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Application of Free-Wilson matrices to the analysis of the tautomerism and aromaticity of azapentalenes: a DFT study

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Abstract

The tautomerism and aromaticity of 44 neutral and the corresponding 60 protonated azapentalenes were studied. The tautomerism was based on the calculated relative energies of the different tautomers, from two to three and nine nitrogen atoms. The aromaticity was estimated from the NICS values of both rings of azapentalenes. The possible relationship between both properties was assessed. The calculation was carried out at the B3LYP/6-311++G** computational level. MEP and NBO analysis were carried out on the studied compounds.

1. Introduction

Azapentalenes **I**, **II**, and **III** formally derive from naphthalene **IV** and the intermediate benzo derivatives **V** and **VI** by replacing CC double bonds by heteroatoms bearing lone pairs (aromatic) or by CH_2 groups (non-aromatic) (Scheme 1).[1] They can also be considered related to the aromatic pentalene dianion **VII**.

Our interest in aromatic azapentalenes has been continuous for some years,[2] including a review,[3] but we have not carried out any theoretical work on these compounds save very recently in the series lacking N atoms at position 3a and 6a.[4] Therefore, we decided to study the compounds represented in Scheme 2 (neutral) and Scheme 3 (protonated). The compounds differ by the number of additional nitrogen atoms (aza substitution, the equivalent of replacing benzene by pyridine), from one (**1**–**3**) or two (**4**–**12**) to six (**13**).

To analyze collections of data, either experimental, e.g., NMR chemical shifts, or calculated, e.g., energies, we have used a simple statistical device called Free-Wilson matrices in medicinal chemistry[5] or absence–presence matrices in other fields.[6] We have been almost alone in using this approach in chemistry.[7] The use of 0, 1 for the two levels that a factor can have is equivalent to (−) and (+) or −1 and +1 used in factorial designs.[8] If a third level is necessary, a 0.5 level (equivalent to 0 in a +1/−1 factorial design) can be used provided it is equidistant from the two others.

2. Results and discussion

2.1. Tautomerism

The calculated energies for neutral and protonated azapentalenes are gathered in Tables 1 and 2, respectively.

We have analyzed the E_{rel} values (in kJ mol^{-1}) of Table 1 using a Free-Wilson matrix (obviously the total energies cannot be analyzed since they depend mostly exclusively on the molecular formula). For the 43 values (**8** has only one tautomer) we have found with an r^2=0.91 the values listed in Table 3. The low correlation coefficient corresponds to a lack of additivity but adding product terms will lead to a too complicated model. A negative value of a coefficient means an increase in stability.

The ring that contains N3a could be a pyrrole (**1a**, **1b**, **2a**, **2b**, **3a**, **3b**, **10a**, **10b**, **11a**, **11b**, **12a**, **12b**), an imidazole (**1c**, **1d**, **2c**, **2d**, **4b**, **4c**, **5b**, **5c**, **7a**, **7b**, **7c**, **7d**, **8**, **9a**, **9b**), a pyrazole (**3c**, **3d**, **4a**, **4d**, **5a**, **5d**, **6a**, **6b**), an 1,2,4-triazole (**10c**, **10d**, **12c**, **12d**), an 1,2,3-triazole (**11c**, **11d**) or a tetrazole (**13a**, **13b**, **13c** contain two tetrazoles). The NNH situation is found

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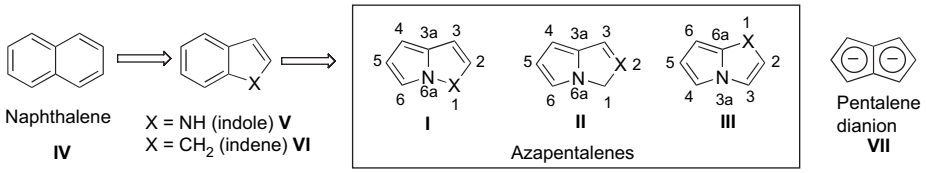
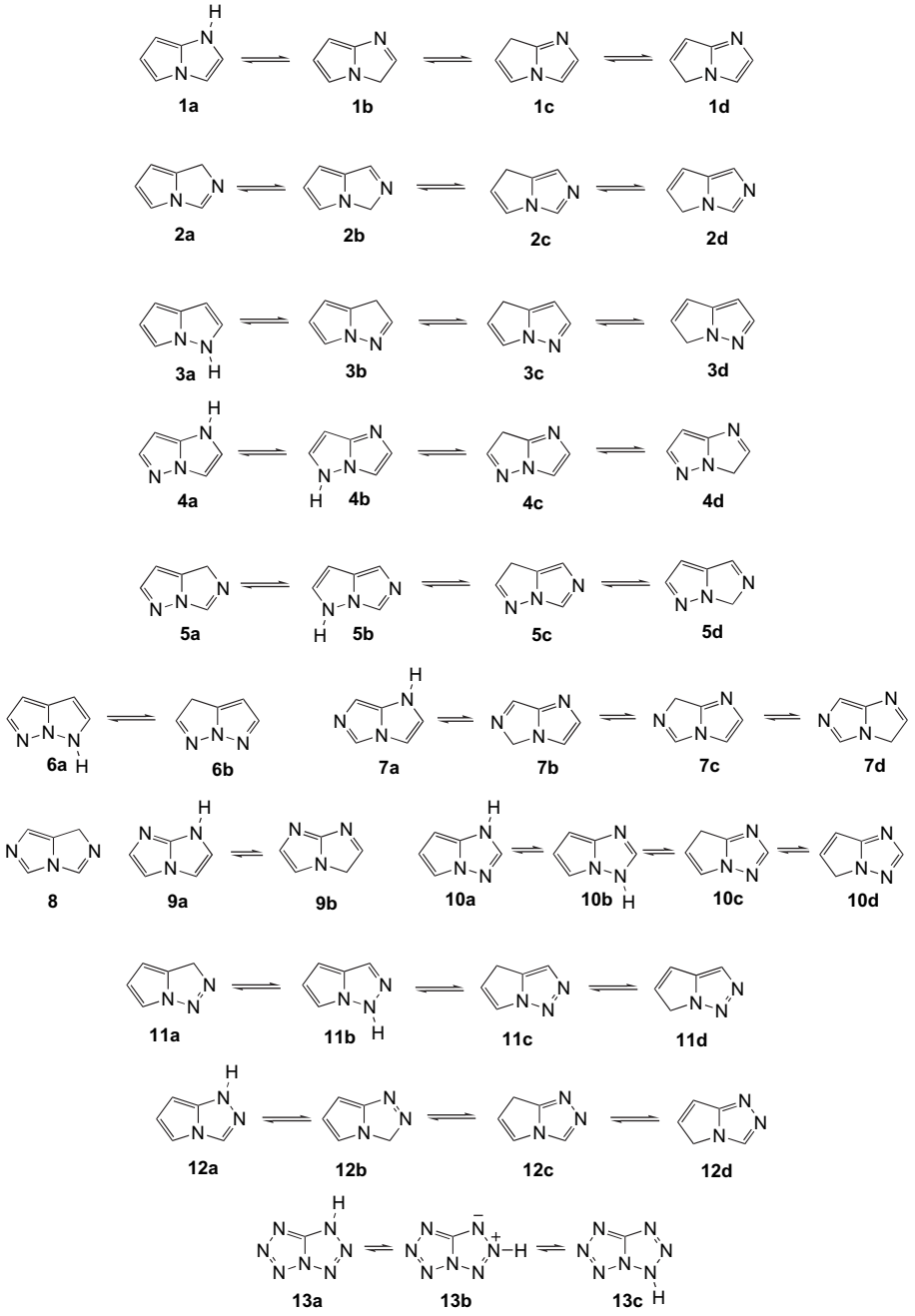


