A New Class of Organosuperbases, N-Alkyl- and N-Aryl-1,3-dialkyl-4,5-dimethylimidazol-2-ylidene Amines: Synthesis, Structure, pK₄BH⁺ Measurements, and Properties


Abstract: A series of stable organosuperbases, N-alkyl- and N-aryl-1,3-dialkyl-4,5-dimethylimidazol-2-ylidene amines, were efficiently synthesized from N,N-dialkylthioureas and 3-hydroxy-2-butanone and their basicities were measured in acetonitrile. The derivatives with ter-alkyl groups on the imino nitrogen were found to be more basic than the iBuP₂(pyr) phospazene base in acetonitrile. The origin of the high basicity of these compounds is discussed. In acetonitrile and in the gas phase, the basicity of the alkylimino derivatives depends on the size of the substituent at the imino group, which influences the degree of aromatization of the imidazole ring, as measured by ¹³C NMR chemical shifts or by the calculated ΔNICS(1) aromaticity parameters, as well as on solvation effects. If a wider range of imino-substituents, including electron-acceptor substituents, is treated in the analysis then the influence of aromatization is less predominant and the gas-phase basicity becomes more dependent on the field-inductive effect, polarizability, and resonance effects of the substituent.

Keywords: amines • aromaticity • basicity • imidazolylidene amines • steric hindrance • substituent effects • superbases

Introduction

Uncharged organosuperbases,[1] such as amidines, guanidines, phosphazenes, and the Verkade phosphatrane bases (Figure 1), are an important class of reagent in modern organic chemistry. The synthesis of organosuperbases,[1c,2] their basicity in solution[2,3,4] and in the gas phase,[3b,5,6] different modifications,[1c,3a,7,8] and potential applications[1a–h] have been extensively studied. Their success is based on the ease of their molecular modification, good solubility in most organic solvents, and recyclability possibilities. In addition, bases such as DBU, TMG or the Schwesinger P₁ phosphazenes are often applied as strong metal-free Brønsted bases in stoichiometric amounts to substrates.[1c] In spite of the aforementioned favorable properties, limitations, such as their nucleophilicity, scope of applicability, functional-group compatibility, high molecular weight, high price, toxicity, stability to air, and hydrolysis, remain. That is the reason that the design, synthesis, and application of new classes of organosuperbases are of general interest in modern organic chemistry. In particular, the search for simple and accessible molecules that display high basicity (comparable to or higher than the P₁-phosphazene bases) and exploit other principles governing basicity is certainly required.

Recently, the outstanding thermal and hydrolytic stability of bis(imidazol-2-ylidene)ammonium cations (BIMAs, Figure 2) in alkaline media was discovered.[9] Their proper-
ties were tentatively attributed to efficient resonance charge delocalization and stabilization of the positive charge over the entire cation. The bulky lipophilic N-alkyl substituents also contribute by stERICALLY protecting the cation. This suggests that the N,N'-dialkyl-4,5-dimethylimidazol-2-ylidene amine motif I serves exceptionally well as the basis for the design of new uncharged strong bases (Figure 2). An examination of the literature data revealed that only one relevant base, 1-methyl-1,5,6,7-tetrahydroimidazo[1,2-a]pyridine (ImPy), Figure 1) has been described so far, for which a reliable experimental value of pK$_{BH+}$ of 24.55 in acetonitrile (MeCN) has been determined.

Herein, we report a new family of lipophilic organosuperbases incorporating a fully substituted pseudo-imidazole core: N-[1,3-dialkyl-4,5-dimethyl-1H-imidazol-2(3H)-ylidene]alkyl- or -arylamines (1 Figure 2). Preliminary experiments indicated that the base 1a (Alk = iPr and R = iBu) has a pK$_{BH+}$ in acetonitrile close to 30. At the same time its cyclic counterpart ImPy has a pK$_{BH+}$ of only 24.55. The dramatic change in solution basicity as a result of small structural changes prompted a detailed analysis of the structure of these compounds. This leads to the hypothesis that a synergistic effect of aromatization and some release of steric strain upon protonation influence their basicity (Figure 3). Herein, the validity of this hypothesis is demonstrated based on an experimental and computational study.

**Experimental Section**

**Synthesis**: A representative synthetic procedure is provided for 1a. The synthesis of compounds 1b–1j is described in the Supporting Information.

