Semiempirical (AM1, PM3 and SAM1) calculations of the protonation enthalpies of proton sponges related to 1,8-diaminonaphthalene. Estimation of the aqueous basicity of new designed superbases

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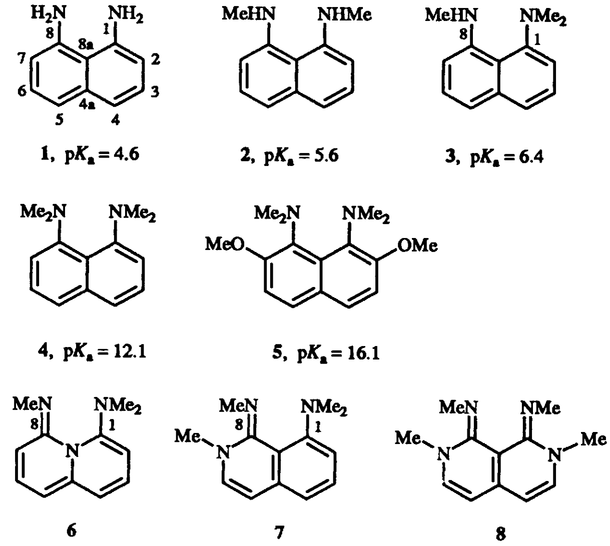
AM1, PM3 and SAM1 calculations have been carried out on eight compounds related to 1,8-diaminonaphthalene, five known proton sponges and three new compounds (a quinolizine, an isoquinoline and a 2,7-naphthyridine). The acceptable results obtained for the correlation between pK_a and protonation enthalpies for the first five compounds using either the AM1 or the SAM1 method, gives confidence to the predicted high basicity (between 19 and 22 pK_a units) for the unknown compounds.

We have been interested in the structure–basicity relationships of proton sponges,[1–8] and in the use of semiempirical methods for the study of the structure of aromatic compounds.[9–11] Consequently, we decided to apply these methods to the estimation of the aqueous basicity (pK_a) of known proton sponges with the aim of predicting the basicity of unknown compounds designed to be superbases.

To approach these large molecules, we have selected two of Dewar's methods: the extensively used AM1[12] and the new SAM1[13] together with Stewart's PM3.[14] The studied molecules are proton sponges **1–5**, covering a range of more than 11 pK_a units, and the unknown compounds **6–8**. We have represented in Scheme 1 the neutral molecules **1–8** and in Scheme 2 the conjugated acids **1H**$^+$–**8H**$^+$ which should have a structure with the acid proton on one of the nitrogen atoms intramolecularly hydrogen bonded to the other nitrogen atom.



1, pK_a = 4.6 **2**, pK_a = 5.6 **3**, pK_a = 6.4

4, pK_a = 12.1 **5**, pK_a = 16.1

6 **7** **8**

Scheme 1

Geometries

We have already discussed in detail the AM1 potential surface of compounds **4** (called DMAN) and **4H**$^+$ with regard to the rotation about the two exocyclic C–N bonds.[8] Table 1 reports several geometrical parameters involving the basic centres of the fully optimized neutral and protonated molecules obtained using the three semiempirical methods. Special care has been taken to find the absolute minimum starting from several conformations about the exocyclic C_{ar}–N bonds.

The most outstanding features can be summarized as follows. In general, all neutral molecules have in common the lack of planarity of the naphthalene ring due to the repulsion of the nitrogen lone pairs, distortion which is drastically reduced when the protonation occurs; this is consistent with crystallographic results.[8,15] The C_{ar}–N distances reflect quite well the influence of the protonation and the intramolecular hydrogen bond (HB) interaction. Thus, for the asymmetric cations, the C_{ar}–N$^+$ bond length is longer than the C_{ar}–N one except when the proton is almost symmetrically placed between both nitrogen atoms as happens in **1H**$^+$ and **2H**$^+$ (SAM1 calculations). Moreover, the elongation of the bond in which the N atom acts as HB-acceptor is also observed in neutral molecules **1** (PM3), **2** (PM3, SAM1) and **3** (PM3). Besides, the PM3 method overestimates the lengths of the single bond while there is a fairly good agreement between the three methods concerning the length of the exocyclic C–N double bond in compounds **6–8**.