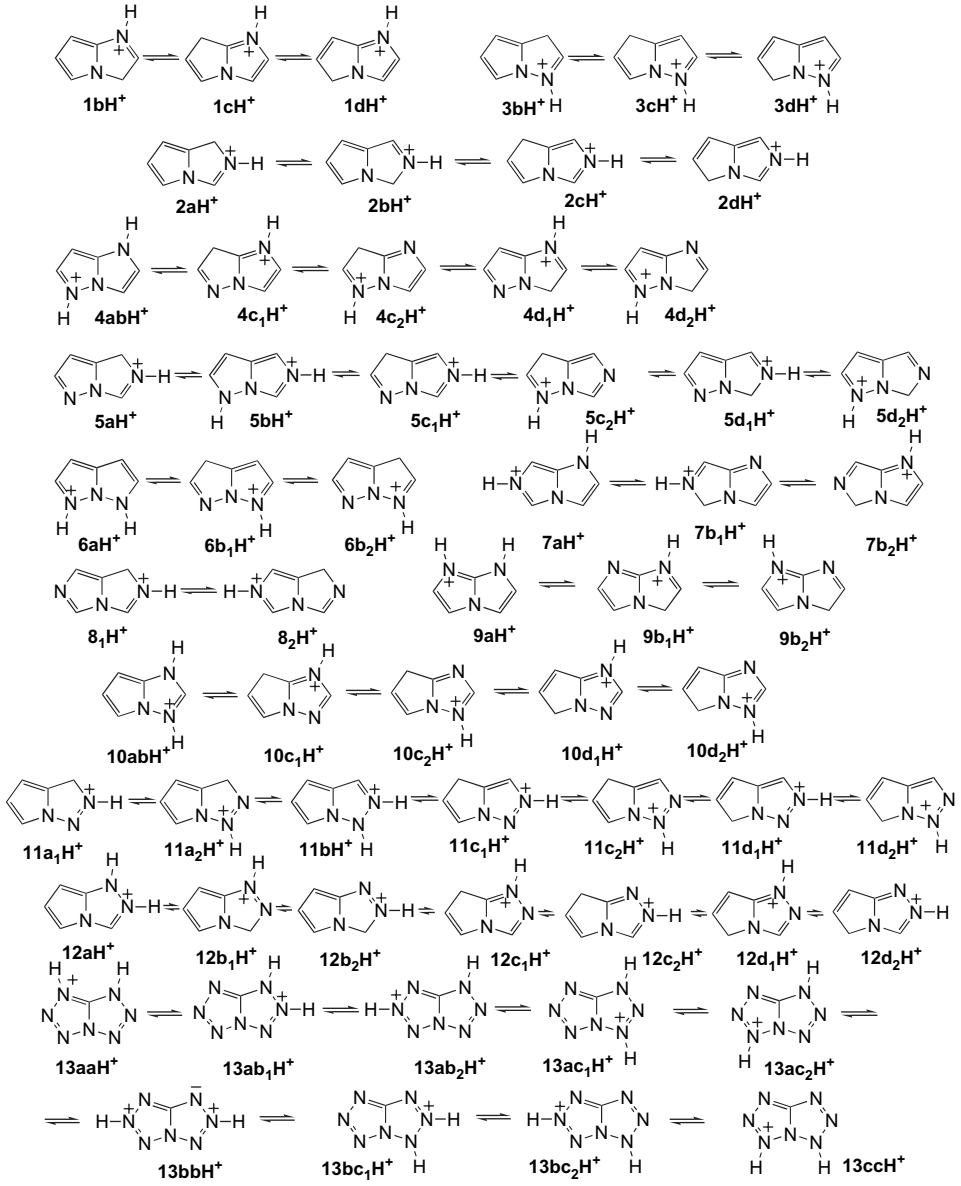
Scheme 1. Relationships between naphthalene **IV**, indole **V** (X=NH), indene **VI** (X=CH_2) azapentalenes **I**, **II**, and **III** (X=NH or CH_2) and pentalene dianion **VII**.

in **3a**, **4b**, **5b**, **6a**, **10b**, **11b**, and **13c**. A NN double bond is present in **11a**, **11c**, and **11d**. The presence of an N atom at position 2 or 5 (structure **II**) is observed in **2a**, **2b**, **2c**, **2d**, **5a**, **5b**, **5c**, **5d**, **11a**, **11b**, **11c**, **11d**, **12a**, **12b**, **12c**, **12d**, **13a** (2), **13b**, and **13c** (2). Three contiguous N atoms including N3a in the middle are present in **6a**, **6b**, **13a**. **13b**, **13c** and two N atoms in *peri* positions in **6b**, **9b**, **13a**, **13b** and **13c**. The complete Free-Wilson matrix can be found in the Supplementary data.

The most interesting coefficients are those associated to the azole. It is highly satisfactory that the values deduced by regression from E_{rel} are linearly related (r^2=0.94, Fig. 1) to Pozharskii aromaticity index Δ*N*, which is a structural index



Scheme 2. The studied neutral azapentalenes.



Scheme 3. The studied protonated azapentalenes.

calculated from bond orders: pyrrole (0.37)<imidazole (0.43)<pyrazole (0.61)<1,2,4-triazole (0.71)<tetrazole (0.81).[9] The ΔN value of 1,2,3-triazole is not known but from our results it should be as aromatic as benzene.

The other terms are either stabilizing [NNN, *peri*-NHN, and N(sp^2)-2,5] or destabilizing (NHN, N=N, and *peri*-NN). The *peri* effects are almost identical in absolute value having the expected sign: attractive between an N–H and an N lone pair and repulsive between two N lone pairs.[9–13] There are few reported experimental studies on the tautomerism of the compounds listed in Table 1 and generally they carry out substituents but in three cases the most stable tautomers agree with the calculations: **1d**, **2d**, and **4a**.[14]

In what concerns the cations shown in Scheme 3, in general the most stable cation results from the most stable neutral azapentalene. Thus **1d**→**1dH**$^+$, **2d**→**2dH**$^+$, **3d**→**3dH**$^+$, **4a**→**4aH**$^+$, **9a**→**9aH**$^+$, **10d**→**10d$_1$H**$^+$, **11d**→**11d$_1$H**$^+$, **12d**→**12d$_1$H**$^+$ (**12d** is only 0.49 kJ mol^{-1} higher in energy than **12a**), **13a**→**13ab$_2$H**$^+$. But there are three exceptions, **5c$_1$H**$^+$ is obtained by protonation of **5c** (25.10 kJ mol^{-1} higher than **5a**), **6aH**$^+$ is obtained by protonation of **6a** (8.39 kJ mol^{-1} higher than **6b**), **7aH**$^+$ is obtained by protonation of **7a** (13.82 kJ mol^{-1} higher than **7b**). This means that the factors that stabilize/destabilize cations are not the same than those that affect the neutral molecules. We have not succeeded in finding a simple model, similar to Table 3, for the cations. There is experimental evidence that the protonation of a *N*-methyl benzo-derivative of **1a** (where no tautomerism is possible) occurs at position 5 (predominant) and at position 7 (less abundant) (Scheme 4).[15]

The difference in energy between neutral and protonated azapentalenes could serve to estimate their gas phase basicity (proton affinity). When the neutral molecule and the cation are directly connected (same tautomer) there is only one value; in

Table 1
Absolute (hartree) and relative (kJ mol^{-1}) energies of azapentalenes **1a**–**13c**

Comp.	E_{total}	E_{rel}	Comp.	E_{total}	E_{rel}	Comp.	E_{total}	E_{rel}
1a	−341.80258	19.59	**5a**	−357.83960	**0.00**	**10a**	−357.83635	26.94
1b	−341.80116	23.33	**5b**	−357.82111	48.54	**10b**	−357.82147	66.00
1c	−341.80687	8.33	**5c**	−357.83004	25.10	**10c**	−357.84393	7.03
1d	−341.81004	**0.00**	**5d**	−357.83850	2.88	**10d**	−357.84661	**0.00**
2a	−341.80568	6.42	**6a**	−357.81111	8.39	**11a**	−357.80327	38.62
2b	−341.80724	2.30	**6b**	−357.81430	**0.00**	**11b**	−357.80412	36.38
2c	−341.80469	9.01				**11c**	−357.81532	6.98
2d	−341.80812	**0.00**	**7a**	−357.885111	13.82	**11d**	−357.81798	**0.00**
			7b	−357.85638	**0.00**			
3a	−341.77230	53.44	**7c**	−357.85554	2.21	**12a**	−357.83515	**0.00**
3b	−341.78137	29.63	**7d**	−357.84981	17.25	**12b**	−357.81816	44.60
3c	−341.79050	5.66				**12c**	−357.83185	8.67
3d	−341.79266	**0.00**	**8**	−357.85306	—	**12d**	−357.83496	0.49
4a	−357.84055	**0.00**	**9a**	−357.86064	**0.00**	**13a**	−421.92311	**0.00**
4b	−357.82505	40.69	**9b**	−357.85138	24.29	**13b**	−421.91325	25.89
4c	−357.83110	24.79				**13c**	−421.90043	59.54
4d	−357.83357	18.31						