**Synthesis of 2-chloro-1,3-diazopropyl-4,5-dimethylimidazolium tetrafluoroborate (5a)** from 1,3-diazopropyl-4,5-dimethylimidazole (1H-imidazole-2(3H)-thione (4a), a one-pot potassium-free protocol: Freshly distilled diglyme (150 mL) was added to a flask with Na (5.80 g, 250 mmol) under an inert atmosphere. The flask was heated with a heat gun until the sodium melted and stirring was continued at this temperature for 10 min. After cooling to room temperature, imidazol-2-thione (4a) (10.6 g, 50.0 mmol) was added and the reaction mixture was stirred at 110°C for 24 h. After again cooling to room temperature, stirring was stopped, and the inorganic residue was allowed to precipitate over 12 h. The supernatant was carefully transferred through a cannula into a second flask (traces of fine white particles are not a problem) and cooled to ~40°C. Hexachloroethane (130.0 g, 550 mmol) was added with vigorous stirring, and the reaction mixture was warmed to room temperature over 2 h. After stirring overnight, toluene (150 mL) was added, and the resulting precipitate was collected on a glass filter over Celite and washed twice with toluene (50 mL). The product/Celite mixture was taken up in CHCl$_3$. The resulting suspension was filtered from Celite and the organic layer was transferred into a separating funnel. A diluted aqueous solution of NaBF$_4$ (27.5 g, 250 mmol) was added, the two-phase mixture was shaken vigorously, and the layers were separated. The aqueous layer was extracted once with a small portion of chloroform. The combined chlorof orm fractions were dried (MgSO$_4$), filtered, and evaporated under reduced pressure, yielding product 5a (9.68 g, 64 %) as a colorless crystalline solid after recrystallization from EtOAc/MeOH (20:1). The analytical data were in agreement with those previously reported.[15]

**Synthesis of 1a-HBF$_4$**: KF (3.49 g, 60.0 mmol) was heated in a reaction flask with a heat gun under vacuum for a few minutes to remove all traces of moisture. After cooling, salt 5a (3.05 g, 10.0 mmol) and a magnetic stirring bar were added, followed by MeCN (30 mL) and iBuNH$_2$ (3.15 mL, 30.0 mmol). The reaction mixture was stirred at ambient temperature for 72 h. Once the $^1$H NMR spectrum of the reaction mixture indicated full conversion of the starting material had occurred, chloroform (30 mL) was added. After stirring for 5 min, the suspension was filtered through a Schott glass filter directly into a separating funnel, and the solid residue was washed a few times with small portions of chloroform. A diluted aqueous solution of NaBF$_4$ (5.50 g, 50.0 mmol) was added to the solution in chloroform, followed by vigorous shaking. The layers were separated. The aqueous layer was extracted once with a small portion of chloroform. The combined chloroform fractions were dried (MgSO$_4$), filtered, and evaporated under reduced pressure, yielding salt 1a-HBF$_4$ (3.05 g, 90 %) as colorless crystals after recrystallization. M.p. 149–150°C (EtOAc); $^1$H NMR (400 MHz, CDCl$_3$, SiMe$_4$): δ = 1.28 (s, 9 H; CMe$_3$), 1.54 (d, J$_{N-H}$ = 7.1 Hz, 12 H; 2 × CHMe$_3$), 2.34 (s, 6 H; 2 × Me), 4.51 (s, 1 H; NH), 5.01 ppm (sept, J$_{N-H}$ = 7.1 Hz, 2 H; 2 × CH); $^1$C NMR (100 MHz, CDCl$_3$): δ = 10.20 (Me), 23.1 (CHMe$_3$), 30.7 (CM)，50.3 (CM), 55.6 (CM), 124.3 (C=C), 141.6 ppm (CNH); IR (neat): v= 1103 (vs), 1053 (vs), 1053 (vs), 1192 (m), 1212 (m), 1373 (m), 1391 (m), 1409 (m), 1472 (w), 1519 (m), 1629 (w), 2982 (w) 3342 cm$^{-1}$ (s); MS (ESI$^+$): m/z (%): 252 (100) [M$^+$]; HRMS (ESI$^+$): m/z (calc) for C$_2$H$_4$N$_3$: 252.2344; found: 252.2344; elemental analysis (calc %)

An efficient and general method for the synthesis of imidazol-2-ylidene amines (hereafter named IMAMs) is described, which allows the variation of the sterically and electronic properties of the substituents Alk and R in the substrates. Their pK$_{BH+}$ values in acetonitrile were determined and a computational study of gas-phase basicities (GB), as well as the nucleus-independent chemical shift (NICS) values, for evaluation of the possible role of aromatization on the basicity of the bases is reported. To support the results a comprehensive study of the role of the field, resonance, polarizability, and steric substituent effect of a wider range of alkyl and electronagative substituents, R (e.g., F, Cl, Me, triflate (OTf), CH$_2$X, etc.), for the subseries of bases 1, in which Alk = iPr, is included in the computational study.
for C\textsubscript{6}H\textsubscript{5}HBF\textsubscript{4}N\textsubscript{2} (339.22): C 53.11, H 8.91, N 12.39; found: C 53.19, H 9.00, N 12.20.

