Brønsted Superbases

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Basicity Limits of Neutral Organic Superbases**

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Abstract: *The potential limits of superbasicity achievable with different families of neutral bases by expanding the molecular framework are explored using DFT computations. A number of different core structures of non-ionic organosuperbases are considered (such as phosphazenes, guanidinophosphazenes, guanidino phosphorus ylides). A simple model for describing the dependence of basicity on the extent of the molecular framework is proposed, validated, and used for quantitatively predicting the ultimate basicities of different compound families and the rates of substituent effect saturation. Some of the considered bases (guanidino phosphorus carbenes) are expected to reach gas-phase basicity around 370 kcal mol^{-1}, thus being the most basic neutral bases ever reported. Also, the classical substituted alkylphosphazenes were predicted to reach pK_a values of around 50 in acetonitrile, which is significantly higher than previously expected.*

Non-ionic organosuperbases[1] are attracting significant interest because of their practical importance as catalysts[1,2] and auxiliary reagents[3] in synthesis and technology as well as for fundamental challenges.[4,5] Design and synthesis of new superbases has been a flourishing field of research during the last decades.[1,4] Numerous families of superbases (such as phosphazenes,[3] phosphatranes,[6] bisphosphazene proton sponges,[7,8] imidazolidines,[9] imidazolidino-phosphazenes[10] and -guanidines,[11] bis-guanidines[12]) have been created and potentially superbasic compound families have been proposed, for example carbenes.[13] More recently different innovative bases have been proposed, such as cyclopropeneimines[14] and silylene bases.[15] Despite a vast range of potential applications,[1] many classes of superbases (guanidino proton sponges,[7] phosphorus ylides[16]) are still almost unexplored.

An early Minireview by Schwesinger[17] summarizes the principal approaches to enhancing the basicity of organosuperbases: 1) the "battery cell" principle,[3] that is, stepwise expansion of the molecular scaffold by forming alternating formal single and double bonds and thereby enhancing the structure where the positive charge can be delocalized (Scheme 1); 2) stabilization of the protonated form by intramolecular hydrogen bond (chelation); and 3) structures that become aromatic on protonation. It was concluded that the most fruitful approach to design of superbases is the battery cell principle. The best known practical example is the phosphazene family of superbases.[3] Creating a structure where the protonated form is stabilized by one or more hydrogen bonds is also frequently used[4,7,8] and often remarkable basicity enhancement is seen, especially in the gas phase. However, in practical usage, not only thermodynamic but also kinetic basicity is important and here is the drawback of the chelating bases, as they generally are kinetically slow.[7]

In this work, we computationally explore (DFT B3LYP 6-311 + G** and DFT BP TZVP) five families of potentially extremely strong superbases with the aim of predicting their basicity limits. These families were chosen according to the extraordinary basicity expected from them[1,3,10] and also the possibility of significant basicity enhancement by adding further P=N units to the molecular scaffold. The investigated bases are presented in Scheme 1 and Scheme 2.

We propose a simple model for describing the dependence of basicity on the extent of the molecular framework, which can be used for numerical prediction of the ultimate basicity achievable with different compound families and the rate of substituent effect saturation. It can facilitate the choice of the most promising core structures for further development. We are aware of only one early work where a similar question has been asked[18] and, as we show below, the basicity limits obtained previously[18] are probably underestimated.

The results of gas-phase basicity (GB) computations (see the Supporting Information) of the investigated families of bases are presented in Scheme 2. The well-known families of dimethylamino (dma) phosphazenes, dma phosphorus ylides, and 2,5-dimethylimidazolidino (imme) phosphazenes are supplemented by families of guanidino phosphorus ylides and guanidino phosphorus carbenes, which are almost uninvestigated as superbases. Extending the molecular scaffold of the base leads to significant basicity increase in all families. With each added P=N unit the basicity gain decreases, but the limit is clearly not reached even at 7 P=N units in any of the families.

The strongest bases are usually large molecules, which hinders their direct computational study at sufficiently high level of theory. At the same time the trends shown in Scheme 2 imply exponential decay of the effect of every next added P=N unit. Saturation of substituent effects is a well-known phenomenon, but its numerical modelling according to the exponential saturation hypothesis has to the best of our knowledge not been attempted. If the hypothesis of expo-

