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Organosuperbases

Very Strong Organosuperbases Formed by Combining Imidazole and Guanidine Bases: Synthesis, Structure, and Basicity**

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In memory of Detlef Schröder

Abstract: *New structural motives for organosuperbases, that are easy to prepare and highly basic are urgently required in many areas of chemistry. The synthesis of N,N′-bis(imidazolyl)guanidine bases (BIG bases) is reported. Their* pK_α *values are determined as 26.1–29.3 in THF. They are thus probably the strongest known phosphorous-free organic bases both in solution and in the gas phase. Calculations help to determine the structural and electronic factors giving rise to the high basicity.*

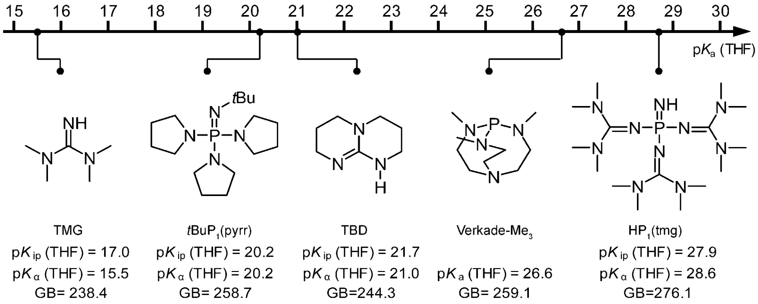
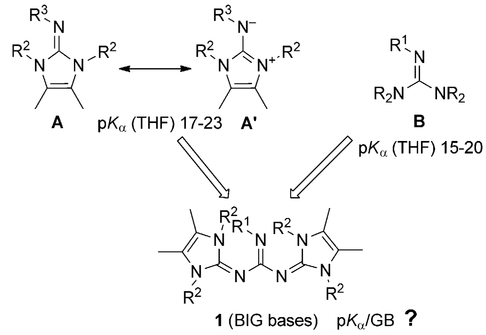


Figure 1. Basicities of some common organosuperbases in THF and in the gas phase (GB in kcal mol^{-1}): TMG;[8,9] *t*BuP$_1$(pyrr);[8,2a] TBD;[8,9] Verkade-Me$_3$;[1c,2a] HP$_1$(tmg).[5c]

The design of uncharged organosuperbases exhibiting high basicity and stability, and a low nucleophilicity under different reaction conditions and in different media has been a challenge for organic chemistry for a long time.[1] Several classes of nonmetallic superbases have been reported over the years (Figure 1), for example phosphazenes (*t*BuP$_1$(pyrr) or HP$_1$(tmg)),[2] phosphatranes (Verkade-Me$_3$),[3] amidines,[4] or guanidines (TMG or TBD).[5] Many of them have demonstrated applicability in organic syntheses[6] and potentially in industrial processes.[1e,7]

However, the existing superbases often have limitations, such as high toxicity, high price, competing nucleophilicity, insufficient solubility in low-polarity solvents, low functional-group compatibility, or low stability. Significantly, these bases are often accessible only through multi-step processes, which makes their application impractical.

A major challenge consists therefore in providing practical routes to new highly basic organic compounds, which would surpass the current limitations and exhibit broad applicability in several branches of chemistry. A partial solution was recently provided with a practical access to lipophilic *N,N′*-dialkyl-4,5-dimethylimidazol-2-ylidene amine organosuperbases **A**, which are a powerful basis for the development of new highly basic compounds (Scheme 1).[10] The unusually high basicity of these compounds in the gas phase and in solution is influenced by the degree of aromatization of the imidazolium ring and the release of steric strain upon protonation.



Scheme 1. Design of the novel superbases **1** based on structural motifs **A** and **B**.

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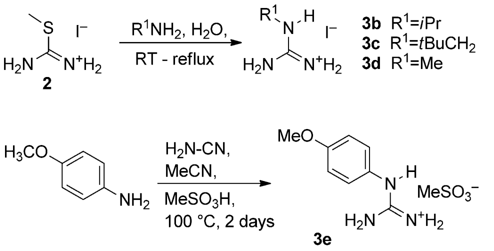
In this work, the imidazoleimine motif **A** is taken a step further making it the structural basis for the preparation of *b*is-*N*,*N*′-(1,3-dialkyl-4,5-dimethyl-1*H*-*i*midazol-2(3*H*)-ylidene) *g*uanidine bases (BIG bases) **1** by merging it with the established guanidine organosuperbase core **B** with the aim of investigating whether a qualitative increase of basicity results. Their experimentally determined basicity proves to be significantly higher than those of the individual classes **A** and **B** (pK_α ranges in THF approximately 17–23 and 15–20, respectively. pK_α is the estimated free ion basicity). The results are supported by computational investigations to rationalize the results and put them in a more general context.