Table 2
Absolute (hartree) and relative (kJ mol^{-1}) energies of azapentalene cations **1bH$^+$**-**13ccH$^+$**

Comp.	E_{total}	E_{rel}	Comp.	E_{total}	E_{rel}	Comp.	E_{total}	E_{rel}
1bH$^+$	−342.15679	101.10	**6aH$^+$**	−358.17528	**0.00**	**11a$_1$H$^+$**	−358.14962	98.94
1cH$^+$	−342.18811	18.86	**6b$_1$H$^+$**	−358.17429	2.60	**11a$_2$H$^+$**	−358.11958	177.80
1dH$^+$	−342.19529	**0.00**	**6b$_2$H$^+$**	−358.14389	82.41	**11bH$^+$**	−358.15430	86.66
						11c$_1$H$^+$	−358.18503	5.99
2aH$^+$	−342.17333	50.20	**7aH$^+$**	−358.23998	**0.00**	**11c$_2$H$^+$**	−358.16526	57.88
2bH$^+$	−342.18008	32.47	**7b$_1$H$^+$**	−358.21348	69.55	**11d$_1$H$^+$**	−358.18731	**0.00**
2cH$^+$	−342.18930	8.27	**7b$_2$H$^+$**	−358.22532	38.46	**11d$_2$H$^+$**	−358.16782	51.17
2dH$^+$	−342.19245	**0.00**						
			8$_1$H$^+$	−358.22532	46.76	**12aH$^+$**	−358.17819	89.20
3bH$^+$	−342.11625	109.65	**8$_2$H$^+$**	−358.22532	**0.00**	**12b$_1$H$^+$**	−358.16260	130.14
3cH$^+$	−342.15494	8.07				**12b$_2$H$^+$**	−358.17952	85.71
3dH$^+$	−342.15801	**0.00**	**9aH$^+$**	−358.24415	**0.00**	**12c$_1$H$^+$**	−358.20436	20.48
			9b$_1$H$^+$	−358.19728	123.06	**12c$_2$H$^+$**	−358.20674	14.23
4abH$^+$	−358.21538	**0.00**	**9b$_2$H$^+$**	−358.22956	38.29	**12d$_1$H$^+$**	−358.21264	**0.00**
4c$_1$H$^+$	−358.20362	30.89				**12d$_2$H$^+$**	−358.21077	3.66
4c$_2$H$^+$	−358.15432	160.33	**10abH$^+$**	−358.18225	81.25			
4d$_1$H$^+$	−358.17467	106.88	**10c$_1$H$^+$**	−358.20562	19.88	**13aaH$^+$**	−422.24457	6.49
4d$_2$H$^+$	−358.18973	67.35	**10c$_2$H$^+$**	−358.19089	58.56	**13ab$_1$H$^+$**	−422.19531	135.82
			10d$_1$H$^+$	−358.21319	**0.00**	**13ab$_2$H$^+$**	−422.24704	**0.00**
5aH$^+$	−358.19656	28.63	**10d$_2$H$^+$**	−358.19473	48.47	**13ac$_1$H$^+$**	−422.20238	51.07
5bH$^+$	−358.20467	7.35				**13ac$_2$H$^+$**	−422.22759	51.07
5c$_1$H$^+$	−358.15177	**0.00**				**13bbH+**	−422.24258	11.73
5c$_2$H$^+$	−358.20847	146.24				**13bc$_1$H+**	−422.17593	186.70
5d$_1$H$^+$	−358.19307	37.82				**13bc$_2$H$^+$**	−422.22315	62.73
5d$_2$H$^+$	−358.18980	46.39				**13ccH$^+$**	−422.19474	137.31

Table 3
Main effects on E_{rel} of neutral azapentalenes (kJ mol^{-1})

*N*H-Pyrrole	+18.0	*N*H-1,2,3-Triazole	−20.1	N(sp^2)-2,5	−7.3
*N*H-Imidazole	+14.1	*N*H-Tetrazole	−7.4	NNN	−22.5
*N*H-Pyrazole	+8.1	NNH	+37.6	*peri*-NHN	−12.8
*N*H-1,2,4-Triazole	+3.5	N=N	+30.8	*peri*-NN	+12.3

the other cases, there are two: from the most stable neutral to the most stable cation (different tautomers) and from the most stable neutral to the most stable cation with the same tautomeric form (Table 4).

These values are related to the azole that is protonated (for instance, imidazoles are more basic than pyrazoles) and to the nature, aromatic or not, of the protonated moiety.

2.2. Aromaticity

We have selected amongst the numerous criteria of aromaticity,[9] Schleyer's NICS (Tables 5 and 6).[16] Although only loosely related [NICS(0)=−(1.41±0.25)+(1.34±0.03) NICS(1), n=208, r^2=0.904] both afford the same information,

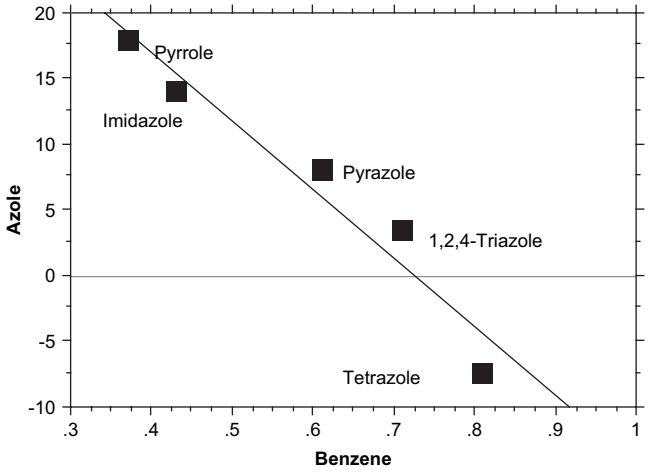
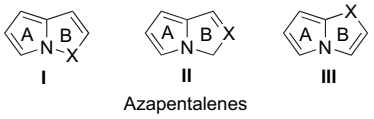


Figure 1. Plot of azole effects of Table 3 versus their aromaticity (ΔN).[28]

so we will only discuss the conclusions based on NICS(1) more removed from the σ-skeleton and therefore more reliable.



2.2.1. General effects: neutral molecules

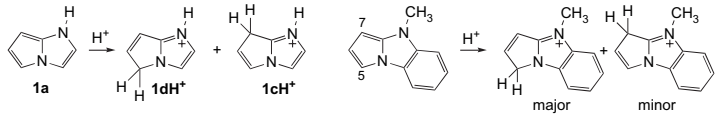
In a first approximation we have classified both rings of neutral azapentalenes into aromatic (1.0), half-aromatic (0.5) and non-aromatic (0.0) (see Table 5). The half-aromatic rings correspond to situation with an external double bond, like B part in **1a**.