**Liberation of base 1a:** Salt 1a-HBF\textsubscript{4} (13.6 g, 40.0 mmol) was dissolved in MeOH (40 mL) and hexane (200 mL) was added, followed by aqueous KOH (50%; 40 mL) with vigorous stirring. The mixture was stirred at ambient temperature for several minutes. The hexane layer was carefully separated through a cannula into a flask filled with argon. Extraction of the mixture with hexane (200 mL) was repeated twice. The combined hexane fractions were dried over BaO\textsubscript{2}, filtered, evaporated, and dried in a high vacuum at 50°C to give pure base 1a (7.6 g, 76%) as a colorless oily substance. H NMR (400 MHz, C\textsubscript{6}D\textsubscript{6}): \( \delta = 1.23 \) (d, \( J_{H-H} = 7.1 \) Hz, 12H; 2\times\text{CHMe})c, 1.57 (s, 9H; CMe)c, 1.72 (s, 6H; 2\times\text{Me}), 4.54 ppm (sept, \( J_{H-H} = 7.3 \) Hz, 2H; 2\times\text{CH})c. \( ^{13}\text{C}\) NMR (101 MHz, C\textsubscript{6}D\textsubscript{6}): \( \delta = 11.1 \) (Me), 21.0 (CHMe)c, 33.7 (CMe)c, 47.1 (CHMe)c, 51.7 (CMe)c, 116.1 (C= C), 146.2 ppm (CN); IR (hexane): \( \varepsilon = 1632 \) (vs), 1679 (m), 1685 cm\(^{-1}\) (m); MS (CI\textsuperscript{+}): \( m/z \) (%): 154 (15) \([\text{M}+\text{H}+\text{C}_4\text{H}_8\text{]}^+)\textsuperscript{+}, 196 (10) \([\text{M}+\text{H}+\text{C}_4\text{H}_8\text{]}^+)\textsuperscript{+}, 208 (24) \([\text{M}+\text{H}+\text{C}_4\text{H}_8\text{]}^+)\textsuperscript{+}, 210 (75) \([\text{M}+\text{H}+\text{C}_4\text{H}_8\text{]}^+)\textsuperscript{+}, 224 (36) \([\text{M}+\text{H}+\text{C}_4\text{H}_8\text{]}^+)\textsuperscript{+}, 250 (20) \([\text{M}+\text{H}^+]\textsuperscript{+}, 251 (68) \([\text{M}^+)\textsuperscript{+}, 252 (100) \([\text{M}+\text{H}^+]\textsuperscript{+}, \text{HRMS (CI\textsuperscript{+}}): \( m/z \) calc. for C\textsubscript{18}H\textsubscript{27}N\textsubscript{3}O\textsubscript{2}: C \textsubscript{18}H\textsubscript{28}N\textsubscript{3}O\textsubscript{2} \textsuperscript{+} found: 325.2445.

**Computational methods:** All calculations were carried out with the Gaussian 09 program package\textsuperscript{10} by using density functional theory (DFT) hybrid functional B3LYP and a 6–31+G** basis set. For optimized structures, vibrational frequencies were calculated to confirm that the stationary point corresponds to a true minimum and to calculate zero-point vibrational energies (ZPVE), enthalpies, and Gibbs free energies.

All NICS values [ppm] were calculated at the B3LYP/6–311+G** level of theory for all neutral and protonated bases. More negative NICS values indicate an increase in the aromatic character, whereas positive values show that the system is antiaromatic. Values close to zero appear if the system has neither aromatic nor antiaromatic character.

NICS(0)\textsuperscript{11,12} values are calculated at the mass center of the ring, however, it has been noted that in the case of smaller rings some of the shielding effect comes from o electrons and therefore NICS(1) values are preferred.\textsuperscript{11} NICS(1) values are calculated 1 Å above and below the mass center of the ring, corresponding to NICS(+1) and NICS(-1), respectively. In this study NICS(1) corresponds to the average of the values, since not all of the substances studied are symmetrical and therefore, in some cases, there are slight differences in the NICS(+1) and NICS(-1) values. The term ANICS(1) denotes the difference in NICS(1) values between the protonated and neutral forms of a substance.

