

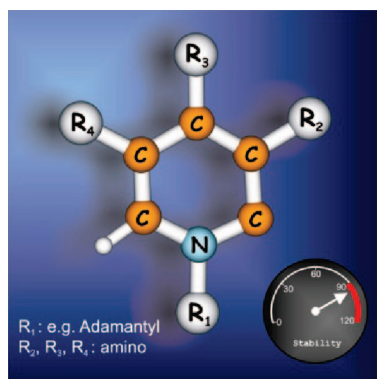
Stabilizing the Hammick Intermediate

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Received January 10, 2008



The possible stabilization of pyridine-2-ylidene has been investigated at B3LYP/6-31+G* and B3LYP/6-311+G** levels of theory. The aromaticity of this compound is a significant contributor to its stability ($ISE_c = 24\text{--}27 \text{ kcal mol}^{-1}$, Bird index = 77, NICS(0) = -6.8 ppm , NICS(1) = -9.1 ppm ; all about 80% of those for the H-shift isomer pyridine). The stabilization energy of the carbene (measured by an appropriate isodesmic reaction) can be influenced by the substitution at nitrogen with bulky groups, and at the carbon atom by amino groups. Considering possible competitive deprotonation reactions of the most likely synthetic route, **1j**, **1k**, and **1l** are suggested as synthesizable new stable carbenes.

Introduction

Stable singlet carbenes¹ are of current interest due to their unusual bonding and applicability as ligands of catalysts in various reactions,^{2,3} often resulting in better stereoselectivity compared with that of phosphino complexes or other catalysts.³ The utility of a carbene complex highly depends on the stability of the ligand,⁴ and hence synthesis of new stable carbenes is essential.

These compounds can be classified as push–pull and push–push carbenes.^{1a} Phosphino-silyl,⁵ bis(phosphino),⁶ and phosphino-2,6-bis(trifluoromethyl)-phenylcarbenes⁷ synthesized first by Bertrand and co-workers, as well as the sulfonyl-trifluoromethyl-carbene⁸ reported by Seppelt (an alternative description is with a triple bond toward the hypervalent heavy atom),⁹ belong to the first category. The first “bottleable” push–push carbenes were imidazole-2-ylidenes, prepared by Arduengo and co-workers,¹⁰ and subsequently a number of further stable N-heterocyclic carbenes have been synthesized, such as derivatives of triazole-3-ylidene,¹¹ thiazole-2-ylidene.¹² In these compounds the divalent carbon atom is stabilized by

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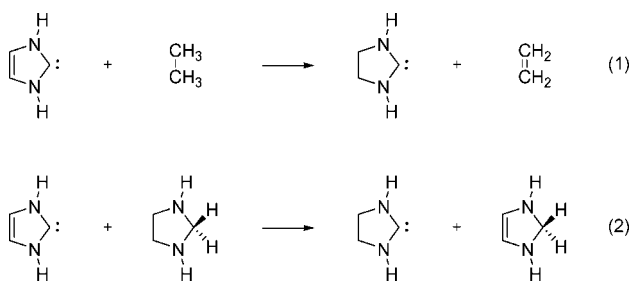
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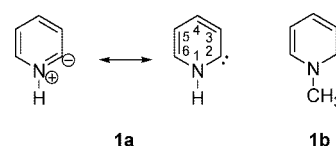
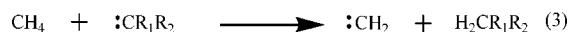
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SCHEME 1. Isodesmic Reactions Used To Evaluate the Aromatic Stabilization of Imidazole-2-ylidene

the presence of the two π -donor heteroatoms and the 6π -electron cyclic delocalization. The stabilizing effect of aromaticity on imidazole-2-ylidene has been estimated by different isodesmic reaction schemes. Whereas in reaction 1, 27.8 kcal mol⁻¹ stabilization has been obtained,¹³ the energies of the homodesmotic reaction 2 (originally¹⁴ written as the difference of the energies of two separated reactions) was 19.4 kcal mol⁻¹ at MP4/6-31G**/HF/6-31G*+ZPE¹⁴ and 13.5 kcal mol⁻¹ at B3LYP/6-311G**//B3LYP/6-31G*¹⁵ (Scheme 1). Magnetic¹⁴ measures and structural investigations¹⁵ also indicate that imidazole-2-ylidene has certain aromatic character.