A more detailed analysis of all the 88 values (44 compounds, r^2=0.953) of Table 5 or of only the aromatic compounds (15 compounds, 30 values, Scheme 4, r^2=0.992) shows some differences between the heterocycles but they are small justifying the aspect of Figure 2. The B ring of compound **13b** is intermediate between a half-aromatic and a fully aromatic, so we have assigned it a 0.8 value. The coefficients for the first case are 10.1 (pyrrole), 10.3 (imidazole, for

Table 5
NICS(0)-A, NICS(0)-B, NICS(1)-A, and NICS(1)-B (all in ppm) of neutral azapentalenes

No.	A	B	NICS(0)-A	NICS(0)-B	NICS(1)-A	NICS(1)-B
1a	1.0	0.5	14.58	11.15	10.64	6.88
1b	1.0	0.0	11.79	0.14	9.00	2.31
1c	0.0	1.0	1.58	10.92	2.28	9.82
1d	0.0	1.0	1.82	10.85	2.36	9.55
2a	1.0	0.0	11.68	1.95	9.49	2.89
2b	1.0	0.0	12.12	1.30	9.80	2.70
2c	0.0	1.0	1.78	11.23	2.00	9.90
2d	0.0	1.0	1.54	10.91	1.80	9.56
3a	1.0	0.5	14.26	7.93	10.48	5.51
3b	1.0	0.0	12.56	0.61	9.54	2.67
3c	0.0	1.0	2.00	11.81	2.42	10.59
3d	0.0	1.0	1.55	11.43	2.25	10.24
4a	1.0	0.5	13.59	11.93	10.99	7.61
4b	0.5	1.0	8.84	12.95	6.46	10.58
4c	0.0	0.0	0.17	11.33	2.85	9.76
4d	1.0	0.0	11.38	−0.01	9.97	2.66
5a	1.0	0.0	11.37	2.13	10.54	3.27
5b	0.5	1.0	7.59	13.63	5.32	11.02
5c	0.0	1.0	0.63	11.64	2.66	9.84
5d	1.0	0.0	11.67	1.18	10.81	3.20
6a	1.0	0.5	13.71	9.68	11.21	6.93
6b	0.0	1.0	0.95	12.31	3.21	10.67
7a	1.0	0.5	14.14	10.64	11.29	6.60
7b	0.0	1.0	1.47	11.26	3.26	10.25
7c	0.0	1.0	1.50	10.34	2.09	9.69
7d	1.0	0.0	10.81	0.27	9.32	2.39
8	1.0	0.0	10.61	1.72	9.82	2.82
9a	1.0	0.5	12.81	11.81	10.36	7.51
9b	1.0	0.0	10.90	0.61	9.40	3.02
10a	1.0	0.5	15.36	10.55	10.98	7.22
10b	1.0	0.5	14.65	7.68	10.68	6.23
10c	0.0	0.0	1.86	10.82	2.67	10.77
10d	0.0	0.0	1.95	10.59	2.80	10.42
11a	1.0	0.0	11.96	1.25	9.56	4.24
11b	1.0	0.5	14.25	8.16	11.01	6.72
11c	0.0	1.0	1.93	11.69	2.65	11.79
11d	0.0	1.0	1.48	11.28	2.37	11.45
12a	1.0	0.5	14.08	11.64	10.52	8.11
12b	1.0	0.0	11.97	−0.11	9.72	3.93
12c	0.0	1.0	1.52	10.23	2.28	10.39
12d	0.0	1.0	1.86	10.09	2.54	10.09
13a	1.0	0.5	12.39	11.26	12.28	9.80
13b	1.0	0.8	13.69	14.70	13.31	12.22
13c	1.0	0.5	12.92	9.69	13.00	9.80

The second and third columns correspond to the aromaticity of A and B rings.



Scheme 4. The protonation of **1a**.

Table 4
PA (kJ mol^{-1}) of azapentalenes

Pair	PA	Pair	PA	Pair	PA	Pair	PA
1d/1dH$^+$	1011.5	**2d/2dH$^+$**	1009.1	**3d/3dH$^+$**	959.2	**4a/4abH$^+$**	984.1
5a/5c$_1$H$^+$	819.6	**6b/6aH$^+$**	947.8	**7b/7aH$^+$**	1007.1	**8/8$_2$H$^+$**	977.4
9a/9aH$^+$	1006.9	**10d/10d$_1$H$^+$**	962.5	**11d/11d$_1$H$^+$**	969.7	**12a/12d$_1$H$^+$**	991.1
13a/13ab$_2$H$^+$	850.5						
5a/5aH$^+$	937.2	**6b/6b$_1$H$^+$**	945.2	**7b/7b$_2$H$^+$**	968.7	**12a/12aH$^+$**	900.7

Table 6
NICS(0)-A, NICS(0)-B, NICS(1)-A, and NICS(1)-B (all in ppm) of protonated azapentalenes

No.	A	B	NICS(0)-A	NICS(0)-B	NICS(1)-A	NICS(1)-B
1bH$^+$	1	0	12.43	1.98	9.67	1.39
1cH$^+$	0	1	2.46	12.65	3.19	9.34
1dH$^+$	0	1	3.00	12.00	3.62	8.69
2aH$^+$	1	0	8.73	4.25	7.67	2.64
2bH$^+$	1	0	10.26	3.84	9.19	2.23
2cH$^+$	0	1	2.57	13.56	3.01	9.75
2dH$^+$	0	1	2.24	12.95	2.79	9.23
3bH$^+$	1	0	12.80	2.62	9.59	2.20
3cH$^+$	0	1	3.45	12.85	3.49	9.99
3dH$^+$	0	1	2.76	12.26	3.24	9.34
4abH$^+$	1	1	13.56	13.74	9.44	9.04
4c$_1$H$^+$	0	1	1.19	13.12	3.77	9.41
4c$_2$H$^+$	0	1	2.64	11.88	2.87	9.95
4d$_1$H$^+$	1	0	12.46	2.15	10.87	2.20
4d$_2$H$^+$	1	0	12.45	1.34	9.30	3.70
5aH$^+$	1	0	9.21	4.13	9.16	2.93
5bH$^+$	1	1	10.45	15.96	7.47	10.74
5c$_1$H$^+$	0	1	1.63	13.96	1.94	10.00
5c$_2$H$^+$	0	1	1.99	12.37	3.65	9.81
5d$_1$H$^+$	1	0	10.59	3.42	10.79	2.89
5d$_2$H$^+$	1	0	12.71	2.48	10.05	4.11
6aH$^+$	1	1	10.76	10.76	8.28	8.28
6b$_1$H$^+$	0	1	2.17	13.19	4.04	10.15
6b$_2$H$^+$	1	0	12.74	2.77	10.70	2.72
7aH$^+$	1	1	16.38	11.99	10.93	8.00
7b$_1$H$^+$	0	1	3.83	10.88	2.84	10.54
7b$_2$H$^+$	0	1	2.74	12.38	4.45	9.50
8$_1$H$^+$	1	0	8.18	4.09	8.33	2.52
8$_2$H$^+$	1	0	13.65	2.64	10.03	3.80
9aH$^+$	1	1	12.99	12.99	8.66	8.66
9b$_1$H$^+$	1	0	12.01	2.63	10.33	2.40
9b$_2$H$^+$	1	0	12.12	1.43	8.69	4.08
10abH$^+$	1	1	17.34	11.44	12.51	6.31
10c$_1$H$^+$	0	1	2.84	12.08	3.51	9.89
10c$_2$H$^+$	0	1	3.31	11.86	3.64	10.12
10d$_1$H$^+$	0	1	3.11	11.33	3.93	9.19
10d$_2$H$^+$	0	1	3.12	11.23	3.59	9.37
11a$_1$H$^+$	1	0	6.33	3.43	6.11	4.00
11a$_2$H$^+$	1	0	10.83	3.88	8.97	4.06
11bH$^+$	1	1	13.17	9.49	10.88	5.54
11c$_1$H$^+$	0	1	2.79	13.75	3.61	11.44
11c$_2$H$^+$	0	1	3.31	12.70	3.84	11.15
11d$_1$H$^+$	0	1	2.02	13.11	3.13	11.03
11d$_2$H$^+$	0	1	2.54	12.06	3.38	10.62
12aH$^+$	1	1	13.23	11.78	10.49	6.82
12b$_1$H$^+$	1	0	11.08	3.03	9.64	3.16
12b$_2$H$^+$	1	0	7.89	3.11	7.92	3.31
12c$_1$H$^+$	0	1	2.21	12.08	3.17	9.94
12c$_2$H$^+$	0	1	2.26	12.79	3.14	10.33
12d$_1$H$^+$	0	1	2.81	11.38	3.74	9.15
12d$_2$H$^+$	0	1	2.54	12.06	3.31	9.61
13aaH$^+$	1	1	12.34	12.34	10.37	10.37
13ab$_1$H$^+$	1	1	13.21	13.91	12.91	10.09
13ab$_2$H$^+$	1	1	15.35	12.78	12.74	10.75
13ac$_1$H$^+$	1	1	13.99	11.67	13.43	9.35
13ac$_2$H$^+$	1	1	11.95	12.69	11.31	10.94
13bbH$^+$	1	1	16.15	16.15	13.15	13.15
13bc$_1$H$^+$	1	1	14.23	13.24	14.26	10.23
13bc$_2$H$^+$	1	1	16.03	12.89	13.24	11.45
13ccH$^+$	1	1	11.83	11.83	11.27	11.27