The main differences between the three methods are those regarding (*i*) the conformation of substituents and (*ii*) the N···N distances (Table 1 and Figs. 1 and 2). Concerning the first aspect, two perpendicular views of **6**, **8** and their corresponding cations **6H**$^+$ and **8H**$^+$ (PM3 and SAM1) are represented in Figs. 1 and 2 to show the conformational differences in the neutral molecules as well as the effects of the protonation. We have checked that the SAM1 energy for compound **8** in conformation (*d*) (Fig. 2, PM3 minimum), is 0.8 kcal mol^{-1} above the true minimum [Fig. 2, conformation (*c*)].† Concerning the second aspect, some common features are found, for instance, the following sequence is observed for all the cations: N$^+$···N (SAM1) < N$^+$···N (PM3) < N$^+$···N (AM1). The SAM1 method tends to prefer symmetric N$^+$–H···N bridges and the agreement in **4H**$^+$ with averaged experimental results is rather good (Table 1).[8] Two striking results are observed: in **8H**$^+$, the hybridization of the N$^+$ atom depends on the method used being sp^2 (SAM1) or sp^3 (AM1,

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† 1 cal = 4.184 J.

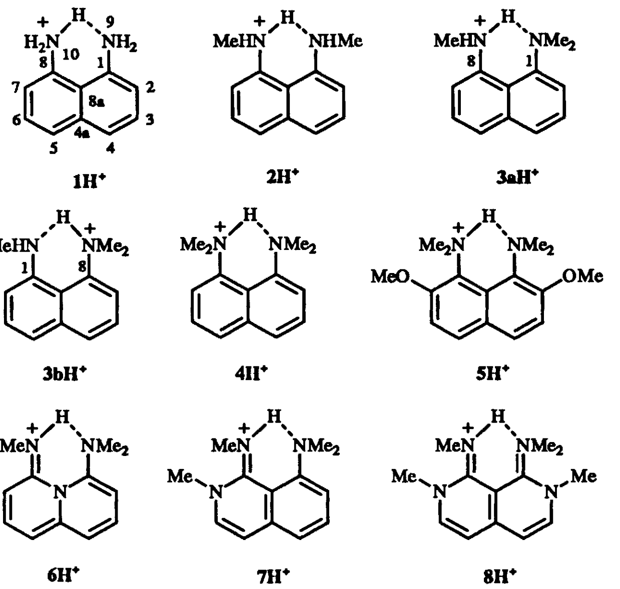
Table 1 Calculated geometries of neutral molecules **1**–**8** and their corresponding cations **1H**$^+$–**8H**$^+$ (bond lengths in Å and bond angles and torsional angles in degrees) according to the numbering system given in Schemes 1 and 2. X1*i* and X2*i* (*i* = 1, 2) stand for methyl groups except in compound **1** (and **1H**$^+$) where they are H atoms[a]