The GB of a base B refers to the reaction given in Equation (1):

\[
\text{B} + \text{H}^+ \rightarrow \text{BH}^+ \quad \text{(1)}
\]

The GB of a base B at a temperature \( T \) is defined to be the negative value of the Gibbs free energy [Eq. (2)] for the reaction given in Equation (1):

\[
\text{GB} = -\Delta G = RT \ln K \quad \text{(2)}
\]

**Crystallographic data for 1b:** C\textsubscript{6}H\textsubscript{5}N\textsubscript{2}O\textsubscript{2}; monoclinic; space group P2\textsubscript{1}2\textsubscript{1}2\textsubscript{1}; \( a = 12.4823(4), b = 10.8254(4), c = 12.9690(5) \) Å; \( \beta = 98.714(2) \)°; \( Z = 4 \); colorless crystal 0.78 \times 0.43 \times 0.32 mm; reflections/parameters 3981/206; \( R(F^2) = 0.044 \) (all data); \( S = 1.03; \Delta R_{	ext{p}} = 0.47 \) e Å\(^{-3}\).

**Synthesis:** The synthesis of monomeric IMAM bases 1a–1h commenced with a condensation reaction of commercially or synthetically available N,N\'-dialkylthioureas 3a or 3b with 3-hydroxybutan-2-one 2 (Scheme 1). The corresponding 1,3-dialkyl-4,5-dimethyl-1H-imidazole-2(3H)-thiones 4a and 4b were obtained in good yields by heating at reflux in amyl alcohol, by following a literature procedure.\textsuperscript{13}

**Results**

Although a two-step procedure for the synthesis of 5 from 4 via the intermediate imidazol-2-ylidenes (N-heterocyclic carbines (NHC))\textsuperscript{20} is documented [9,15,21] a significantly modified and simplified one-pot protocol was developed, enabling the synthesis of 5a from 4a in multigram quantities. Heating of 4a with sodium in diglyme at 110°C, followed by quenching of the intermediate NHC with hexachloroethane provided 5a in an overall yield of 64% by using neither potassium nor reflux conditions.

The IMAM salts 1aI\textsuperscript{+}–1fI\textsuperscript{+} were synthesized in good yields by KF-mediated coupling of 2-chloroimidazolium salts 5a or literature-known compound 5b\textsuperscript{19} with the corre-
sponding primary amines in acetonitrile. The presence of KF was mandatory for the synthesis of the IMAM salts with no conversion of 5a being observed with an excess of tert-butylamine in [D₆]-acetonitrile after 1 day of heating in the absence of KF. It was firmly proven that KF played a dual role in this synthesis. On the one hand, it served as an activating agent, forming the intermediate 2-fluorimidazolium salt 6, which is a significantly better electrophile than 2-chloroimidazolium salt 5. On the other hand, it acted as a strong base, scavenging protons and thus driving the process to completion.

The IMAM bases 1a–1h were liberated in high yields from the corresponding salts by using a 1:1 v/v mixture of aqueous KOH (50%) and methanol, which is similar to the conditions Schwesinger et al.[22] applied for the liberation of P₁ bases from their salts.

Unfortunately, para-anisidine underwent a fast double substitution reaction with 5a, affording the dicationic salt 7 (Scheme 2). Consequently, to obtain the desired product afforded bicyclic salts 1iH⁺ and 1jH⁺. The IMAM bases 1i and 1j were liberated, as described above for 1a–1h, in high yields.

An attempt to perform a Staudinger-type synthesis of base 1a from an N-tert-butyl triazene precursor[9] was unsuccessful. Its thermolysis under various conditions led invariably to extrusion of isobutene and nitrogen, yielding 1k (Figure 2, Alk = Pr, R = H). Alternatively, base 1k was obtained through the corresponding N-trimethyl silyl (TMS)-derivative in 60% yield, by following a literature procedure.[29]

IMAM bases are stable liquids (1a–1f and 1i) or crystalline solids (1g, 1h, 1j, and 1k) that can be stored for several months as stock solutions in hexane at 5°C over BaO. They are readily miscible with common aprotic organic solvents, including hydrocarbons. The most basic representatives were found to be sensitive to atmospheric moisture and CO₂, since they rapidly convert to the protonated form (probably as the bicarbonate salt). Despite its highly hydrophobic substitution pattern, base 1a is soluble in D₂O, in which it exists in the fully ionized form 1aH⁺–OD⁻, as shown in the ¹³C NMR spectrum. It is quite stable towards hydrolysis, and no changes were observed after heating at 100°C in D₂O for one hour.