The synthesis of BIG bases **1** is straightforward and convergent. The central guanidine fragments **3b–d** were prepared by a reaction of alkyl amines and methyl isothiouronium iodide (**2**; Scheme 2). The guanidine salt **3e** was more conveniently prepared by the reaction of *p*-anisidine, cyanamide, and methanesulfonic acid. The crude guanidines **3b–e** were sufficiently pure as obtained to be used directly in subsequent transformations.



Scheme 2. Preparation of guanidinum salts **3b–e**.

The chloroimidazolium salts **4a** and **4b** were prepared in three steps as described elsewhere[10] and subsequently coupled with commercial guanidinium chloride (**3a**) or guanidines **3b–e** in the presence of potassium fluoride (Table 1). KF played a double role as a strong base and as a reagent transforming the 2-chloroimidazolium substrates into 2-fluoroimidazolium salts, which are the better electrophiles. The BIG hydrotetrafluoroborates **5a–g** were isolated in 59–88% yield (entries 1–7). Bases **1a–g** were liberated in 74–96% yield using a slight excess of *t*BuOK in dry degassed THF.[11]

Table 1 reveals that bases **1a–g** are in THF approximately 10 orders of magnitude stronger than the well-established amidine and guanidine bases (such as DBU or 7-methyl-1,5,7-triazabicyclo[4.4.0]-dec-5-ene)[5c,8a] and beat the alkyl P_1 and P_2 phosphazene superbases by several orders of magnitude.[5c,8a] The pK_a values of **1a–g** in acetonitrile (MeCN) can be estimated to lay approximately between 35 and 38. These values have been obtained by extrapolation from a correlation analysis of a range of bases including those giving sterically shielded cations on protonation, because the current acetonitrile basicity scale reaches only to $pK_a = 32$ (Figure 2).[12]

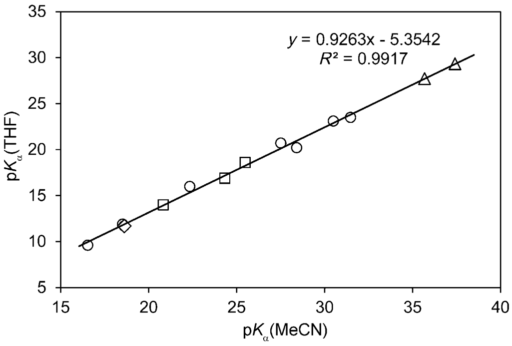
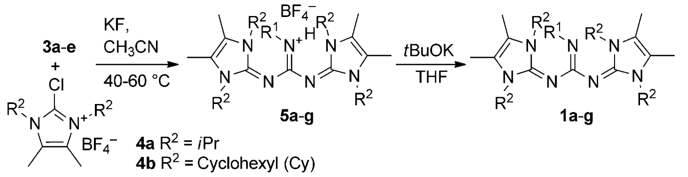


Figure 2. Correlation analysis of pK_α values in THF versus pK_a values in MeCN. ○ phosphazenes, □ guanidines, ◇ 1,8-bis(dimethylamino)-naphthalene, △ **1d** and **1f**, which only have experimental pK_α-(THF) values.

The measured basicities of **1a–g** in THF and the computational gas-phase basicity (GB) values follow a logical pattern except for **1e** in the gas phase. For **1e** we do not have a satisfactory explanation. Since "size matters" in the gas phase,[2a,13] all compounds carrying cyclohexyl substituents at the imidazole nitrogen atoms have higher GB values than their isopropyl-substituted counterparts. In compounds with $R^2 = i$Pr the GB increases in the following order of imino substituents: $t\text{BuCH}_2 < \text{H} < \text{Me} < i\text{Pr}$. In solution the solvation of the protonated form of the base changes the picture. Both compounds with $R^2 = \text{Cy}$ are weaker bases than their

Table 1: Preparation of BIG tetrafluoroborates **5a–g** and BIG bases **1a–g**, and their experimental solution basicity data, calculated gas-phase basicity and ΔNICS(1) values.