Comp.	Method	$N^9 \cdots N^{10}$	C^1–N^9	C^8–N^{10}	N^+–H	C^2–C^1–N^9–X^{11}	C^2–C^1–N^9–X^{12}/H^{12}	C^7–C^8–N^{10}–X^{21}	C^7–C^8–N^{10}–X^{22}/H^{22}	C^7–C^8–N^{10}–H
1	AM1	2.823	1.404	1.404	—	9.7	138.8	9.7	138.8	—
	PM3	2.688	1.457	1.422	—	38.4	−80.3	−36.2	−163.4	—
	SAM1	2.781	1.397	1.397	—	8.1	143.7	8.1	143.7	—
2	AM1	2.803	1.407	1.407	—	5.6	140.7	5.6	140.7	—
	PM3	2.704	1.429	1.466	—	−36.5	−168.4	−69.9	51.9	—
	SAM1	2.679	1.390	1.430	—	16.2	168.7	−29.2	99.1	—
3	AM1	2.829	1.422	1.417	—	−112.2	24.1	−114.6	13.6	—
	PM3	2.709	1.429	1.473	—	−148.6	−16.7	−64.6	63.7	—
	SAM1	2.845	1.423	1.420	—	−101.5	36.9	−103.8	24.5	—
4	AM1	2.810	1.423	1.423	—	−110.3	25.5	−110.3	25.5	—
	PM3	2.741	1.467	1.467	—	−68.1	62.3	−62.3	68.1	—
	SAM1	2.814	1.436	1.436	—	−91.9	45.9	−91.9	45.9	—
5	AM1	2.776	1.433	1.433	—	−74.1	57.6	−74.1	57.6	—
	PM3	2.675	1.462	1.462	—	−69.7	64.6	−69.7	64.6	—
	SAM1	2.789	1.430	1.430	—	−87.8	48.7	−87.8	48.7	—
6	AM1	2.847	1.442	1.307	—	74.4	−57.1	5.0	—	—
	PM3	2.809	1.465	1.304	—	68.6	−60.8	5.2	—	—
	SAM1	2.786	1.424	1.295	—	34.4	−109.9	5.9	—	—
7	AM1	2.889	1.413	1.299	—	120.7	−20.9	−2.3	—	—
	PM3	2.914	1.466	1.296	—	57.7	−71.7	−6.5	—	—
	SAM1	2.882	1.439	1.284	—	71.6	−67.3	−4.0	—	—
8	AM1	3.162	1.302	1.302	—	2.6	—	−174.6	—	—
	PM3	3.569	1.303	1.303	—	177.2	—	177.2	—	—
	SAM1	3.225	1.289	1.294	—	2.0	—	−175.4	—	—
1H$^+$	AM1	2.697	1.433	1.461	1.07	−60.2	60.2	−60.0	60.0	180.0
	PM3	2.660	1.463	1.473	1.04	−59.0	59.0	−59.7	59.7	180.0
	SAM1	2.502	1.445	1.445	1.28	−60.9	60.9	−60.9	60.9	180.0
2H$^+$	AM1	2.711	1.438	1.466	1.07	−58.0	65.6	−56.1	65.4	−173.9
	PM3	2.670	1.469	1.481	1.04	−54.0	67.1	−52.8	67.5	−171.7
	SAM1	2.529	1.455	1.455	1.29	−63.6	60.0	−63.6	60.0	−177.2
3bH$^+$	AM1	2.718	1.438	1.473	1.07	−66.1	57.6	−61.8	62.8	−179.6
3aH$^+$	PM3	2.668	1.476	1.480	1.04	−62.6	64.4	−69.4	51.0	170.2
3aH$^+$	SAM1	2.565	1.462	1.462	1.18	−66.1	62.6	−58.7	64.6	178.6
4H$^+$	AM1	2.720	1.445	1.473	1.07	−64.2	64.2	−62.2	62.2	179.9
	PM3	2.678	1.476	1.490	1.05	−63.6	63.6	−62.1	62.1	180.0
	SAM1	2.582	1.462	1.474	1.20	−64.1	64.3	−63.9	64.1	−179.9
5H$^+$	AM1	2.691	1.442	1.468	1.07	−64.6	64.6	−62.9	62.9	180.0
	PM3	2.665	1.473	1.487	1.04	−65.5	65.1	−64.4	63.1	179.4
	SAM1	2.584	1.454	1.466	1.19	−52.9	74.8	−53.2	74.1	−171.1
6H$^+$	AM1	2.762	1.437	1.369	1.00	46.8	−85.2	6.4	—	172.3
	PM3	2.635	1.470	1.393	1.02	59.9	−68.1	17.7	—	167.4
	SAM1	2.578	1.449	1.361	1.02	72.3	−58.2	−3.6	—	−175.7
7H$^+$	AM1	2.758	1.436	1.355	1.02	86.4	−44.1	7.6	—	−171.5
	PM3	2.644	1.475	1.367	1.03	61.2	−66.6	5.2	—	175.8
	SAM1	2.617	1.450	1.348	1.05	65.3	−65.3	0.0	—	180.0
8H$^+$	AM1	2.864	1.297	1.379	1.00	0.2	—	44.0	—	−166.3
	PM3	2.641	1.306	1.418	1.02	0.0	—	67.0	—	−162.0
	SAM1	2.538	1.300	1.348	1.06	−0.2	—	−0.8	—	179.1

[a] Experimental N $\cdots$ N and C_{ar}–N values for neutral molecules are: **1**, 2.728 and 1.411 Å; **4**, 2.792 and 1.397 Å; **5**, 2.756 and 1.431 Å; weighted values for 24 crystal structure determinations of **4H**$^+$ using different anions: $N^+ \cdots N$ = 2.584(18), N^+–H = 1.14(8), C_{ar}–N^+ = 1.469(13) and C_{ar}–N = 1.458(7) Å (the standard deviation of the sample is given in parentheses).[8]