The nucleophilicities of bases 1a and 1f were compared to that of the known compound tBuP₁(pyr) by use of NMR competition experiments. Equimolar mixtures of 1a/tBuP₁(pyr) or 1f/tBuP₁(pyr) and methyl iodide in [D₆]-MeCN were monitored by ¹H NMR spectroscopy at room temperature. The nucleophilicity of 1a and 1f proved to be approximately 60 and 5 times higher than that of tBuP₁(pyr), respectively.

**Selected solid-state structures:** The solid-state structures of the free base 1h (Figure 4) and the salts 1b·HBF₄ (Figure 5), 1a·HBF₄, 1g·BF₃, 1i·OTs, and 1j·HBF₄ (for the last four structures, see the Supporting Information) were characterized by X-ray crystal-structure analysis.[19] The average N1(3)-C2-N4-C14 torsion angle (34.8°) for base 1h indicates a deviation of the C2–N4 double bond from a planar geometry. A slight distortion of the exo-nitrogen atom (N4) out of the imidazole ring plane (6.8°) was also observed for base 1h. On protonation of base 1h, the N1(3)–C2 and N1(3)–C5(4) bonds were shortened by 0.010–0.036 Å, whereas the C4–C5 bond was elongated by 0.013 Å, thus averaging of the bond lengths in the planar imidazolium ring in cation 1hH⁺ is observed. The C2–N4 bond was elongated by 0.064 Å. The average N1(3)–C2–N4–C14 torsion angle became closer to orthogonal, at 70.0°, for salt 1hH⁺.

**Basicity of imidazol-2-ylidene amines 1a–1k:** The alkyl-substituted imidazol-2-ylidene amines (bases 1a–1g) are strong bases in acetonitrile, the strongest of which are those containing a sterically demanding alkyl substituent on the imine nitrogen atom (Table 1). However, increasing the steric demand beyond a tert-butyl substituent does not significant-

### Scheme 2. Formation of dication 7. a) 5a, KF, MeCN, 60°C, 3 d.

1hH⁺, the intermediate 2-fluorimidazolium salt 6a was isolated first, followed by direct coupling with an excess of para-anisidine in the absence of KF (Scheme 1, 5 → 6 → 1H⁺ pathway). A similar indirect coupling approach was also used for the synthesis of 1gH⁺ because a considerably better yield was achieved.

The synthesis of the bicyclic IMAM bases 1i and 1j was accomplished from 2. Its reaction with butylamine,[23] followed by condensation of the intermediate α-aminoketone with cyanamide,[24] gave an aminimidazolium salt, which was converted into the free base 8 by deprotonation with ammonia (Scheme 3). Alkylation of 8 with 1,3-propylene ditosylate or 2,2-dimethyl-1,3-propylene bis(triflate) (0.5 equiv) over two steps afforded cyclic salts 1iH⁺ and 1jH⁺. The IMAM bases 1i and 1j were liberated, as described above for 1a–1h, in high yields.

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[Note: The image contains chemical structures and schemes, which are not transcribed but are described in the text.]
ly change the basicity in acetonitrile (1a vs. 1f and 1g). Some variability of the substituents in the 1 and 3 positions is possible without diminishing the basicity significantly (1a vs. 1b). As the steric demand of the imino substituent decreases, the basicity generally becomes lower (1a > 1c > 1e > 1k). Surprisingly, the N-methyl derivative 1e is slightly more basic than the N-neopentyl imidazole 1d and one of the most hindered derivatives 1g is slightly less basic than 1a. In the gas phase, the same base pairs have almost equal basicity. These differences imply the importance of solvation on the basicity in MeCN. The solvation effect gives additional stability to the protonated forms of the bases and the solvent molecules interact preferentially with the protonated basicity center. The bulkier the imino substituent, the more hindered the solvation of this center. Nevertheless, the intrinsically higher basicity of the compounds with bulkier imino substituents outweighs the solvation effects.

Compound 1h with an aromatic imino substituent displayed by far the weakest basicity among bases 1. Bicyclic compounds 1i and 1j display a significantly lower basicity than the monocyclic bases, but still a higher one than 1k and ImPyr (Figure 1). The difference in basicity between 1i and ImPyr provides an estimation of the contribution of two additional donor methyl groups to the bicyclic system to be calculated, giving a value of approximately one pK₉H⁺ unit.