Also the diphospha analogue of the triazol-3-ylidene has recently been reported.¹⁶ It has been shown that stable carbenes can be realized with proper steric protection even without the beneficial aromatic stabilization.¹⁷ Furthermore, a monoaminocarbene with a (bulky) spectator substituent could also be synthesized as a stable compound at ambient temperature.¹⁸ Very recently a stable carbocyclic carbene has been reported, benefiting from the 2π -electron aromaticity and the exocyclic π -donor amino groups.¹⁹ Considering the stabilizing factors of the hitherto synthesized carbenes, it is surprising that the six-membered ring carbene **1a**, which has a stabilizing nitrogen substituent and six π -electrons has not yet been reported as a stable compound so far.

There is some scattered information about this pyridine isomer as an unstable compound, first proposed as a reaction intermediate by Hammick 70 years ago.²⁰ The decarboxylation reaction of picolinic acid was observed to be much faster than the corresponding reactions of nicotinic acid or isonicotinic acid. Thus, it has been assumed²⁰ that the departing carboxyl group

SCHEME 2. Structure and Numbering of Pyridine-2-ylidene, the So-Called Hammick Intermediate**SCHEME 3. Isodesmic Reaction Used To Evaluate the Stability of Carbenes**

and the nitrogen interact and a relatively stable pyridine-2-ylidene **1a** (Scheme 2) intermediate is formed.

A few decades later, the stability of the pyridine-2-ylidene was studied by Gleiter and Hoffmann, who predicted extended stability due to its 6π aromatic character and the π -electron donating N-atom attached to the hypovalent carbon atom.²¹

Without reference to Hammick, further indirect evidence has been found by Shevlin for the existence of **1b**.²² He investigated the ring expansion reaction of 1-methylpyrrole with atomic carbon generated by an electric discharge, considering the presence of 1-methylpyridine-2-ylidene.

The parent **1a** itself has been generated and detected in the gas phase by neutralization reionization mass spectroscopy (NRMS) by Terlouw et al.²³ This compound was stable for milliseconds in the gas phase and did not isomerize to pyridine. The NRMS results have been confirmed by B3LYP/6-31G** and MP2/6-31G** level computations, showing that the ca. 40 kcal mol⁻¹ barrier of the monomolecular isomerization process leading to pyridine (which is more stable than **1a** by about 50 kcal mol⁻¹) prevents the isomerization. In a different computational approach the stability of **1a** has been estimated by the isodesmic reaction (reaction 3, Scheme 3), and a stabilization energy of 88.3 kcal mol⁻¹ (MP2/6-311+G(2D)) and 85.5 kcal mol⁻¹ at B3LYP/6-311+G(2D)) has been reported.²⁴ The energy of reaction 3 was shown to give an excellent linear correlation with the dimerization energy of the carbene.²⁴

This energy is somewhat smaller than for imidazole-2-ylidene (109.0 kcal mol⁻¹), but it is comparable to the stabilization energy of imidazolidine-2-ylidene (91.2 kcal mol⁻¹), which has also been synthesized with mesityl or *tert*-butyl substituents at the nitrogens.¹⁷ Thus, it is reasonable to assume that with a proper substitution pattern the Hammick intermediate can be stabilized. Complexes of this carbene with certain transition metals have already been synthesized.²⁵

Since the dimerization is a characteristic reaction of carbenes, information on the possible dimer of pyridine-2-ylidenes has to be considered. Although such compounds have not been synthesized in a pure form, two electron reduction of some known 1,1'-

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dimethyl-2,2'-bipyridinium dications^{26,27} have been successfully accomplished, presumably yielding derivatives of the dimer.²⁷ Unfortunately, neither spectroscopic data nor structural characterization is available for the reduction products. The presence of the pyridine-2-ylidene derivative has not been considered.