Table 2 Results of the AM1, PM3 and SAM1 calculations (values in kcal mol^{-1}): neutral molecule ($\Delta_f H°$), difference neutral − protonated molecule ($\Delta_p H$), calculated pK_a

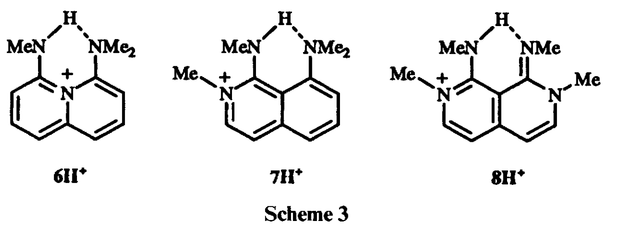
		AM1			PM3			SAM1		
Comp.	Exp. pK_a	$\Delta_f H°$	$-\Delta_p H$	pK_a calc	$\Delta_f H°$	$-\Delta_p H$	pK_a calc	$\Delta_f H°$	$-\Delta_p H$	pK_a calc
1	4.6	42.33	146.14	4.49	43.30	140.80	7.16	39.10	121.30	5.06
2	5.6	50.93	144.03	5.82	41.72	142.72	5.22	43.58	118.86	6.20
3	6.4	58.19	141.85	7.19	40.29	142.16	5.79	45.75	118.54	6.35
4	12.1	69.31	136.31	10.67	45.76	137.92	10.07	57.01	109.90	10.36
5	16.1	−0.31	126.82	16.63	−22.16	131.48	16.56	−8.74	95.99	16.83
6	—	108.14	118.98	21.55	69.96	127.28	20.80	91.11	91.20	19.06
7	—	85.97	123.53	18.70	56.34	130.80	17.25	71.09	93.15	18.15
8	—	109.02	118.17	22.06	73.87	129.63	18.43	92.42	85.33	21.79



Scheme 2

PM3); the cation resulting from the protonation of proton sponge **3** has the proton bonded to the NHMe group **3aH**$^+$ (PM3, SAM1) [to a lesser extent, this situation is also observed in **6H**$^+$ (AM1, SAM1 *vs.* PM3, respectively) Figs. 1(*g*), (*h*)] or to the NMe$_2$ group **3bH**$^+$ (AM1).

An examination of the C_{ar}–N bond lengths of cations **6H**$^+$–**8H**$^+$ shows that these entities are better represented by the canonical forms of Scheme 3 (in particular, see Table 1, the C^8–N^{10} double bond becomes longer on protonation). It is worth noticing that optimization of the geometry for these cations leads to structures **6H**$^+$ and **7H**$^+$ with the proton on the sp^2 nitrogen atom N^9.



Scheme 3

During the preparation of this work, an *ab initio* study of **4** and **4H**$^+$ appeared.[16] Although the N ··· N and N$^+$–H lengths of 2.670 and 1.05 Å are similar to those calculated within the PM3 framework, the averaged C_{ar}–N bonds (1.466 Å) are closer to those obtained using the SAM1 method.

Protonation enthalpies

Since we aimed exclusively at determining the relative aqueous basicities, we have considered only the difference in heats of formation between the neutral and the protonated proton sponge without subtracting the heat of formation of the proton (367.2 kcal mol^{-1}). The results are presented in Table 2.

Concerning the $-\Delta_p H$ calculated values, a first comment is that these values are roughly proportional: the r^2 values are 0.952 (AM1/PM3), 0.986 (AM1/SAM1) and 0.937 (SAM1/PM3). Clearly, AM1 and SAM1 values are mutually more consistent than the comparisons which involve the PM3 method.

Although we have warned that PM3 and AM1 calculations severely underestimate lone pair–lone pair repulsions[6,9] (one of the reasons proton sponges are such strong bases), this term could be the same for all compounds **1**–**8**. The regression eqns. (1)–(3) relate pK_a values for compounds **1**–**5** to calculated protonation enthalpies.

$$\mathrm{p}K_a = 96.29 - (0.628 \pm 0.065)(-\Delta_p H, \mathrm{AM1}) \qquad r^2 = 0.969 \quad (1)$$

$$\mathrm{p}K_a = 149.19 - (1.009 \pm 0.212)(-\Delta_p H, \mathrm{PM3}) \qquad r^2 = 0.883 \quad (2)$$

$$\mathrm{p}K_a = 61.46 - (0.465 \pm 0.056)(-\Delta_p H, \mathrm{SAM1}) \qquad r^2 = 0.944 \quad (3)$$

It must be stated clearly that for eqns. (1)–(3) to hold, several effects must cancel: pK_a values are free energies, while $-\Delta_p H$ values are enthalpies (this implies that entropy changes are constant or are proportional to ΔH); moreover, the first values are aqueous measurements and the second ones, in some sense, gas phase values.