Entry	R^1	R^2	**5** [%][a]	**1** [%][b]	pK_{ip}[c,d]	pK_α[d]	GB [kcal mol^{-1}]	ΔNICS(1)[e]
1	H	*i*Pr	**a** 88	**a** 94	27.5	27.8	275.2	−1.44
2	H	Cy	**b** 74	**b** 75	27.0	27.8	277.8	−1.93
3	*i*Pr	*i*Pr	**c** 68	**c** 83	28.4	29.2	277.2	−1.65
4	*i*Pr	Cy	**d** 61	**d** 83	26.5	27.7	278.1	−1.35
5	tBuCH$_2$	*i*Pr	**e** 59	**e** 95	28.0	29.0	273.7	−1.71
6	Me	*i*Pr	**f** 79	**f** 74	28.5	29.3	276.6	−1.66
7	*p*-MeOPh	*i*Pr	**g** 65	**g** 96	24.9	26.1	272.1	−1.38

[a] Conditions: KF (32.0 mmol), **4a** or **4b** (4.0 mmol), guanidinium salt (2.0 mmol), room temperature or 40 to 60 °C. [b] Conditions: **5a–g** (0.47 mmol), *t*BuOK (0.58 mmol), −78 °C to room temperature, 30 min. [c] pK_{ip} = ion pair basicity. [d] In THF; pK_α is the estimated free ion basicity.[8] [e] NICS = nucleus-independent chemical shift. ΔNICS(1) indicates the change in aromaticity upon protonation (the more negative the value, the greater the gain in aromaticity).

$R^2 = i$Pr counterparts and the basicity order of *i*Pr substituted compounds is now $H < t\text{BuCH}_2 < i\text{Pr} < \text{Me}$. This parallels the order observed earlier for alkylphosphazenes, where methyl and ethyl as imino substituents display a higher basicity than *t*Bu.[8] Base **1g** with the aromatic substituent is weaker both in THF and in the gas phase because the free base is resonance-stabilized, this stabilization is lost on protonation.

The bases **1a**–**g** can be regarded as guanidines in which the amino hydrogen atoms have been replaced by the imidazole-2-ylidene groups. Taking tetramethylguanidine (pK_α = 15.5;[14] GB = 238.4 kcal mol^{-1}[9]) as the benchmark base, this replacement increases the pK_α value by 12–14 units to 27.7–29.3 in THF. The basicity increase in the gas phase is even more impressive, reaching close to 30 kcal mol^{-1} or more than 20 orders of magnitude. The basicity of the recently introduced imidazole-2-ylidene amines **A**[10] was enhanced by several orders of magnitude by the synergistic effect of aromatization on protonation and steric strain release through the bulky substituents at the imidazole rings. Bases **1a**–**g** are around 7–9 orders of magnitude more basic in solution and around 15 orders of magnitude more basic in the gas phase than the imidazoline bases **A**. Bases **1a**–**g** contain two imidazole rings, which are farther away from the basicity center and not in plane with the guanidine fragment—the dihedral angles are in the range of 26° to 76° (see Table S3 in the Supporting Information for the dihedral angles and Figure S1 and S2 for sample geometries of the structures). As a result, the degree of aromatization of the imidazole rings is lower than in bases **A**.[10] The ΔNICS(1) values (Table 1)[15] reveal that aromatization is a factor contributing to the basicity, but the extent of aromatization is not correlated to the basicity of the compounds. The release of steric strain on protonation does also not seem to be directly correlated to the basicity of **1a**–**g**, because the dihedral angles between the planes of the guanidine fragment and the imidazoline rings are different from 0°, both in salts **5** and in bases **1**.

A significantly contributing factor to the basicity (especially in the gas phase) is certainly the sheer size of bases **1**, which is significantly larger than that of bases **A** enabling efficient delocalization of the positive charge in the protonated forms over a significantly larger volume.

In conclusion, **1a**–**g** are probably the strongest reported organic non-phosphorus superbases having pK_α values of 26.1–29.3 in THF. They are prepared in a straightforward manner in only four steps from inexpensive chemicals. They are stable, lipophilic, and comparable to or better than P_2-phosphazenes[2e] and Kolomeitsev's guanidinophosphazenes.[5c] The design allows for more research in several directions as these bases are not only expected to be useful as auxiliary bases in general organic synthesis. They may also serve as blueprints for chiral bases in asymmetric synthesis or Lewis basic organocatalysts.

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[11] Although no information on the basicity of KO*t*Bu in THF is available, it is potentially unable to liberate bases **1a–g** irreversibly. However, the combined effect of precipitation of KBF_4 and removal of *t*BuOH during evaporation drive the equilibrium toward **1**.

[12] $pK_\alpha(THF) = b_0 + b_1 pK_a(MeCN)$, $b_0 = -5.4(7)$, $b_1 = 0.93(3)$, $R^2 = 0.991$, $n = 11$, $S = 0.45$. Only bases with sterically shielded basicity centers were chosen. They included three amidines, seven phosphazenes, and one proton sponge. pK_α(THF) and pK_a(MeCN) values were taken from Refs. [5c,8a,12a,16]. A much more extensive correlation of 77 bases of diverse properties and geometries gave the following correlation parameters: $b_0 = -4.4(4)$, $b_1 = 0.90(2)$, $R^2 = 0.963$, $n = 77$, $S = 1.01$. The pK_a(MeCN) values predicted for the bases **1** from this correlation were virtually the same.

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