The aim of the present work is to investigate computationally the possible stabilization of this cyclic carbene, by selecting the proper substituents.

Computational Methods

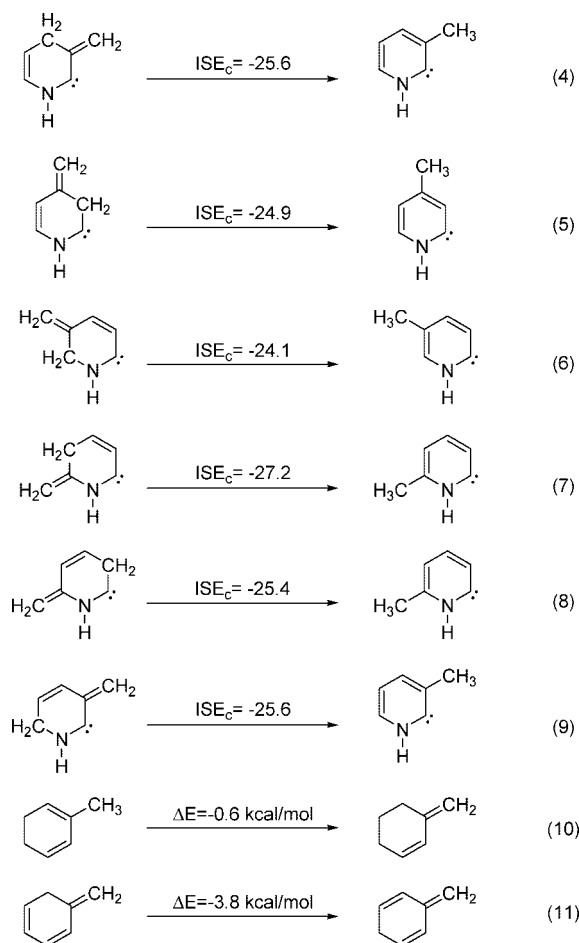
All calculations were carried out with the Gaussian 98 program package,²⁸ at the B3LYP/6-31+G* and B3LYP/6-311+G** levels.²⁹ We have shown in earlier work²⁴ that the stabilization energies at this level are smaller than at MP2 or MP4, and thus this economic method is unlikely to result in overestimated stability of the investigated compounds. Full geometry optimizations were performed for all molecules, and vibrational frequencies were calculated to establish the nature of stationary points obtained. NICS values³⁰ were calculated as the negative of the magnetic shielding at the geometric center of the ring at the B3LYP/6-311+G** level. Bird indices³¹ were calculated by using the Gordy bond orders³² of the ring, using the B3LYP/6-311+G** bond distances of the simplest single- and double-bonded compounds (CH₃-CH₃, CH₂=CH₂, CH₃-NH₂, and CH₂=NH) as references.

Results and Discussion

The presence of six π -electrons in the planar pyridine-2-ylidene suggests that aromaticity can play an important role in the stability of this compound. Hence the energetic, geometric, and magnetic aspects of the aromaticity of this carbene have been investigated first. Utilizing the concept of ISE (isomerization stabilization energy) for the evaluation of the aromatic stabilization energy of pyridine and benzene used recently by Schleyer and Pühlhofer,³³ the stabilization energy of the Hammick intermediate can be estimated by the energy of the reactions seen in Scheme 4.

In order to cancel out the *anti-syn* mismatches (similarly to the case of pyridine),³³ the energies of the reactions 4–7 in Scheme 4 have been corrected with the energy of reaction 10, while reactions 8 and 9 have been corrected with the energy of reaction 11.³³ Considering this correction, ISE_c values lie within a 3.1 kcal mol⁻¹ range, showing the reliability of the ap-

SCHEME 4. Corrected (See Text) B3LYP/6-311+G** ISE Energies (kcal mol⁻¹) for 1a



proximately 24–27 kcal mol⁻¹ aromatic stabilization. Significant aromaticity is shown also by the Bird index (76.8) and the NICS(0) and the NICS(1) values (–5.6 and –9.1 ppm, respectively), which are approximately 80% of those for pyridine (cf. ISE_c = –33 kcal mol⁻¹,³³ BI = 97, NICS(0) = –6.8 ppm, NICS(1) = –10.2 ppm).