**Basicity of 1a-1k in solution and the effect of aromaticity:** The contribution of aromatic resonance structure 1' (Figure 2) to the structure of bases 1a-1k affects their chemical shifts. Aromaticity is reflected by a net leveling of the differences in the chemical shifts at C2 and C4,5 of the imidazole ring. Thus, the ¹³C NMR chemical-shift difference δ = δ(C2) − δ(C4,5) can be used to assess the level of aromaticity in the imidazole rings in bases 1a-1k, as well as in their salts (see Table S7 in the Supporting Information). The smaller the value of δ, the larger the contribution of the aromaticity to the structure. The δ values of the free bases 1 increase in the order: 1a (R = tBu, 30.1 ppm) < 1c (R = iPr, 32.6 ppm) < 1e (R = Me, 35.9 ppm) < 1k (R = H, 40.1 ppm). The same order is found for the salts 1H⁺: 1aH⁺ (R = tBu, 17.3 ppm) < 1cH⁺ (R = iPr, 19.5 ppm) < 1eH⁺ (R = Me, 21.6 ppm) < 1kH⁺ (R = H, 23.4 ppm). The steric hindrance caused by the substituent on the Nₓ atom increases in the opposite order. This suggests that as the steric bulk of the substituent at Nₓ increases and the steric repulsion with the iPr substituents on N1 or N3 increases, the double-bond character of the imine is reduced and the contribution of the aromatic imidazolium amide resonance structure 1' increases.

Reasonable linear correlations were found when the chemical shift differences, δ, for bases 1a-1k and the corresponding salts 1aH⁺:1kH⁺ were plotted against the measured pK₉H⁺ values (Figure 6). The correlation holds even better for the average δ values of bases 1 and their protonated forms (middle line). Thus, the more bulky the Nₓ substituent, the stronger the contribution of the aromatic resonance structure 1'. This rationale is also supported by the lower basicity of 1i and 1j than that of the monocyclic compounds. The additional rigid six-membered ring prevents C≡N rotation upon protonation, thus thwarting the synergis-
tic effect of aromatization and the steric-strain release. Compounds 1i and 1j were consequently found to have basicities almost five orders of magnitude lower than that of the monocyclic base 1a. This correlation is only valid if the substituents on Nexo have a similar electronic nature. Therefore, the correlation does not hold for compound 1h.

Basicity of imidazol-2-ylidene amines in the gas phase and the effect of aromaticity: A computational study into the gas-phase basicities and ΔNICS(1) values of compounds 1a–1k (Table 1) and representative other imidazole-2-ylidene amines (see Tables S5 and S6 in the Supporting Information) was carried out to further dissect the contributing factors to basicity. The ΔNICS(1) values characterize the increase in aromatization of the imidazole ring upon protonation (see Table S6 in the Supporting Information). The influence of the substituents on the GB can be quantitatively described by two essentially similar linear free-energy relationship (LFER) approaches, which take into account the field-inductive (∑sF or ∑sF constants),[13,14,26–29] polarizability (∑sa constants or molecular refractivity (MRD)[26,27]), resonance (∑sR, ∑sR, or ∑sR, constants)[13,14,29] and steric effects (expressed by the Charton ν constant)[30] of the substituents. Equation (3) serves as the basis for elucidating the relationship between the molecular structure and basicity of members of compound class 1 (Alk = iPr).

\[
\text{GB} = a_0 + a_1 \sum_{sF} + a_2 \sum_{sa} + a_3 \sum_{sR} + a_4 \nu + a_5 \nu
\]

The GB values for the N-alkyl derivatives are within the range 253.1–259.2 kcal mol⁻¹, the highest in a large series of compounds. Attachment of other, especially electronegative, substituents to the imine nitrogen atom leads to a decrease in the GB to the level of 222.2–249.4 kcal mol⁻¹.