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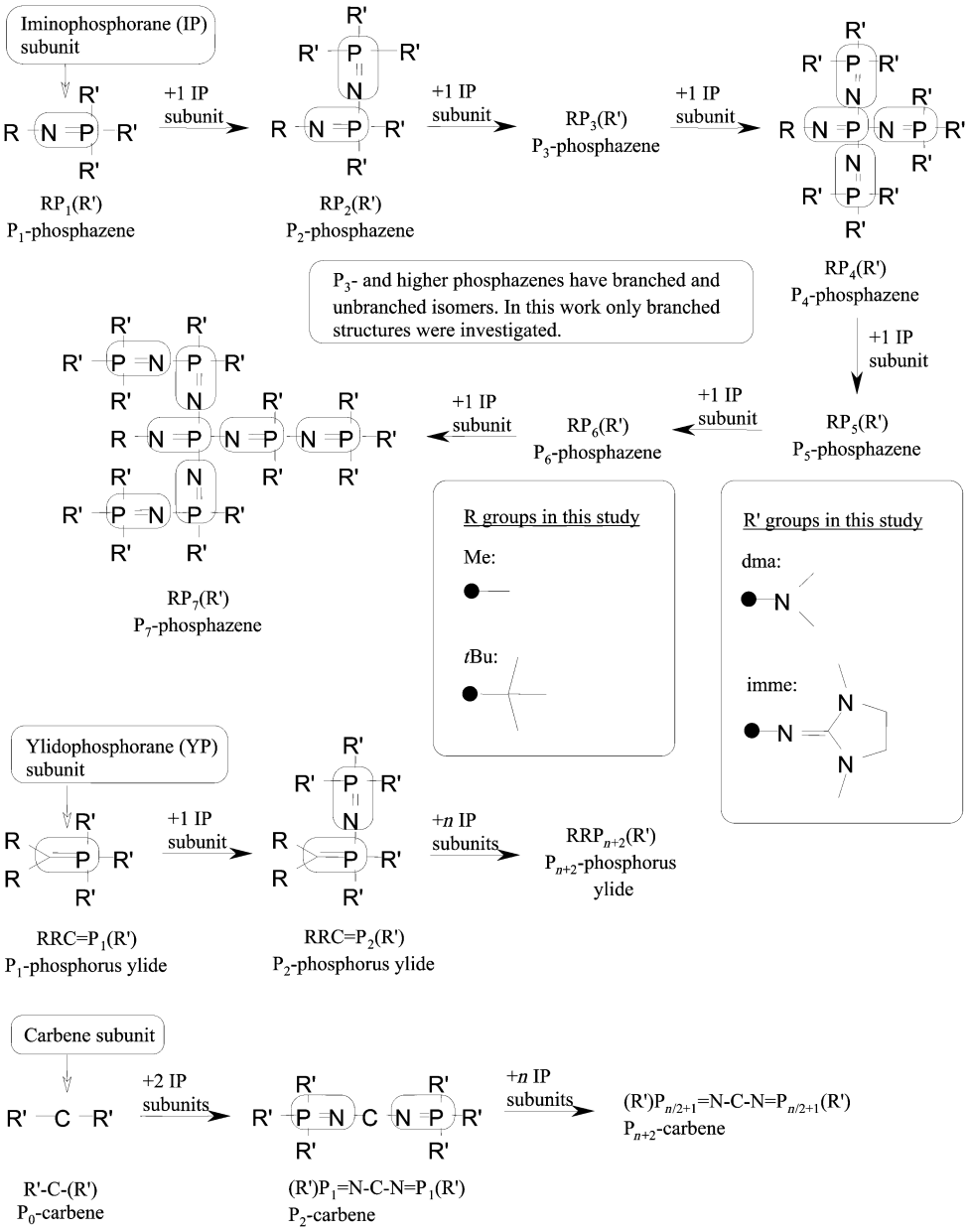


Scheme 1. The "battery cell" principle to enhance the basicity of phosphazenes, phosphorus ylides, and carbenes.

nential saturation holds then it can be described by the following model:

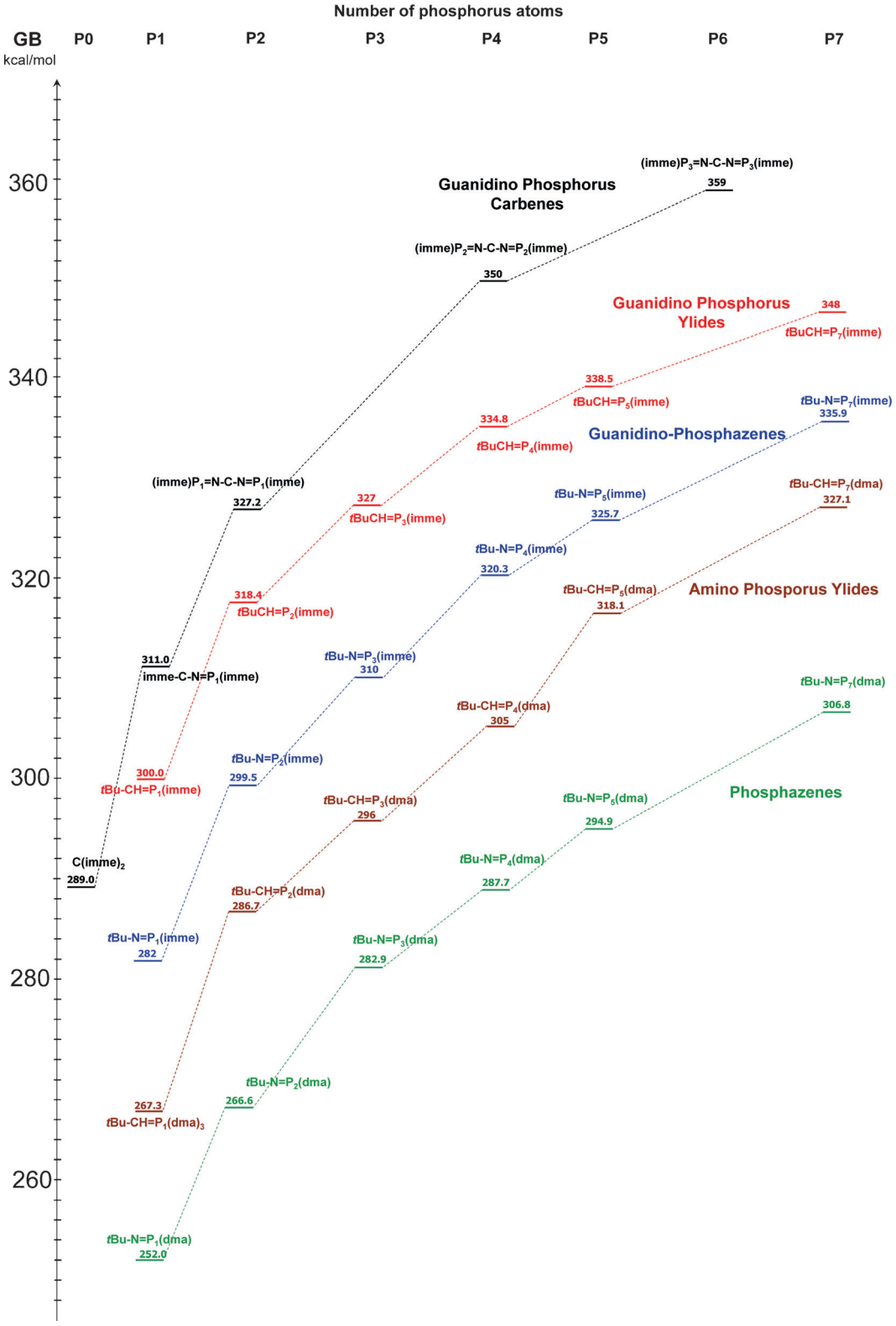
$$GB = GB_{max}(1-a\,e^{-bn}) \quad (1)$$

where n is the number of phosphorus atoms, GB is the gas-phase basicity, GB_{max} is the maximum GB obtainable with the particular series, and a and b are coefficients. a describes the extent of basicity increase obtainable from the (often hypothetical) compound with zero P atoms and b describes the rate of substituent effect saturation, whereby $e^b \equiv k$ can be termed as substituent effect decay rate. It is not expected of this simple model to describe all nuances of basicity change. For example, in the range P1–P4, every additional P=N unit is connected to P1; starting from P5, the P=N units are connected to P2–P4. This leads to a lower basicity increase on P4→P5 than is predicted by the model. Nevertheless, the big picture is represented very well (see below).

The model was applied to all series in Scheme 2 as well as to simpler validation series, namely HN=P_n(H), HN=P_n(Me), H_2C=P_n(Me), (iPr)$_2$C=P_n(H) (studied computationally) and to the experimental GB data[20] of primary and tertiary amines (see the Supporting Information for full details on validation). The parameters a, b, and GB_{max} were found by least-squares minimization of the differences between experimental/calculated GB values and those computed by the model. The obtained parameters for the different series, as well as the ultimate basicities, are presented in Table 1.