As a reference, the concept of ISE has also been used to estimate the aromaticity of imidazol-2-ylidene as compared to that of imidazole (Scheme 5). The ISE value of imidazole-2-ylidene is about 70% of that for the H-shift isomer imidazole, and their Bird index and NICS(0) values exhibit even smaller differences (BI = 60, NICS(0) = –13.0 ppm, NICS(1) = –10.1 ppm for imidazole-2-ylidene; BI = 69, NICS(0) = –13.1 ppm, NICS(1) = –10.5 ppm for imidazole). It is worthy to note that because of its balanced nature ISE (14.4 kcal mol⁻¹) provides a better estimate for the aromatic stabilization, than the energy of the ring fragmentation reaction 1,¹³ and in fact it is in good agreement with the 13.5 kcal mol⁻¹ stabilization at B3LYP/6-311G**//B3LYP/6-31G*¹⁵ concluded from the energy of reaction 2 (Scheme 1).

The nitrogen atom is pyramidal in most of the amines (the planarization energy for NH₃ is about 5 kcal mol⁻¹).³⁴ As in other aminocarbenes,³⁵ the nitrogen atom of **1a** is, however,

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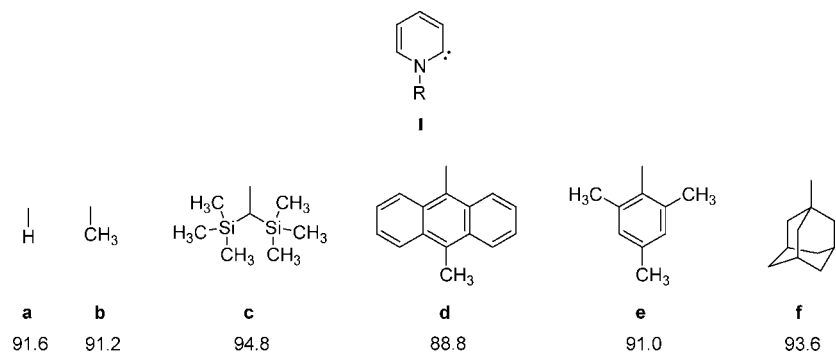
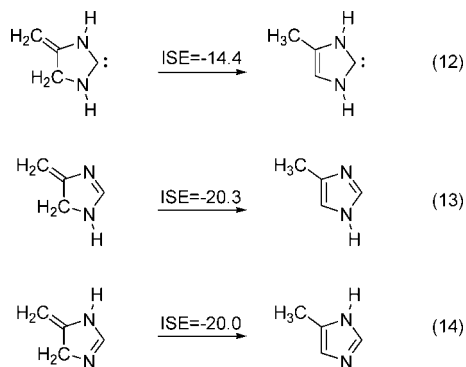
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CHART 1. Structure and Isodesmic Reaction Energy (at B3LYP/6-31+G* Level, in kcal mol⁻¹) of the Examined Pyridine-2-ylidenes

SCHEME 5. Possible ISE Reactions for Imidazol-2-ylidene and Imidazole and Their Energies (kcal mol⁻¹, at the B3LYP/6-311+G Level)**