Examination of the correlation statistics (Table 2) shows that the first three terms in Equation (3)—the field-inductive (∑sF), polarizability (∑sa), and resonance (∑sR) components—are all statistically significant (at a probability of 0.99), whereas the steric term ∑sR is insignificant. The CN substituent deviates significantly from Equation (3) and thus was excluded from the general correlation. This is valid because independent calculations at the DFT 6–311 + G* level showed that protonation of the neutral base is expected to take place on the nitrogen atom of the cyano group and not, as in all other members of the series, at the nitrogen atom of the imino group (Figure 3). The sensitivity coef-

| Table 1. Summary of basicity measurements and calculations for compounds 1. |
|----------------------|-----------------|-----------------|------------------|
| Base Structure | Basicity pK_{BH} | ΔNICS(1) | Change in dihedral angle on protonation |
| 1a | \(30.21\) | 257.8 | \(-4.23\) | 24.6 → 84.5 (exp: 87.7) | \([a]\) |
| 1b | \(29.90\) | 256.2 | \(-4.01\) | 22.6 → 73.9 |
| 1c | \(27.98\) | 254.7 | \(-3.88\) | 13.1 → 80.5 |
| 1d | \(26.29\) | 253.1 | \(-3.44\) | 15.8 → 30.1 |
| 1e | \(27.2\) | 253.4 | \(-2.90\) | 11.5 → 72.0 |
| 1f | \(29.97\) | 259.2 | \(-3.89\) | 30.6 → 89.4 |
| 1g | \(29.47\) | 257.6 | \(-4.38\) | 25.7 → 89.9 (exp: 88.5) |
| 1h | \(23.26\) | 249.4 | \(-2.98\) | 28.3 (exp: 34.8) → 57.5 (exp: 70.0) |
| 1i | \(25.54\) | 250.2 | \(-2.18\) | 4.2 → 3.4 (exp: 7.9) |
| 1j | \(25.33\) | 251.0 | \(-2.31\) | 2.8 → 10.5 (exp: 12.7) |
| 1k | \(24.46\) | 248.0 | \(-2.52\) | 0.8 → 20.1 |

[a] Value obtained from the crystal structure.
Table 2. The statistical least-squares treatment of GB data for the derivatives of 1.

<table>
<thead>
<tr>
<th>Scales</th>
<th>$a_1$</th>
<th>$a_2$</th>
<th>$a_3$</th>
<th>$a_4$</th>
<th>$R^2$</th>
<th>$p$</th>
<th>$n/n_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma_D$, $\sigma_R$, $\sigma_N$, $\nu$</td>
<td>249.1 ± 1.4</td>
<td>−32.8 ± 1.9</td>
<td>−9.99 ± 2.00</td>
<td>−18.0 ± 5.0</td>
<td>1.21 ± 1.29</td>
<td>0.981</td>
<td>1.95</td>
</tr>
<tr>
<td>$\sigma_D$, $\sigma_R$, $\sigma_N$</td>
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<td>0.981</td>
<td>1.95</td>
</tr>
</tbody>
</table>

[a] $R^2$ = correlation coefficient. [b] $s$ = standard deviation. [c] $n_0$ reflects the total number of data points involved in the correlation; $n$ = the number of points remaining after exclusion of significantly deviating points. [d] The CN derivative was excluded.

![Figure 6. Dependence of the $pK_{BH}$ values (in MeCN) of the bases on the $^{13}C$ NMR chemical shift differences of bases 1a-1k and the corresponding salts. Compound 1h is not shown.](image63x562_to_271x683)

![Figure 7. Correlation between GB and ANICS(1) values of bases 1.](image298x397_to_559x533)

The calculated GB and experimental $pK_{BH}$ values were calculated (Figure 7). For some subfamilies of compounds with fixed $\sigma_R$ values of zero or close to zero, for example, for R = Alkyl, H ($\sigma_R = 0$), or Ph ($\sigma_R = 0.1$), a linear correlation between the GB and ANICS(1) values was found. Among the remaining substituents, due to the noticeable variation in their $\sigma_R$ values, a scattered “Milky-Way-like” picture with much worse statistical characteristics and no linear relationship between GB and ANICS(1) values emerges. It follows from this NICS analysis and from a correlation analysis in terms of both Equation (3) and the slope of the linear region in Figure 7 for the alkyl substituents and those with $\sigma_R$ values close to zero that there is only a modest share of the “aromatization” in these compounds (3.6 kcal mol$^{-1}$ of GB for every ANICS(1) unit).
Discussion

The high basicity of compounds 1a–1k deserves comment. This is the first class of practically useful bases with a basicity markedly increased by forced aromatization of a substructure.[32] This is based on the synergistic effect of three crucial structural features on the unsaturated imidazole ring—a bulky imino substituent, bulky substituents in the 1 and 3 positions, and the methyl groups in the 4 and 5 positions. The alkyl substituents on the imidazole ring increase the electron density and stabilize the positive charge in the developing imidazolium cation. The extent to which the methyl groups in the 4 and 5 positions increase the calculated GB of compound 10 amounts to approximately 5 kcal mol\(^{-1}\) (Figure 9). Enlarging the substituents on the 1 and 3 positions from methyl in 10 to isopropyl in 1e increases the GB by approximately 4 kcal mol\(^{-1}\). This increase in crowding places the bulky substituents in the 1 and 3 positions into an orientation in which steric interactions with the imine substituent are maximized, leading to another 4.4 kcal mol\(^{-1}\) gain in GB for the most hindered derivatives, such as 1a.

