide Polymerization. *ACS Macro Lett.* **2015**, *4*, 853–856.
- (28) Bandar, J. S.; Sauer, G. S.; Wulff, W. D.; Lambert, T. H.; Veticatt, M. J. Transition State Analysis of Enantioselective Brønsted Base Catalysis by Chiral Cyclopropenimines. *J. Am. Chem. Soc.* **2014**, *136*, 10700–10707.
- (29) Bandar, J. S.; Barthelme, A.; Mazori, A. Y.; Lambert, T. H. Structure–Activity Relationship Studies of Cyclopropenimines as Enantioselective Brønsted Base Catalysts. *Chem. Sci.* **2015**, *6*, 1537–1547.
- (30) Nacsa, E. D.; Lambert, T. H. Higher-Order Cyclopropenimine Superbases: Direct Neutral Brønsted Base Catalyzed Michael Reactions with α -Aryl Esters. *J. Am. Chem. Soc.* **2015**, *137*, 10246–10253.
- (31) Jardel, D.; Davies, C.; Peruch, F.; Massip, S.; Bibal, B. Protonated Phosphazenes: Structures and Hydrogen-Bonding Organocatalysts for Carbonyl Bond Activation. *Adv. Synth. Catal.* **2016**, *358*, 1110–1118.
- (32) Kakuchi, T.; Chen, Y.; Kitakado, J.; Mori, K.; Fuchise, K.; Satoh, T. Organic Superbase as an Efficient Catalyst for Group Transfer Polymerization of Methyl Methacrylate. *Macromolecules* **2011**, *44*, 4641–4647.
- (33) Farley, A. J. M.; Jakubec, P.; Goldys, A. M.; Dixon, D. J. Bifunctional Iminophosphorane Superbases: Potent Organocatalysts for Enantio- and Diastereoselective Michael Addition Reactions. *Tetrahedron* **2018**, *74*, 5206–5212.
- (34) Uchida, N.; Kuwabara, J.; Taketoshi, A.; Kanbara, T. Molecular Design of Organic Superbases, Azacalix[3](2,6)Pyridines: Catalysts for 1,2- and 1,4-Additions. *J. Org. Chem.* **2012**, *77*, 10631–10637.
- (35) Dauben, H. J.; Rhoades, D. F. Synthesis and Properties of Tropenylidenimmonium (8-Azatropenium) Salts. *J. Am. Chem. Soc.* **1967**, *89*, 6764–6766.
- (36) Okamoto, K.; Komatsu, K.; Sakaguchi, O. The One-Electron Reduction of Carbonium Ions. VIII. The Reducibility of Hetero-Substituted Tropylium Ions as Measured by the Competitive Reduction Method with Zinc Powder. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2431–2436.
- (37) Bauld, N. L.; Rim, Y. S. Tropenylidenimmonium Salts and Tropenylidenimines. *J. Am. Chem. Soc.* **1967**, *89*, 6763–6764.
- (38) Haug, E.; Föhlich, B. Tropylium-Ionen Und Tropilidene, II. Notiz Über Eine Einfache Synthese von Alkylamino- Und Dialkylamino-Tropyliumsalzen. *Chem. Ber.* **1971**, *104*, 2338–2340.
- (39) Haug, E.; Föhlich, B. Tropylium-Ionen Und Tropilidene, III Die Reaktion von Chlortropylium- Und Alkoxytropyliumsalzen Mit Malodinitril. *Chem. Ber.* **1971**, *104*, 2670–2680.
- (40) Cid, M. M.; Seijas, J. A.; Villaverde, M. C.; Castedo, L. New Synthesis of Cyproheptadine and Related Compounds Using Low Valent Titanium. *Tetrahedron* **1988**, *44*, 6197–6200.
- (41) Loza, M. I.; Sanz, F.; Cadavid, M. I.; Honrubia, M.; Orallo, F.; Fontenla, J. A.; Calleja, J. M.; Dot, T.; Manaut, F.; Cid, M. M.; Dominguez, R.; Seijas, J. A.; Villaverde, M. C. Cyproheptadine Analogues: Synthesis, Antiserotonergic Activity, and Structure-Activity Relationships. *J. Pharm. Sci.* **1993**, *82*, 1090–1093.
- (42) Wolf, C.; Schunack, W. Synthesis and Pharmacology of Combined Histamine H1-/H2-Receptor Antagonists Containing Diphenhydramine and Cyproheptadine Derivatives. *Arch. Pharm.* **1996**, *329*, 87–94.
- (43) Kupracz, L.; Kirschning, A. Multiple Organolithium Generation in the Continuous Flow Synthesis of Amitriptyline. *Adv. Synth. Catal.* **2013**, *355*, 3375–3380.
- (44) Iino, Y.; Nitta, M. On the Reactions of (Vinylimino) Phosphoranes and Related Compounds. Part 28. Synthesis and Chemical Properties of Dicyclohepta [b, d] Pyrrole Ring System. *J. Chem. Soc., Perkin Trans. 1* **1994**, *No. 18*, 2579–2583.
- (45) Beeby, J.; Garratt, P. J. Synthesis of 1, 7- and 1, 11-Dihydrobenzo [1, 2: 4, 5] Dicycloheptene and 1H-Benzo [1, 2: 4, 5] Dicycloheptenium Tetrafluoroborate (-). *J. Org. Chem.* **1973**, *38*, 3051–3052.
- (46) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. The Aza-Wittig Reaction: An Efficient Tool for the