planar. Apparently, the stabilizing π -acceptor interaction between the nitrogen lone pair and the empty carbene orbital overcomes the planarization energy of the amino group, further stabilization of the planar structure is gained from aromaticity. Saturating, however, the valences at the divalent carbon in a chemical reaction (e.g., dimerization), this stabilization is not effective anymore, and the reaction product benefits energetically from the pyramidalization. By other words, there is a hidden inherent destabilization in planar aminocarbenes, which is activated if the divalent carbon is getting saturated. Hence, further stabilization of the carbene is likely, if the nitrogen atom is forced to remain planar by some external means.³⁶ Accordingly, we have chosen the bulky adamantyl, 10-methylanthracen-9-yl, bis(trimethylsilyl)-methyl, and mesityl groups. The stability of the corresponding N-substituted pyridine-2-ylidene has been estimated by the isodesmic reaction (3) in Scheme 2. The examined structures and the calculated B3LYP/6-31+G* level energies are given in Chart 1. The adamantyl and the bis(trimethylsilyl)-methyl substituents³⁷ have been found to be the most appropriate, with a stabilization energy of 93.6 and 94.8

(36) It should be noted that in the case of phosphorus the planarization barrier is significantly larger than for nitrogen, and thus the energetic consequence of the planarization is larger there. From planarized tricoordinate phosphorus larger π -stabilization can be expected than from nitrogen (Kapp, J.; Schade, C.; El-Nahasha, A. M.; Schleyer, P. v. R. *Angew. Chem., Int. Ed.* **1996**, *35*, 2236–2238) giving rise to highly aromatic phosphorus containing rings (Nyulászi, L. *Tetrahedron* **2000**, *56*, 7984. Nyulászi, L. *Chem. Rev.* **2001**, *101*, 1229–1246).

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TABLE 1. Effect of Substitution on the Stabilization Energy of 1-Methylpyridine-2-ylidene (B3LYP/6-31+G*)

R				
-NH ₂	95.7	95.1	94.8	92.4
-OMe	90.7	93.7	93.3	91.4
-BH ₂	80.6	88.0	81.1	88.6
-CH ₃	90.7	91.6	92.3	91.9
Phenyl	91.0	91.9	90.7	91.2

kcal mol⁻¹, respectively. The somewhat higher stabilities of these two structures with respect to other structures having a bulky group on the nitrogen may be partly attributed to the electron-donating effect of the adamantyl and bis(trimethylsilyl)-methyl substituents. These stabilization energies are somewhat higher than the 91.6 kcal mol⁻¹ value (at the same level of the theory) for the parent Hammick intermediate **1a**, and expectedly further persistency is provided by steric effects, hindering any dimerization reaction.

Substitution at the carbon atoms of the pyridine ring is likely to have further effect. Stabilization energies in reaction 4 of the 1-methylpyridine-2-ylidene with an amino, boro, and methyl group at the 3, 4, 5, or 6 positions have been calculated and are shown in Table 1.

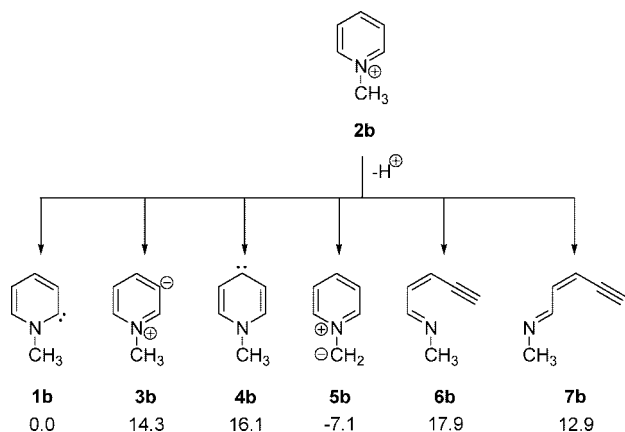
An amino group at the 3, 4, or 5 positions stabilizes the structure by 4.5, 3.9, or 3.6 kcal mol⁻¹ with respect to the unsubstituted molecule. π -Electron withdrawing substituents reduce the stability, the alkyl, and aryl substitution having no significant effect. Thus, the most likely synthetic targets are aminopyridine-2-ylidenes, substituted with a bulky alkyl group at the nitrogen.