In acetonitrile, an effective weakening of the C–N double bond in bases 1a–1k with increasing bulkiness of the imine substituent and a significantly more pronounced contribution of the imidazolium amide resonance structure 1' is expected to contribute to the increase in basicity. The correlations between \(^{13}\)C NMR chemical shift/NICS values and solution basicity/GB support this hypothesis. Another factor contributing to the observed basicity is the release of steric strain on protonation, for which the effective bond order of the C–N double bond is reduced and the substituent in the 2 position can rotate to minimize steric interactions. In contrast to bases 1a–1k, an increase in steric hindrance beyond an N-methyl group leads to a decrease in the basicity of P1 phosphazene bases in acetonitrile.[16,22]

A recent publication by Mayr et al.[32] concluded that both aromatic and saturated NHCS display similar nucleophilicities (and similar basicities). The same was shown earlier for the effect of ligation of NHCS to metals.[20,33] Although cyclic guanidines[34] and imidazoline-2-imines[34c,35] have been described as superbases, no experimental \(pK_{\text{HB}}\) values are available. To determine the contribution of aromaticity to the basicity of 1, the GB of structurally analogous compounds 9 and 10 and of saturated analogues 11, 12, and 13 was calculated. The unsubstituted derivative 11 displays only a 1.6 kcal mol\(^{-1}\) lower basicity than the unsaturated compound 9. Comparing the GB of saturated compound 12 to that of compound 1a, the latter is 10.8 kcal mol\(^{-1}\) more basic. The GB difference decreases by 4 kcal mol\(^{-1}\) for tetramethyl-substituted compound 13 in comparison with 1a. In the gas phase, the number and size of the alkyl fragments near the basicity center significantly affect the basicity. In addition, two methyl groups in positions 4 and 5 in 13 can have an additional steric influence on the isopropyl groups that is not present in 1a. Thus, structure 12 can be considered to be the closest analogue of 1a and a significant part of the GB difference can be traced to the contribution of the aromaticity in 1a.

The computational analysis of the contributing factors to the GB of a larger series of imidazole-2-imines demonstrates that if a wide range of electronically different substituents at the 2 position is considered, their field-inductive effect dominates the gas-phase basicity (affecting it by up to 20 powers of ten). The influence of resonance and the polarizability effects of substituents in the 2 position are less pronounced, but still significant. In contrast, steric effects are negligible for this type of proton transfer. The GB values of all of these compounds are, however, lower than those of 1a–1k.

Conclusion

A series of stable organosuperbases, N-alkyl- and N-aryl-1,3-dialkyl-4,5-dimethylimidazol-2-ylidene amine, have been designed. Their synthesis was accomplished in 4–5 steps, starting from \(N,N'\)-dialkylthioureas, with overall yields of 27–44%. This unified synthetic strategy is based on a KF-mediated coupling of 2-chloroimidazolium salts with primary amines, allowing the synthesis of a large number of imidazol-2-ylidene amines with widely varying substitution patterns. The structures of the 2-aminimidazolium cations 1aH\(^{1}\)=–JH\(^{1}\) and the neutral bases 1a–1j were elucidated in depth. The origin of the high basicity of these compounds is discussed. It is demonstrated that the increase in the basicity of the compounds in the gas phase and in solution is influ-
enced by the degree of aromatization of the imidazolium ring as measured by the 13C NMR chemical shifts in solution, as well as by the calculated ANICS(1) values in the gas phase. If a wider range of imino substituents, including electron-acceptor substituents, is studied, the influence of the field-inductive effect, polarizability, and resonance effects of the substituent becomes more significant than aromatization.

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[34] a) J. R. Bell, H. Luo, S. Dai, Tetrahedron Lett. 2011, 52, 3723–3725; b) T. Ishikawa, Chem. Pharm. Bull. 2010, 58, 1555–1564; c) the calculated MeCN pK_{BH+} for mono-/1,8-bis(dimethylethylene


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