Construction of Carbon–Nitrogen Double Bonds. *Tetrahedron* **2007**, *63*, 523–575.

(47) King, R. B.; Efraty, A. Reactions of Transition Metal Compounds with Macrocyclic Alkadiynes. I. Intramolecular Transannular Cyclizations with Cyclopentadienyldicarbonylcobalt. *J. Am. Chem. Soc.* **1972**, *94*, 3021–3025.

(48) Reinecke, M. G.; Newsom, J. G.; Chen, L.-J. Thermolysis of Thiophenedicarboxylic Acid Anhydrides as a Route to Five-Membered Hetarynes. *J. Am. Chem. Soc.* **1981**, *103*, 2760–2769.

(49) Berris, B. C.; Hovakeemian, G. H.; Lai, Y. H.; Mestdagh, H.; Vollhardt, K. P. C. A New Approach to the Construction of Biphenylenes by the Cobalt-Catalyzed Cocyclization of *o*-Diethynylbenzenes with Alkynes. Application to an Iterative Approach to [3] Phenylene, the First Member of a Novel Class of Benzocyclobutadienoid Hydrocarbons. *J. Am. Chem. Soc.* **1985**, *107*, S670–S687.

(50) Naghipur, A.; Reszka, K.; Sapse, A. M.; Lown, J. W. Formation of Benzoxathiete under Mild Conditions and Its Valence Tautomerism in Solution to Monothio-*o*-Benzoquinone: An Experimental and Quantum Chemical Study. *J. Am. Chem. Soc.* **1989**, *111*, 258–268.

(51) Iyoda, M.; Kabir, S. M. H.; Vorasingha, A.; Kuwatani, Y.; Yoshida, M. Novel Synthesis of Biphenylene and Its Derivatives Using Intramolecular Coupling of Zinccyclopentadienes. *Tetrahedron Lett.* **1998**, *39*, 5393–5396.

(52) Singh, K. N.; Singh, P.; Sharma, E.; Kaur, M.; Deol, Y. S. Aryne-Mediated Arylation of the 3-Benzazepine Scaffold: One-Pot Synthesis of 1-Aryl-3-Methyl-2, 3, 4, 5-Tetrahydro-1H-3-Benzazepines. *Synthesis* **2015**, *47*, 3212–3220.