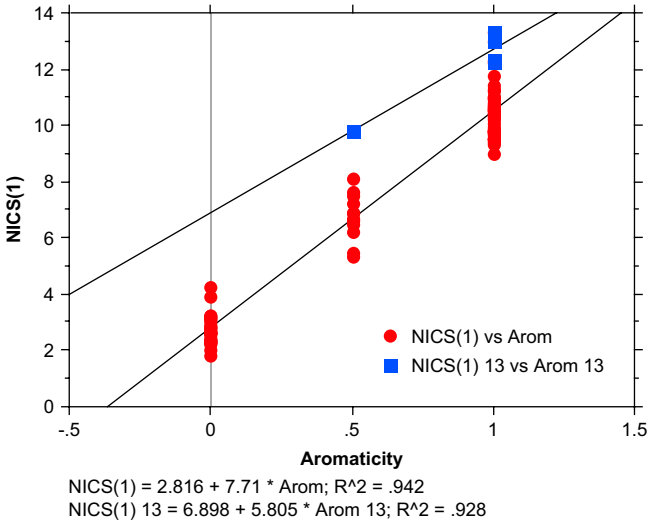


Figure 2. Plot of NIC(1) versus aromaticity.

imidazole itself we have calculated 10.6 ppm), 10.8 (pyrazole), 11.0 (1,2,4-triazole), 11.8 (1,2,3-triazole), and 12.1 (tetrazole), showing a smooth variation with increasing N atoms.

2.2.2. General effects: cations

The total aromaticity of the cations is preferable to the aromaticities of A and B parts due to the delocalization of the positive charge. The two most significant effects are the aromaticity (columns 2 and 3 of Table 5) and the number of N atoms of the molecules (2, 3 or 7) (Fig. 3). Considering both together, we found NICS(1) [A+B rings]=(4.3±0.4)+(4.7±0.4)aromaticity[A+B rings]+(1.4±0.1)*N*[number of nitrogen atoms], n=60, r^2=0.93.

2.3. Relationship between tautomerism and aromaticity

As expected there is no relationship between the thermodynamic criterium of aromaticity (the most stable tautomer) and the NICS values. Using the sum of the NICS(1) of rings A and B, the compounds where stability and magnetic aromaticity coincide are the aromatic compounds **4a**, **9a**, **12a**, **4abH$^+$**, **6aH$^+$**, **7aH$^+$**, and **9aH$^+$** (since they are only two protonated **8** azapentalenes, the fact that **8$_2$H$^+$** is more stable and more aromatic than **8$_1$H$^+$** is not very significant).

2.4. MEP and NBO analysis of neutral azapentalenes

A significant conclusion reported in the review already cited,[3] is that 'aromatic' (fully-conjugated) azapentalenes should present a delocalization of the charge from the ring bearing the NH to the other ring resulting in the dipolar resonance form being important in the total contribution. This model was used to rationalize their reactivity.

The NICS are not sensitive to these electron transfers probably because the values of cationic, anionic, and neutral azoles are very similar, for instance, for imidazole: −10.13 ppm (imidazolium cation), −10.97 ppm (imidazolate anion), and −10.57 ppm (imidazole).[17]

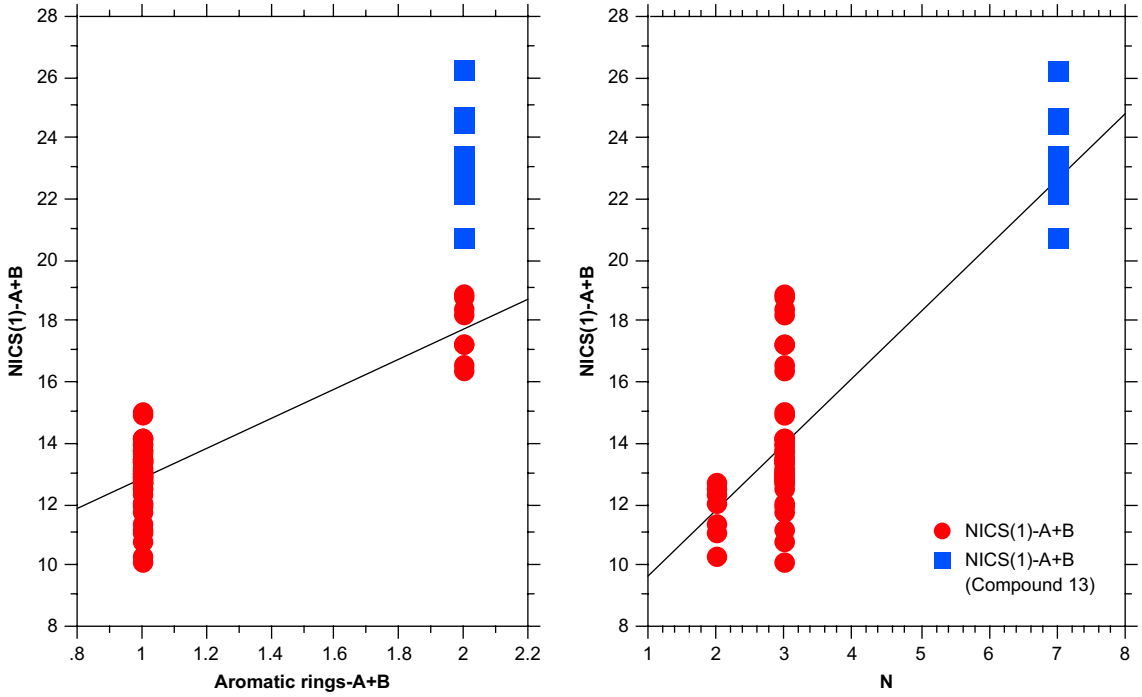


Figure 3. Sum of the NICS(1) of A and B versus the sum of aromaticities (A+B) and versus the number of N atoms.

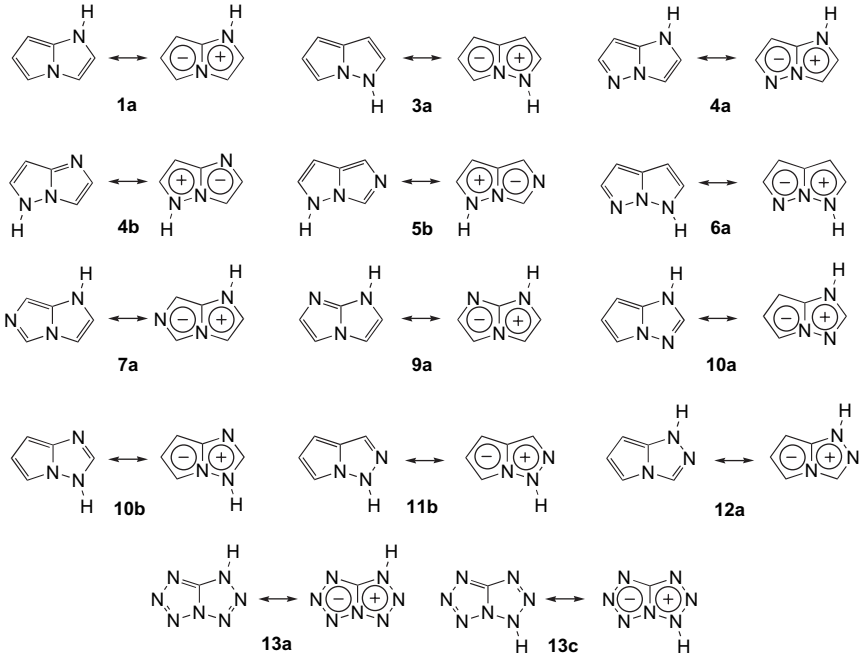
This failure lead us to approach the situation depicted in Scheme 5 using MEPs (Molecular Electrostatic Potential)[18] and carrying out a Natural Resonance Theory analysis within the NBO methodology.[19]

2.4.1. MEP

Figure 4 contains the MEPs for the compounds of Scheme 6. In all cases there is a region of negative charge around the peripheral atoms of the anionic part. The N atoms 'pyridine-like' add and perturbates the picture. When the N bearing a LP is in the positively charged half it maintains its negative contribution to the MEP (**10a**, **10b**, **11b**, **12b**) although in some cases it is very small (**13a**, **13c**). The charge is not uniformly distributed along the 4 and 6 positions, which should be relevant for their reactivity with electrophiles.