Considerations Related to the Possible Synthesis. The most general method for the preparation of stable carbenes involves deprotonation of the appropriate cationic precursors by strong bases. Thus, pyridine-2-ylidenes may be synthesizable from the well-known pyridinium salts. The pyridinium salts **2b**,³⁸ **2d**,³⁹

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CHART 2. H-Shift Isomers of 1-Methylpyridine-2-ylidene and Their Relative Energies (in kcal mol⁻¹, at the B3LYP/6-311+G** Level)



and **2f**⁴⁰ (formally generated by protonating the carbenes **1b**, **1d**, and **1f** at the hypovalent carbon atom, respectively) have been synthesized in previous works.

It is however possible that competitive deprotonation reactions prevent the formation of the carbene;⁴¹ hence we compared the B3LYP/6-311+G** energies of the most relevant isomers of **1b** (Chart 2).

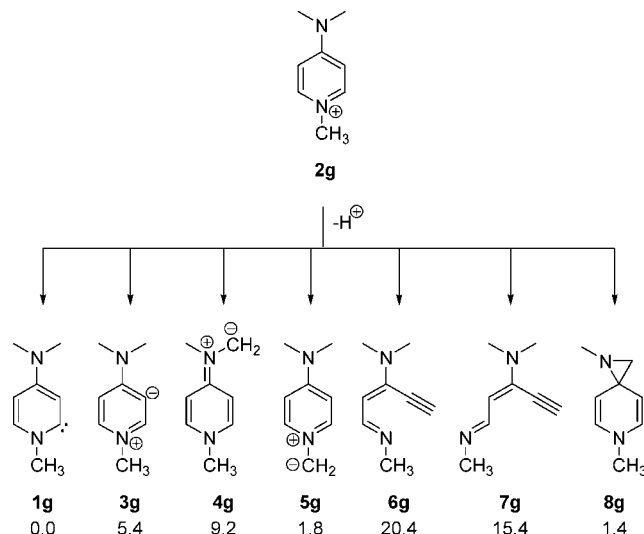
While **1b** is the most stable carbene structure and the ring-opened **6b** and **7b** are also rather unstable, the pyridinium-ylide **5b** has the lowest energy (by 7.1 kcal mol⁻¹) among the investigated structures. Accordingly, assuming that the deprotonation is thermodynamically controlled, from a methylpyridinium salt **5b** should form, and in order to be able to isolate **1**, the substituent at the nitrogen should be either an aromatic or an alkyl moiety with a quaternerized carbon atom, such as the adamantyl or tris(trimethylsilyl)methyl group.⁴²

Although the deprotonation at the 3- or 4-position of the ring is energetically more demanding than at the 2-position (**1b** is more stable than **3b** or **4b**), the steric shielding of the bulky substituent on the nitrogen atom might inhibit the deprotonation at the 2-position. Furthermore, the monomolecular 1,3 H-shift of **3b** to **1b** has a barrier of 62.1 kcal mol⁻¹ (at the B3LYP/6-311+G** level), and thus the formation of the pyridine-2-ylidene is prohibited on this path. A ring-opening process of **3b** (having a barrier of 24.9 kcal mol⁻¹) and a subsequent low barrier rotation might yield **7b**, which has a rather acidic hydrogen at the sp carbon atom. It is likely that the strong base used in the synthesis deprotonates **7b**, presumably leading to an anionic polymerization.

A dimethylamino substituent at the 4-position reduces somewhat the energy difference of the isomers, leaving the carbene **1g** the most stable isomer, as is seen in Chart 3.

The presence of dimethylamino groups at the 3- and 5-positions, however, stabilizes carbene **1h** significantly with respect to its possible isomers (Chart 4). Beneficially, if the N atom is suitably substituted, the steric hindrance of the different ring

CHART 3. H-Shift Isomers of 4-Dimethylamino-1-methylpyridine-2-ylidene and Their Relative Energies (in kcal mol⁻¹, at the B3LYP/6-311+G** Level)



positions are going to be similar at this arrangement of the substituents, and thus it is likely that thermodynamics will determine the deprotonation in this compound.