(53) Barić, D. Utilizing the Azaazulene Scaffolds in the Design of New Organic Superbases. *ACS Omega* **2019**, *4*, 15197–15207.

(54) Schleyer, P.; von, R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. van E. Nucleus-Independent Chemical Shifts: A Simple and Efficient Aromaticity Probe. *J. Am. Chem. Soc.* **1996**, *118*, 6317–6318.

(55) Geuenich, D.; Hess, K.; Köhler, F.; Herges, R. Anisotropy of the Induced Current Density (ACID), a General Method To Quantify and Visualize Electronic Delocalization. *Chem. Rev.* **2005**, *105*, 3758–3772.

(56) Leito, I.; Koppel, I. I. A.; Koppel, I. I. A.; Kaupmees, K.; Tshepelevitsh, S.; Saame, J. Basicity Limits of Neutral Organic Superbases. *Angew. Chem., Int. Ed.* **2015**, *54*, 9262–9265.

(57) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G.; Peters, E.-M.; Peters, K.; von Schnering, H. G.; Walz, L. Extremely Strong, Uncharged Auxiliary Bases; Monomeric and Polymer-Supported Polyaminophosphazenes (P2-P5). *Liebigs Ann.* **2006**, *1996*, 1055–1081.

(58) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Function. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

(59) Weigend, F.; Ahlrichs, R. Balanced Basis Sets of Split Valence, Triple Zeta Valence and Quadruple Zeta Valence Quality for H to Rn: Design and Assessment of Accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.

(60) Bauernschmitt, R.; Ahlrichs, R. Stability Analysis for Solutions of the Closed Shell Kohn-Sham Equation. *J. Chem. Phys.* **1996**, *104*, 9047–9052.

(61) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

(62) Fifen, J. J.; Dhauadi, Z.; Nsangou, M. Revision of the Thermodynamics of the Proton in Gas Phase. *J. Phys. Chem. A* **2014**, *118*, 11090–11097.

(63) Toth, A. M.; Liptak, M. D.; Phillips, D. L.; Shields, G. C. Accurate Relative PK a Calculations for Carboxylic Acids Using Complete Basis Set and Gaussian-n Models Combined with Continuum Solvation Methods. *J. Chem. Phys.* **2001**, *114*, 4595–4606.

(64) Bandar, J. S.; Lambert, T. H. Enantioselective Bronsted Base Catalysis with Chiral Cyclopropenimines. *J. Am. Chem. Soc.* **2012**, *134*, 5552–5555.

(65) Lu, T.; Chen, F. Multiwfn: A Multifunctional Wavefunction Analyzer. *J. Comput. Chem.* **2012**, *33*, S80–S92.

(66) Wolinski, K.; Hinton, J. F.; Pulay, P. Efficient Implementation of the Gauge-Independent Atomic Orbital Method for NMR Chemical Shift Calculations. *J. Am. Chem. Soc.* **1990**, *112*, 8251–8260.

(67) Wiitala, K. W.; Hoye, T. R.; Cramer, C. J. Hybrid Density Functional Methods Empirically Optimized for the Computation of ¹³C and ¹H Chemical Shifts in Chloroform Solution. *J. Chem. Theory Comput.* **2006**, *2*, 1085–1092.

(68) Keith, T. A.; Bader, R. F. W. Calculation of Magnetic Response Properties Using a Continuous Set of Gauge Transformations. *Chem. Phys. Lett.* **1993**, *210*, 223–231.

(69) Afonin, A. V.; Vashchenko, A. V.; Sigalov, M. V. Estimating the Energy of Intramolecular Hydrogen Bonds from ¹H NMR and QTAIM Calculations. *Org. Biomol. Chem.* **2016**, *14*, 11199–11211.

(70) Keith, T. A. *AIMAll*, version 10.05.04; TK Gristmill Software: Overland Park KS, U.S.A. (). 2010.

(71) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T., Jr; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; 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.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision E.01; Gaussian Inc.: Wallingford, CT, 2009.