2.4.2. NRT

Natural resonance theory furnishes the weight of each of the contributing Lewis structures to the ab initio wave function. Application of NRT to the six-membered aromatic



Scheme 5. 'Aromatic' azapentalenes.

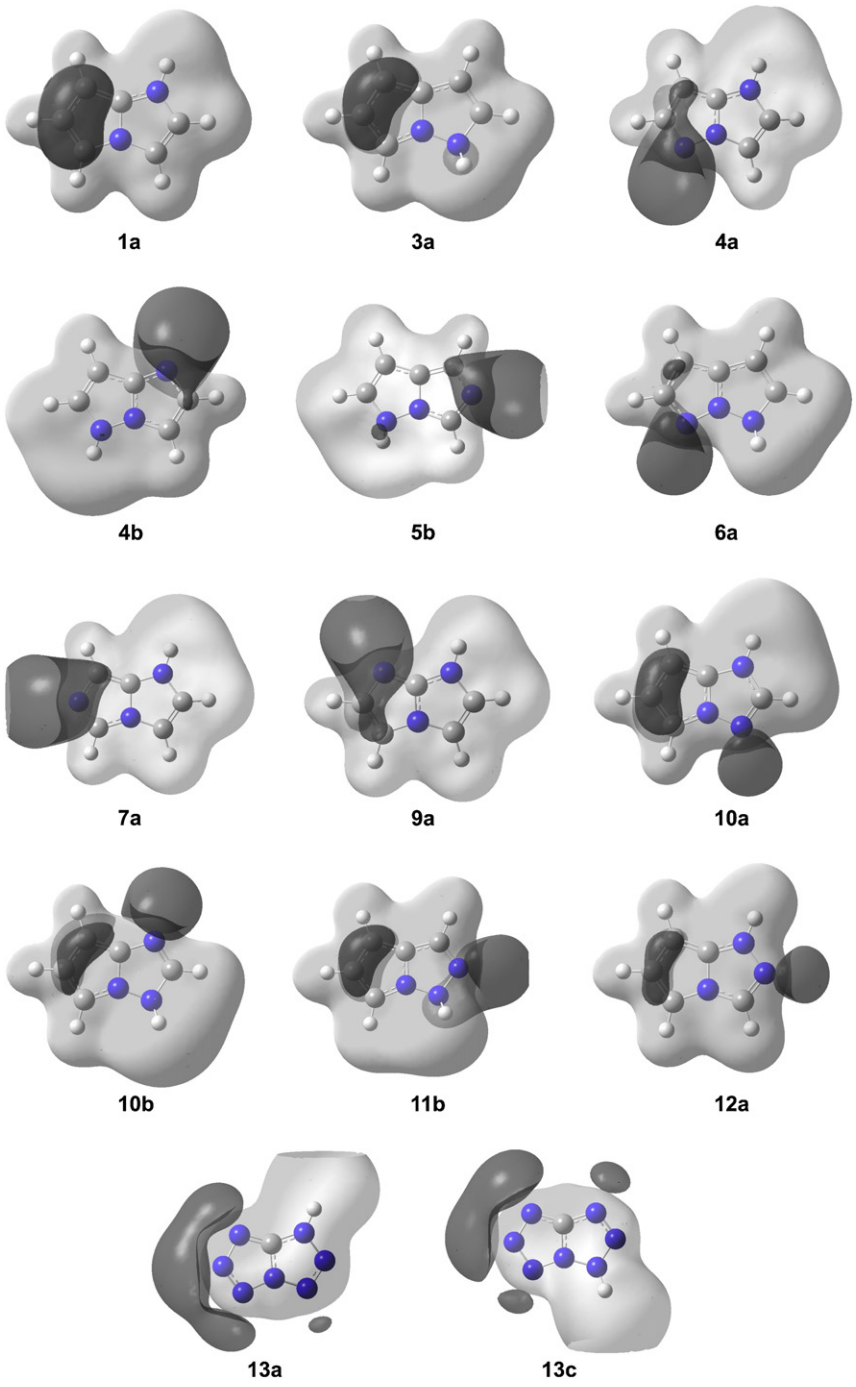
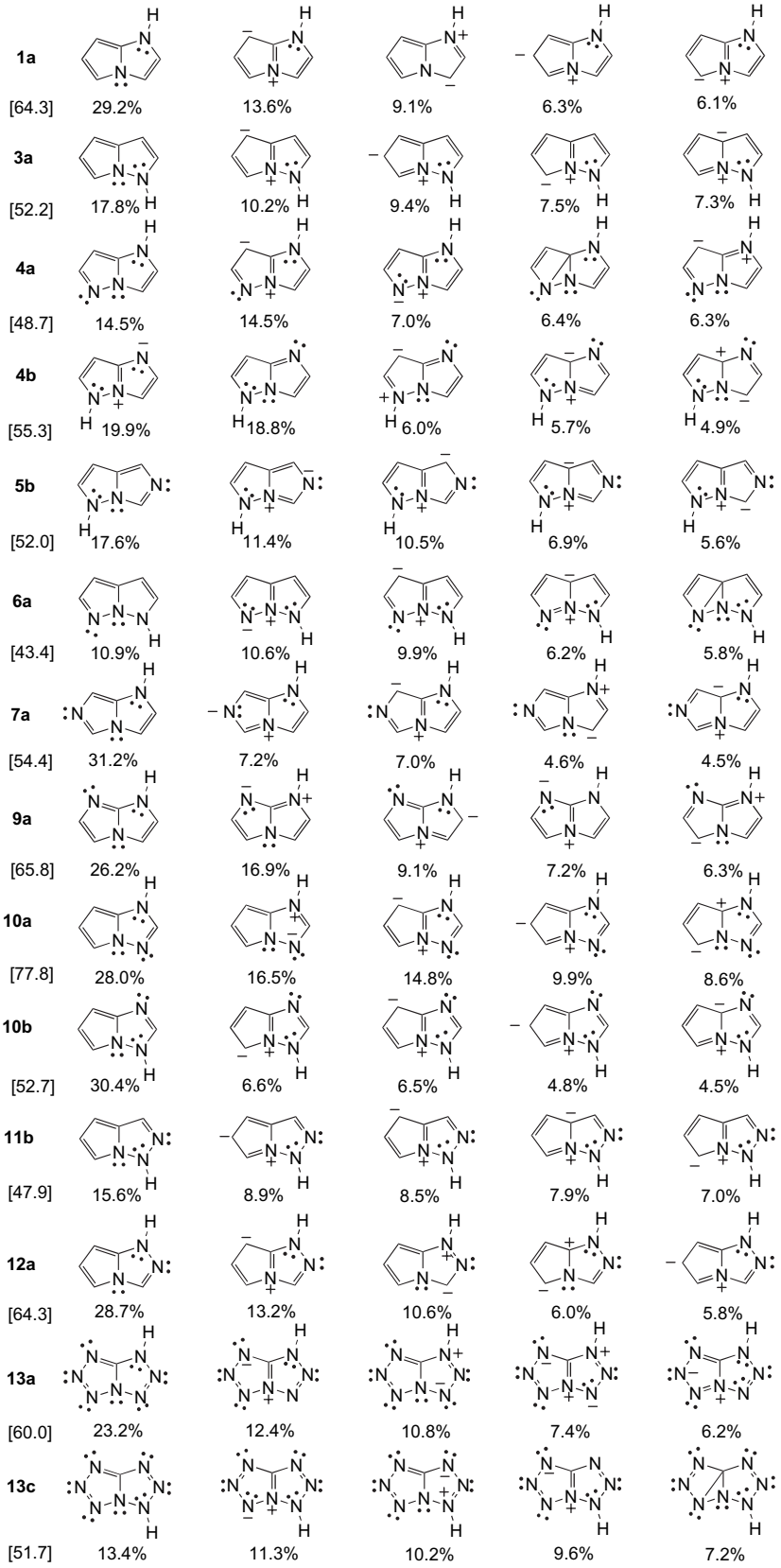


Figure 4. MEPs of neutral azapentalenes. Dark and light regions represent negative and positive MEP values, respectively.

compounds, benzene, pyridine, etc., results in two equivalent structures, each having a resonance weight of 35–46%, in agreement with the Kekulé picture for these compounds. The remaining structures involve charge separation. For the five-membered heteroaromatic compounds (azoles), the single principal, or Kekulé, structure, accounts for as much as 70%.[20] One might expect that the percentage of the 'non-Kekulé' or charge separated structures, should increase with the aromaticity of these compounds.