Further stabilization can be expected by the presence of a third amino group, which can only be realized in an annulated ring system (**1i**), to maintain the coplanar arrangement of all amino moieties. The relative energies of the H-shift isomers of **1i** are much higher relative to the carbene (Chart 5), and the differences are greater than in the cases above, so from this point of view this is the most appropriate substitution pattern of a stable pyridine-2-ylidene.

Combining the stabilizing effect of the substituents on the nitrogen and on the carbon atoms, supposedly the most stable derivatives of the pyridine-2-ylidene are shown in Chart 6, together with their stabilization energies.

The stabilization energies of the carbenes in Chart 6 are the highest among the investigated structures, and comparable to or in case of **1L** even higher than that for the already synthesized and thermally stable 1,3-dimethylimidazole-2-ylidene (105.7 kcal mol⁻¹ at the same level of theory). Thus, these derivatives of the pyridine-2-ylidene are the most suitable targets for synthesis.

Conclusion

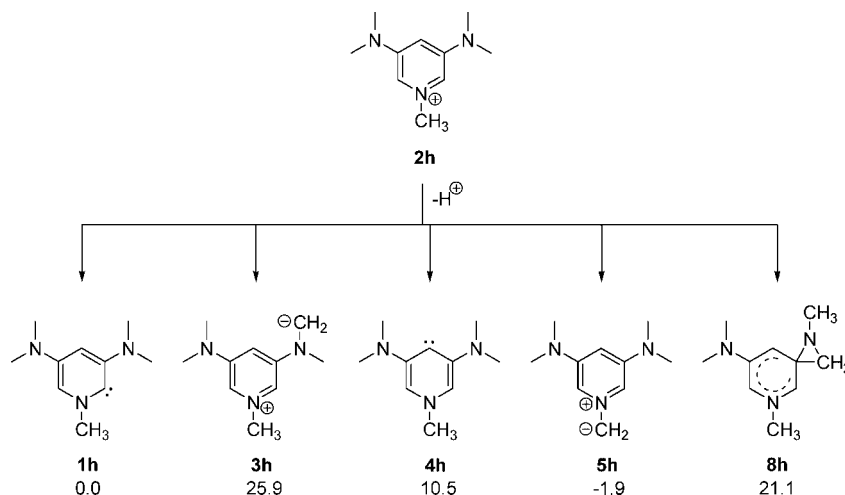
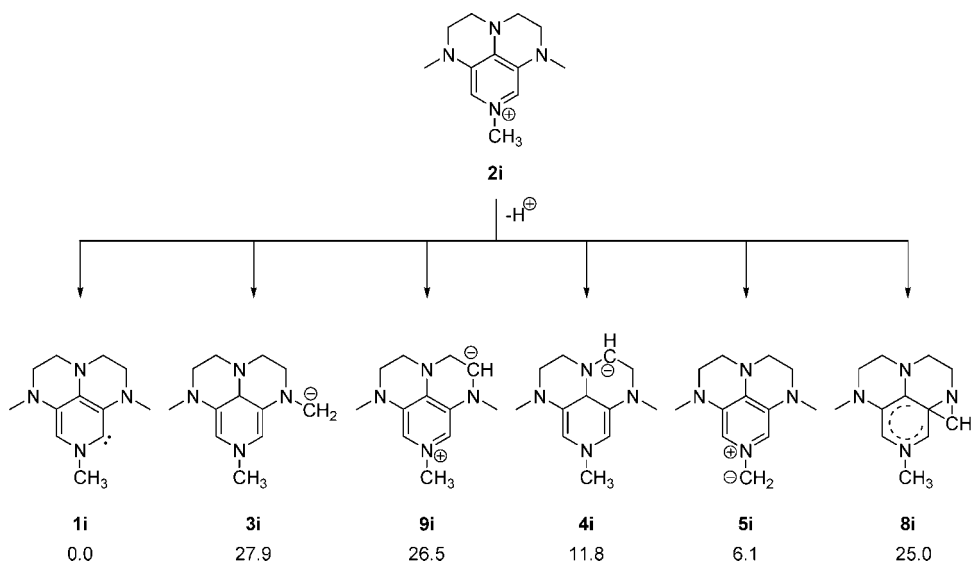
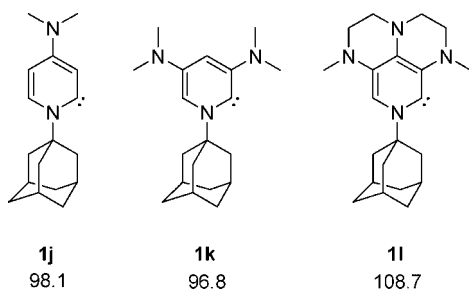
Pyridine-2-ylidene (the so-called the Hammick intermediate) had been proposed to be an intermediate in certain reactions and synthesized as ligand in several transition metal complexes. In the present work, the possible stabilization of the free pyridine-2-ylidene has been investigated at the B3LYP/6-31+G* and the B3LYP/6-311+G** levels of theory. The aromaticity of the parent compound has been found to be significant (ISE_c = 24–27 kcal mol⁻¹, BI = 77, NICS(0) = -6.8 ppm NICS(1) = -9.1 ppm; all about 80% of those for the H-shift isomer pyridine).