The results show that the basicities of various bases calculated in this work cover the range of 250–359 kcal mol^{-1}. The iconic tBu-N=P_4(dma) phosphazene has a GB value of 287.8 kcal mol^{-1}, but replacing dimethylamino groups with dimethylimidazolidino (imme) groups enhances its GB to 320.3 kcal mol^{-1}. Yet, predictions by Equation (1) show that dimethylamino phosphazenes can also reach GB values beyond 300 kcal mol^{-1} starting from 7 P atoms. If dimethylamino groups are replaced by imme groups, basicities beyond 340 kcal mol^{-1} are attainable. Phosphorus ylides are significantly more basic than phosphazenes and are expected to reach basicities of more than 350 kcal mol^{-1}. However, convincingly the highest basicity limit is displayed by the guanidino phosphorus carbenes. Carbenes were recognized by Alder two decades ago as potential superbases,[13] but have not been developed or exploited as such. Besides the highly stable protonated form, the superbasicity of carbenes relies on the significantly destabilized neutral form.[19] Carbenes are highly reactive species unless the carbene center is sterically hindered, in which case they can be reasonably stable.[13]

The k values are insightful in determining the efficiency of expanding the molecular scaffold of the base (the lower the k value, the more efficient the expanding). The systems with



Scheme 2. Trends of basicity changes in compound families. The *Y*-axis shows computational gas-phase basicities; the *X*-axis shows the number of phosphorus atoms in molecular scaffolds.

basicities least affected by enlargement of the molecule (k in the range of 1.6–1.8) are, as expected, the primary amines and simple unsubstituted phosphazene bases as their substituents do not exhibit the electron-donating effect. The base families in Scheme 2 all have k lower than 1.4, indicating good efficiency of molecular scaffold expansion.

The success of Equation (1) in the gas phase prompted us to investigate basicities (pK_a values) of some strong bases in

Table 1: Results of model validation and basicity limit predictions with Equation (1).[a]

Base series	a	k[b]		
Gas phase			GB_{max} [kcal mol^{-1}]	RMSD[c] [kcal mol^{-1}]
Validation:				
HN=P$_n$(H)	0.32	1.78	268	1.6
HN=P$_n$(Me)	0.27	1.29	307	1.8
(*i*Pr)$_2$C=P$_n$(H)	0.18	1.43	290	1.8
H$_2$C=P$_n$(Me)	0.26	1.34	325	1.9
R–NH$_2$	0.05	1.61	214	0.5
R^{1}R^{2}R^{3}N	0.15	1.40	231	0.6
Prediction:				
*t*Bu–N=P$_n$(dma)	0.28	1.30	320	1.6
*t*Bu–CH=P$_n$(dma)	0.29	1.25	348	1.8
*t*Bu–N=P$_n$(imme)	0.25	1.33	347	0.7
*t*Bu–CH=P$_n$(imme)	0.21	1.38	355	0.9
(imme)P$_n$=N–C–N=P$_m$(imme)	0.22	1.37	372	0.8

Solution			pK_{a_max}	RMSD
Prediction:				
Ph–N=P$_n$(dma) in THF	0.79	1.45	32	0.4
*t*Bu–N=P$_n$(dma) in MeCN	0.67	1.29	56	0.1

[a] The GB computations were carried out using the DFT B3LYP 6-311 + G** and DFT BP TZVP methods. See the Supporting Information for full details. [b] $k \equiv e^b$; see text. [c] Root-mean-square deviation of the computed/experimental GB values from those predicted by Equation (1).

solution. The only continuous series with sufficient experimental data available are the *t*Bu-N=P$_n$(dma) series (in acetonitrile)[3] and the Ph-N=P$_n$(dma) series (in tetrahydrofuran).[10,21] The results in Table 1 show that, contrary to the earlier conclusion,[3] even at P$_7$ level the basicity limit of simple alkyl phosphazenes is not reached and in principle basicities higher than pK_a = 50 in MeCN are reachable (pK_a 50 is expected at P$_8$). Interestingly, the *t*Bu-N=P$_n$(dma) system has the best fit (RMSD = 0.1) of all the investigated systems, and one of the lowest k values. The excellent fit indirectly supports the high quality of the MeCN pK_a values, which is remarkable, since the pK_a values of the higher members of the series have been obtained by extrapolation from data in THF.[3]

The highest GB values reported here are significantly higher than any hitherto reported GB values for neutral bases, including the strongest inorganic alkali metal oxides[22] Rb$_2$O (331.9 kcal mol^{-1}) and Cs$_2$O (324.4 kcal mol^{-1}) as well as the K$_3$N superbase (340.7 kcal mol^{-1}).[5]

The proposed quantitative model for predicting basicity increase resulting from expanding the molecular framework demonstrates that the GB region around 350 kcal mol^{-1} and beyond is well reachable with non-chelating organosuperbases. Since high-molecular-weight bases are inconvenient in practical use (owing to the large amount of base required), the real challenge in superbase design lies not in the highest possible basicity at any cost but rather in finding structural units that are both efficient in increasing basicity and being smaller. Possible examples can be seen for example in the recently reported BIG bases[11] and cyclopropenimine bases.[14]

Keywords: Brønsted superbases · carbenes · density functional calculations · phosphazenes · phosphorus ylides

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