We report in Scheme 6 the five Lewis structures with larger weights (the sum is given between brackets). The most important Kekulé structures (left side formulae) represent between 11 and 31%. Only in the case of **4b** there is a charge separated structure with a larger weight (19.9%) than the Kekulé one (18.8%). The sum of the percentages of 'non-Kekulé' structures (100–Kekulé) is neither related to the relative energies (for instance for azapentalenes having three N atoms **4a**–**12a**) nor the sum of NICS(1) of A and B. In a few cases, Dewar-type structures are observed: **4a** (6.4%) **6a** (5.8%), and **13c** (7.2%).

In general, the structures with a negative charge located on the atoms of ring A of Scheme 6 correspond to important contributions. For instance, in **1a** the sum of the three negatively



Scheme 6. Lewis structures of 'aromatic' azapentalenes.

charged structures on ring A accounts for 26.0% and in **9a** for 30.4%.

3. Computational details

The geometry of the systems has been fully optimized with the hybrid HF/DFT B3LYP[21,22] computational method and the 6-311++G(d,p) basis set[23] within the Gaussian 03 package.[24] Frequency calculations have been carried out to confirm that the structures obtained correspond to energetic minima.

The NICS values have been obtained at the geometrical center of the rings, NICS(0), and 1 Å above/below them, NICS(1), with the GIAO method.[25] The natural resonance theory calculations have been performed using the NBO 5 code[26] implemented on the Gaussian 98 program.[27]

4. Conclusions

The main conclusions of the present work on azapentalenes are:

(i) the most stable tautomer cannot be predicted using qualitative models; only calculations can do it.
(ii) When a large number of data are available, the only concise and efficient way to discuss them is using a statistical approach like the Free-Wilson one.
(iii) The calculations also allow to establish the structure of the most stable conjugated acid and to determine their proton affinities.
(iv) Aromaticity as defined by Schleyer's NICS(1) values provide a coherent picture for azapentalenes but this picture is not consistent with other descriptions.
(v) MEP and NBO analyses provide a quantitative image of the charge distribution in azapentalenes but not as clear as we would have liked.

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Supplementary data

Free-Wilson matrix and regression analysis. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.01.141.

References and notes

1. Armit, J. W.; Robinson, R. *J. Chem. Soc.* **1925**, *127*, 1604–1618.
2. (a) Elguero, J.; Jacquier, R.; Shimizu, B. *Bull. Soc. Chim. Fr.* **1971**, 1497–1499; (b) Aubagnac, J.-L.; Elguero, J.; Robert, R. *Bull. Soc. Chim. Fr.* **1972**, 2868–2879; (c) Elguero, J.; Jacquier, R.; Summers, A. J. H. *Bull. Soc. Chim. Fr* **1972**, 3968–3973; (d) Summers, A. J. H.; Elguero, J. *Bull. Soc. Chim. Fr.* **1972**, 3974–3976; (e) Mignonac-Mondon, S.; Elguero, J.; Lazaro, R. *C.R. Acad. Sci.* **1973**, *276C*, 1533–1535; (f) Elguero, J.; Jacquier, R.; Mignonac-Mondon, S. *J. Heterocycl. Chem.* **1973**, *10*, 411–412; (g) Faure, R.; Vincent, E. J.; Elguero, J. *Tetrahedron Lett.* **1973**, 2703–2706; (h) de Mendoza, J.; Elguero, J. *Bull. Soc. Chim. Fr.* **1974**, 1675–1677; (i) Faure, R.; Giusti, G.; Galy, J. P.; Vincent, E. J.; Elguero, J. *Bull. Soc. Chim. Fr.* **1974**, 2967–2968; (j) de Mendoza, J.; Elguero, J. *Bull. Soc. Chim. Fr.* **1974**, 2987–2988; (k) Elguero, J.; Fruchier, A.; Knutsson, L.; Lazaro, R.; Sandström, J. *Can. J. Chem.* **1974**, *52*, 2744–2750; (l) Forniés-Marquina, J. M.; Courseille, C.; Elguero, J. *Cryst. Struct. Commun.* **1974**, 7–9; (m) Claramunt, R. M.; Fabregá, J. M.; Elguero, J. *J. Heterocycl. Chem.* **1974**, *11*, 751–754; (n) Alcalde, E.; de Mendoza, J.; Elguero, J. *J. Heterocycl. Chem.* **1974**, *11*, 921–928; (o) Faure, R.; Galy, J.-P.; Giusti, G.; Vincent, E.-J.; Elguero, J. *Org. Magn. Reson.* **1974**, *6*, 485–486; (p) Elguero, J.; Knutsson, L.; Mignonac-Mondon, S. *Bull. Soc. Chim. Fr.* **1975**, 255–256; (q) Vertut, M.-C.; Fayet, J.-P.; Gonzalez, E.; Sarlin, R.; Elguero, J. *Bull. Soc. Chim. Fr.* **1975**, 1871–1872; (r) Fayet, J.-P.; Vertut, M.-C.; Mauret, P.; de Mendoza, J.; Elguero, J. *J. Heterocycl. Chem.* **1975**, *12*, 197–198; (s) Gonzalez, E.; Sarlin, R.; Elguero, J. *J. Heterocycl. Chem.* **1975**, *12*, 279–285; (t) Claramunt, R. M.; Fayet, J.-P.; Vertut, M.-C.; Mauret, P.; Elguero, J. *Tetrahedron* **1975**, *31*, 545–548; (u) Faure, R.; Vincent, E.-J.; Claramunt, R. M.; Fabrega, J.-M.; Elguero, J. *Tetrahedron* **1976**, *32*, 341–348; (v) Gonzalez, E.; Sarlin, R.; Elguero, J. *Bull. Soc. Chim. Belg.* **1976**, *85*, 829–832; (w) Claramunt, R. M.; Elguero, J.; Fruchier, A.; Nye, M. J. *Afinidad* **1977**, *34*, 545–551; (x) Faure, R.; Galy, J.-P.; Vincent, E.-J.; Elguero, J.; Mauret, P.; Fayet, J.-P.; Vertut, M.-C. *Bull. Soc. Chim. Fr.* **1977**, 288–294; (y) Faure, R.; Galy, J.-P.; Vincent, E.-J.; Mauret, P.; Fayet, J.-P.; Vertut, M.-C.; Elguero, J. *Can. J. Chem.* **1977**, *55*, 1728–1735; (z) Faure, R.; Vincent, E.-J.; Claramunt, R. M.; Elguero, J. *Org. Magn. Reson.* **1977**, *9*, 508–511; (aa) Faure, R.; Galy, J.-P.; Vincent, E.-J.; Elguero, J. *Org. Magn. Reson.* **1977**, *10*, S249–S250; (ab) Knutsson, L.; Elguero, J. *An. Quim.* **1978**, *74*, 795–798; (ac) Faure, R.; Vincent, E.-J.; Elguero, J.; de Mendoza, J.; Rull, P. *Bull. Soc. Chim. Fr.* **1978**, 273–278; (ad) Faure, R.; Galy, J.-P.; Vincent, E.-J.; Elguero, J. *Can. J. Chem.* **1978**, *56*, 46–53; (ae) Alcalde, E.; Claramunt, R. M.; Elguero, J.; Huber, C. P. S. *J. Heterocycl. Chem.* **1978**, *15*, 395–399; (af) Lazaro, R.; Elguero, J. *J. Heterocycl. Chem.* **1978**, *15*, 715–720; (ag) Faure, R.; Galy, J.-P.; Vincent, E.-J.; Elguero, J. *Org. Magn. Reson.* **1978**, *11*, 507–509; (ah) Butler, R. N.; Mcevoy, T.; Alcalde, E.; Claramunt, R. M.; Elguero, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2886–2890; (ai) Alcalde, E.; Claramunt, R. M.; Elguero, J. *An. Quim.* **1983**, *79C*, 248–250; (aj) Alajarin, M.; Molina, P.; Tarraga, A.; Vilaplana, M. J.; Foces, M. C.; Cano, F. H.; Claramunt, R. M.; Elguero, J. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 735–744; (ak) Alajarín, M.; Molina, P.; Pérez de Vega, M. J.; Foces-Foces, M. C.; Cano, F. H.; Claramunt, R. M.; Elguero, J. *Chem. Scripta* **1985**, *25*, 230–238; (al) Valls, N.; Marín, A.; Alcalde, E.; Elguero, J. *Il Farmaco, Ed. Sci.* **1985**, *40*, 34–48; (am) Marín, A.; Valls, N.; Berenguer, F. J.; Alonso, M. T.; Martínez, A. R.; Martínez, M. M.; Elguero, J. *Il Farmaco* **1992**, *47*, 63–75; (an) Hanoun, J.-P.; Faure, R.; Galy, J.-P.; Elguero, J. *J. Heterocycl. Chem.* **1996**, *33*, 747–750; (ao) Claramunt, R. M.; Trofimenko, S.; Rozas, I.; Elguero, J. *Spectrosc. Int. J.* **1997**, *13*, 113–123.
3. Elguero, J.; Claramunt, R. M.; Summers, A. J. H. *Adv. Heterocycl. Chem.* **1978**, *22*, 183–320.
4. Alkorta, I.; Blanco, F.; Elguero, J. *J. Mol. Struct. (Theochem)* **2008**, *851*, 75–83.
5. (a) Free, S. M. J.; Wilson, J. W. *J. Med. Chem.* **1964**, *7*, 395–399; (b) Kubinyi, H. QSAR: Hansch Analysis and Related Approaches. *Methods and Principles in Medicinal Chemistry*; Mannhold, R., Krogsgaard-Larsen, P., Timmerman, H., Eds.; VCH: Weinheim, 1993; Vol. 1.
6. (a) Gotelli, N. J.; McCabe, D. J. *Ecology* **2002**, *83*, 2091–2096; (b) Miklós, I.; Podani, J. *Ecology* **2004**, *85*, 86–92.
7. (a) Cativiela, C.; Elguero, J.; Mathieu, D.; Phan Tan Luu, R. *Eur. J. Med. Chem.* **1983**, *18*, 359–363; (b) Cativiela, C.; García, J.-I.; Elguero, J. *An. Quim.* **1987**, *83C*, 278–282; (c) Cativiela, C.; Elguero, J.; García, J.-I.; Mathieu, D. *Qsar in Drug Design and Toxicology*; Hadzi, D., Jerman-Blazik, B., Eds.; Elsevier: Amsterdam, 1987; pp 55–57; (d) Cativiela,