The stability can be influenced by the substitution at nitrogen with bulky groups, such as the adamantyl group, keeping the nitrogen planar, thus enabling the effective π -overlap. (Further stabilization is expected from steric effects.) Stability can be increased by substitution at the carbon atoms of the ring with π -electron donating (most effectively -NR₂) substituents.

(40) (a) Sokolenko, V. A.; Svirskaya, N. M. *Izvest. Akad. Nauk SSSR, Seriya Khim.* **1984**, *4*, 1677–1680. (b) Sokolenko, V. A.; Svirskaya, N. M. *Khim. Getero. Soed.* **1987**, *6*, 817–819.

(41) Cattoen, X.; Sole, S.; Pradel, C.; Gornitzka, H.; Miqueu, K.; Bourissou, D.; Bertrand, G. *J. Org. Chem.* **2003**, *68*, 911–913.

(42) In case of the bis(trimethylsilyl)methyl substituent, the relative energy of the pyridinium-ylide is even lower (-8.3 kcal mol⁻¹) on the B3LYP/6-311+G** level compared to **1c**. It is also worth of noting that *t*Bu substitution of the pyridinium salts is known to result in isobutylene elimination, and thus *t*Bu substitution is not a viable alternative.

CHART 4. H-Shift Isomers of 3,5-Bis(dimethylamino)-1-methylpyridine-2-ylidene and Their Relative Energies (in kcal mol⁻¹, at the B3LYP/6-311+G** Level)**CHART 5.** H-Shift Isomers of 1i and Their Relative Energies (in kcal mol⁻¹, at the B3LYP/6-311+G** Level)**CHART 6.** Derivatives of Pyridine-2-ylidene Expected To Be Most Stable and Their Stabilization Energies in Reaction 3 at the B3LYP/6-31+G* Level (in kcal mol⁻¹)

Possible competitive reactions of the most common synthetic route, which includes a deprotonation reaction of a cationic species, have also been investigated. Deprotonation at the substituent attached to the nitrogen atom yields a pyridinium-ylide that is somewhat more stable than the carbene. The carbene, however, can be stabilized more effectively by amino

groups at the ring carbon than the pyridinium-ylide, and furthermore the use of substituents with tertiary carbon (e.g., adamantyl group) at the nitrogen eliminates the possibility of the formation of this isomer.

The most suitable targets for synthesis are given (**1j**, **1k**, and **1l**), and according to the isodesmic reaction (3), **1l** has a stabilization of 108.7 kcal mol⁻¹, which indicates even higher stability than that for the already synthesized and thermally stable 1,3-dimethylimidazole-2-ylidene.

Acknowledgment. Financial support from the Hungarian Scientific Research Fund (OTKA T049258) is gratefully acknowledged.

Supporting Information Available: S1 geometries (in Cartesian coordinates) and total energies of the optimized structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO8000035