In Table 2 are gathered the pK_a values calculated with eqns. (1)–(3). All methods underestimate the basicity of compound **4** (DMAN) the most representative proton sponge (pK_a predicted, *ca.* 10–11, pK_a experimental, 12.1). Concerning the prediction for compounds **6**–**8** (Table 2), excluding those from PM3 calculations whose r^2 coefficient [eqn. (2)] is clearly inferior, both AM1 and SAM1 predict that compounds **6** and **8** should be superbases and that isoquinoline **7** although still very basic should be weaker.

The derivatives of quinolizine **6** and of 2,7-naphthyridine **8** are not known, but among the strongest bases reported are compounds of structure **9** which have pK_a values of *ca.* 30 in acetonitrile.[17]

There is no way to estimate the pK_a in water of compound **9**: DMAN (**4**) has $\mathrm{p}K_{a(H_2O)} = 12.1$ (ref. 18) and $\mathrm{p}K_{a(CH_3CN)} = 18.2$ (ref. 19). Thus, the predicted values of $\mathrm{p}K_{a(H_2O)} = 19–22$ for compounds **6** and **8** compare well with the $\mathrm{p}K_{a(CH_3CN)}$ of **9**.

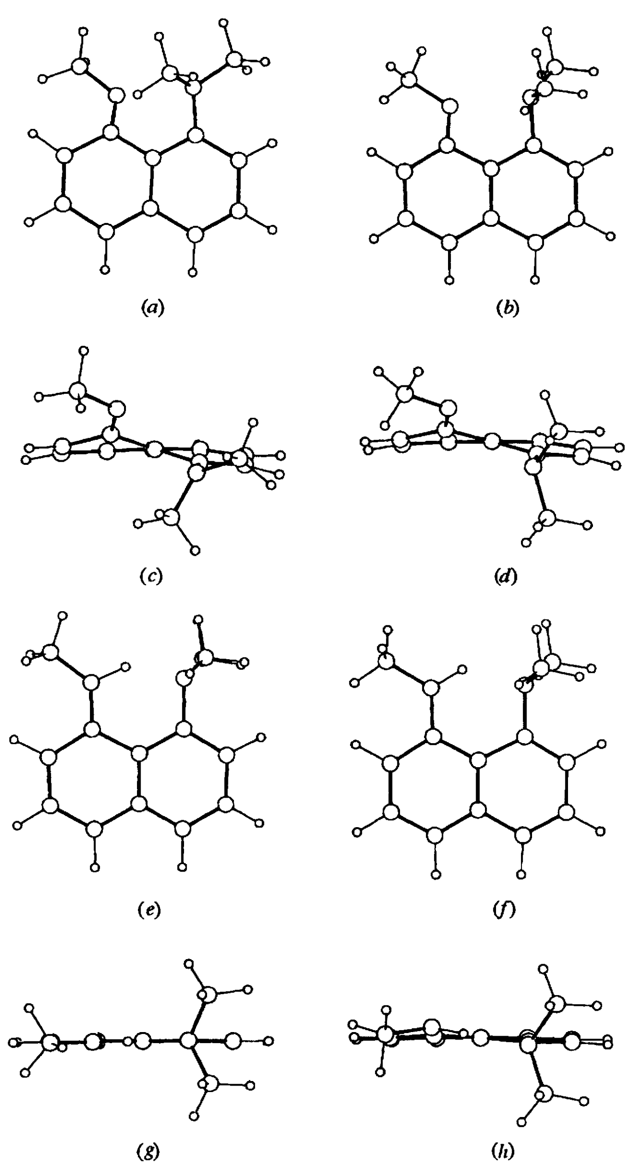
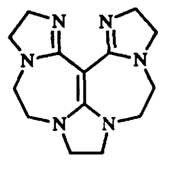