C.; García, J.-I.; Elguero, J.; Mathieu, D.; Phan Tan Luu, R. *Quant. Struct.-Act. Relat.* **1987**, *6*, 173–178; (e) Alkorta, I.; Rozas, I.; Elguero, J. *J. Phys. Chem. A* **1998**, *102*, 9278–9285; (f) Jiménez, J. A.; Claramunt, R. M.; Escolástico, C.; Elguero, J. *Struct. Chem.* **2000**, *11*, 77–83; (g) Alkorta, I.; Rozas, I.; Elguero, J. *J. Phys. Chem. A* **2001**, *105*, 743–749; (h) Alkorta, I.; Elguero, J.; Mó, O.; Yáñez, M.; Del Bene, J. E. *Mol. Phys.* **2004**, *102*, 2563–2574; (i) Alkorta, I.; Elguero, J. *Struct. Chem.* **2005**, *16*, 507–514; (j) Goswami, S.; Dey, S.; Gallagher, J. F.; Lough, A. J.; García-Granda, S.; Torre-Fernández, L.; Alkorta, I.; Elguero, J. *J. Mol. Struct.* **2007**, *846*, 97–107; (k) Alkorta, I.; Solimannejad, M.; Provasi, P.; Elguero, J. *J. Phys. Chem. A* **2007**, *111*, 7154–7161; (l) Alkorta, I.; Blanco, F.; Elguero, J. *ARKIVOC* **2008**, *vii*, 48–56.
8. (a) Atkinson, A. C.; Donev, A. N. *Optimum Experimental Designs*. Oxford Statistical Science Series; Oxford Science, Clarendon: Oxford, 1992; Vol. 8; (b) Carlson, R. *Design and Optimization in Organic Synthesis*. Data Handling in Science and Technology; Elsevier: Amsterdam, 1992; Vol. 8.
9. Minkin, V. I.; Glukhovtsev, M. N.; Simkin, B. Ya. *Aromaticity and Antiaromaticity*; John Wiley and Sons: New York, NY, 1994; p 220.
10. Taft, R. W.; Anvia, F.; Taagepera, M.; Catalán, J.; Elguero, J. *J. Am. Chem. Soc.* **1986**, *108*, 3237–3239.
11. Tomás, F.; Catalán, J.; Pérez, P.; Elguero, J. *J. Org. Chem.* **1994**, *59*, 2799–2802.
12. Bird, C. W. *Tetrahedron* **1997**, *53*, 13111–13118.
13. Berthelot, M.; Laurence, C.; Safar, M.; Besseau, F. *J. Chem. Soc., Perkin Trans. 2* **1998**, 283–290.
14. Alkorta, I.; Elguero, J. *J. Phys. Org. Chem.* **2005**, *18*, 719–724.
15. Elguero, J.; Claramunt, R. M.; Summers, A. J. H. *Adv. Heterocycl. Chem.* **1978**, *22*, 249.
16. Elguero, J.; Claramunt, R. M.; Summers, A. J. H. *Adv. Heterocycl. Chem.* **1978**, *22*, 266.
17. (a) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H. J.; Hommes, N. J. R. V. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317–6318; (b) Chen, Z. F.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Chem. Rev.* **2005**, *105*, 3842–3888.
18. Alkorta, I.; Elguero, J. *Top. Heterocycl. Chem.*, in press.
19. (a) *Molecular Electrostatic Potentials: Concepts and Applications*; Murray, J. S., Sen, K., Eds.; Theoretical and Computational Chemistry; Elsevier: Amsterdam, 1996; Vol. 3; (b) Cramer, C. J. *Computational Chemistry: Theories and Models*; John Wiley: Chichester, UK, 2004.
20. (a) Glendening, E. D.; Weinhold, F. *J. Comput. Chem.* **1998**, *19*, 593–609; (b) Glendening, E. D.; Weinhold, F. *J. Comput. Chem.* **1998**, *19*, 610–627; (c) Glendening, E. D.; Badenhoop, J. K.; Weinhold, F. *J. Comput. Chem.* **1998**, *19*, 628–646; (d) Feldgus, S.; Landis, C. R.; Glendening, E. D.; Weinhold, F. *J. Comput. Chem.* **2000**, *21*, 411–413; (e) Weinhold, F.; Landis, C. R. *Valency and Bonding*; Cambridge University Press: Cambridge, 2005.
21. Bean, G. P. *J. Org. Chem.* **1998**, *63*, 2497–2506.
22. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
23. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
24. Frisch, M. J.; Pople, J. A.; Krishnam, R.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265–3269.
25. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*; Gaussian: Pittsburgh, PA, 2003.
26. Ditchfield, R. *Mol. Phys.* **1974**, *27*, 789–807; London, F. *J. Phys. Radium* **1937**, *8*, 397–409.
27. Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C.M.; Weinhold, F. *NBO 5.0*, Madison, WI, 2001.
28. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian: Pittsburgh, PA, 1998.