(a) (b) (c) (d) (e) (f) (g) (h)

Fig. 1 A view of molecule **6** projected on the naphthalene plane (*a*: SAM1; *b*: PM3) and a lateral view (*c*: SAM1; *d*, PM3) showing the different conformation obtained by both methods. Also for **6H**$^+$ (*e*, *g*: SAM1; *f*, *h*: PM3).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Conclusions

Considering geometries and energies together, the new SAM1 method does not offer clear advantages over the classical AM1, at least in respect of the protonation enthalpies of proton sponges and their correlation with aqueous basicities. Nevertheless, since experimental results in solution may well differ significantly from those calculated for the gas phase and since we have no way to check our $-\Delta_pH$ results against gas phase experimental data, it may be that SAM1 values describe the gas phase proton affinity of proton sponges better than AM1. Finally, the approach here presented could be applied to any super base candidate before undertaking its synthesis.

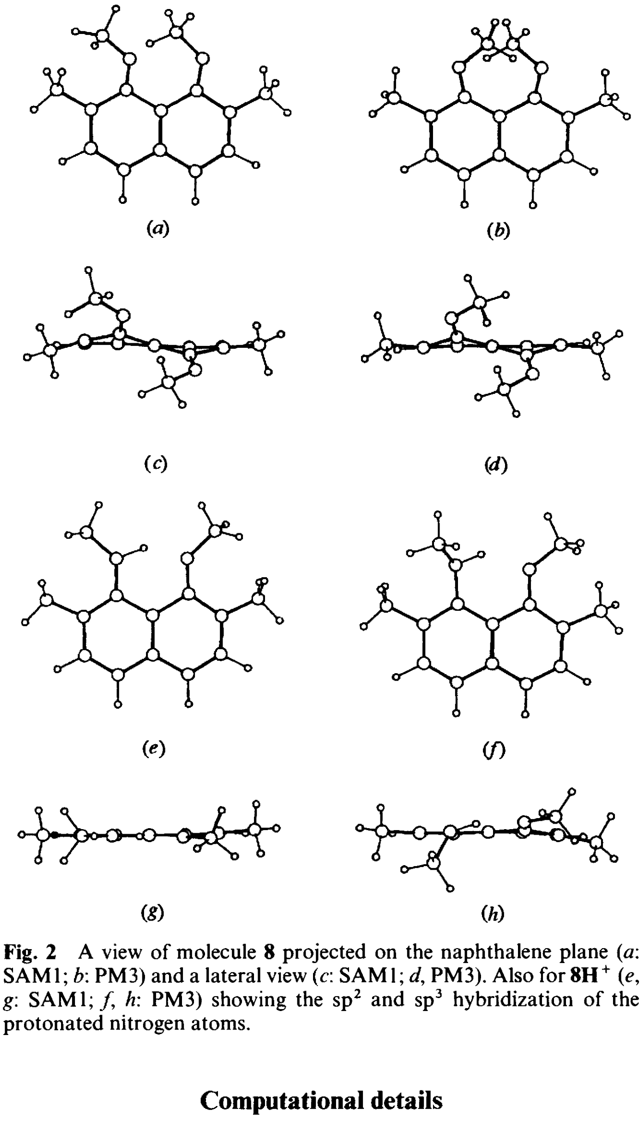
(a) (b) (c) (d) (e) (f) (g) (h)

Fig. 2 A view of molecule **8** projected on the naphthalene plane (*a*: SAM1; *b*: PM3) and a lateral view (*c*: SAM1; *d*, PM3). Also for **8H**$^+$ (*e*, *g*: SAM1; *f*, *h*: PM3) showing the sp^2 and sp^3 hybridization of the protonated nitrogen atoms.

Computational details

Structures and energies were obtained by means of the AM1,[12] SAM[13] and PM3[14] semiempirical methods, as implemented in the AMPAC 5.0 and MOPAC V5.0 program packages.[20,21] In all cases, the PRECISE keyword was used and full geometry optimization was carried out (with the Fletcher–Powell algorithm) without any symmetry constraint. Great care was taken to avoid false minima; for this purpose, several input geometries were used corresponding to different conformations about the exocyclic C_{ar}–N bonds. The following computers and workstations were used: VAX 9210 and VAX 4610 as well as ALPHA 3400 and Apple Macintosh IIfx.

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