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Homoheteroaromaticity: the case study of azepine and dibenzazepine †

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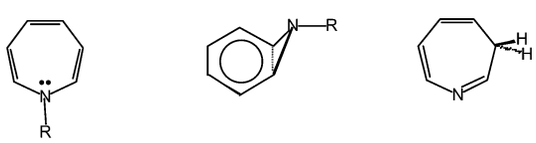
Geometrical and energetic DFT calculations as well as GIAO and NICS chemical shifts have been calculated for 1*H*-azepine and 5*H*-dibenz[*b*,*f*]azepine and their cations. The last compound has been studied experimentally by ^{1}H and ^{13}C NMR in neutral and acidic conditions establishing that the cation corresponds to an *N*-protonated structure. The conclusion is that the neutral molecules are antiaromatic while the cations are aromatic (homoheteroaromaticity).

Introduction

In Minkin's book "Aromaticity and Antiaromaticity" [1] there is a chapter on "Heteroaromaticity" (chapter 5) and another on "Homoaromaticity" (chapter 6) but no example of a compound belonging to both concepts is mentioned. However, Paquette [2] has discussed the question of the antiaromaticity of 1*H*-azepines **I** (see also Dewar and Trinajstic [3]) and even the possible *azahomoaromaticity* of **II**, concluding that these compounds are truly polyenes. Toyota *et al*. have carried out an MCSCF/6-31G(d,p) study of **I** and related heterocycles to elucidate the nature of a pseudo-Jahn–Teller distortion from planarity.[4]



I **II** **III**

When R = H, the antiaromaticity of **I** could be relieved by tautomerization to the 3*H*-structure **III**.[5–7] In the present paper we want to discuss the antiaromaticity of **I** and its dibenzo derivative (5*H*-dibenz[*b*,*f*]azepine),[5,6] as well as the possible homoaromatic character of the cations obtained by protonation. It is known that most examples of homoaromaticity concern cations to the point that Minkin asks in his book "can neutral molecules manifest homoaromaticity?" Therefore, **II** is possibly not a good candidate for studying homoheteroaromaticity.

Our strategy will be the following one. First, we will discuss on theoretical grounds the structure of the cations obtained by protonation of **1a** (Scheme 1) and **1b** (Scheme 2) and calculate through homodesmotic equilibria the antiaromaticity of these molecules. Then, we will discuss the structure and possible homoheteroaromaticity of cations **3a** and **3b**. Finally, we will carry out NMR experiments to determine the structure, **2b** or **3b**, of the cation obtained by protonation of **1b**.

† Electronic supplementary information (ESI) available: absolute chemical shieldings calculated at the B3LYP/6-311++G**//B3LYP/6-311++G** computational level for compounds **1b**, **2b**, **4b** and **5b**. See http://www.rsc.org/suppdata/ob/b3/b314742h/

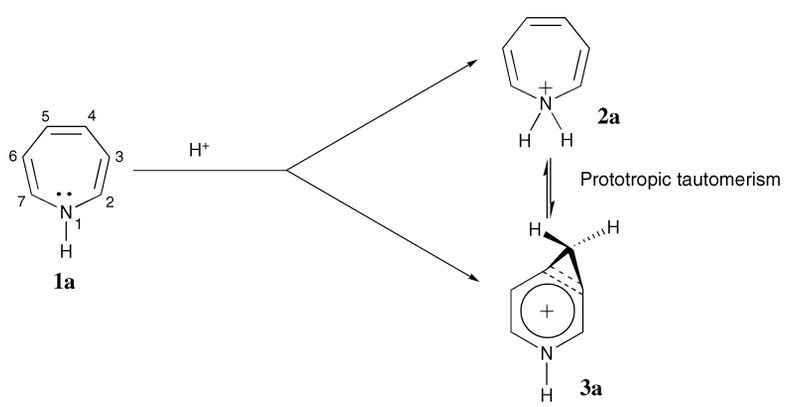
Results and discussion

Theoretical calculations

Our approach involves the use of DFT methods (B3LYP/6-31G* and B3LYP/6-311++G**). Since Schaefer *et al*. have pointed out the failure of DFT for [10]annulene (an aromatic compound according to Hückel's rule),[8] we have checked the validity of our conclusions in the **a** series carrying out MP2/6-311++G** calculations on compounds **1a**–**5a**. Note that we[9–11] and many others have used DFT, especially B3LYP, methods for the study of problems related to aromaticity.[12,13] The point groups of the optimised geometries are: **1a** C_s, **2a** C_s, **3a** C_1, **1b** C_s, **2b** C_s, **3b** C_1, **4a** C_2, **5a** C_1, **4b** C_2 and **5b** C_1.

Geometries

The minimum energy structure of **1a** reported by Toyota *et al*. is a boat of C_s conformation.[4] Its most characteristic geometric parameters are the CC double/single bond alternation (0.913 ratio) and the four dihedral angles: C6C5C4C3 (0.0°), C5C4C3C2 (27.3°), C4C3C2N1 (−0.1°) and C3C2N1C7



Scheme 1 Cations that could be formed by protonation of 1*H*-azepine **1a**.

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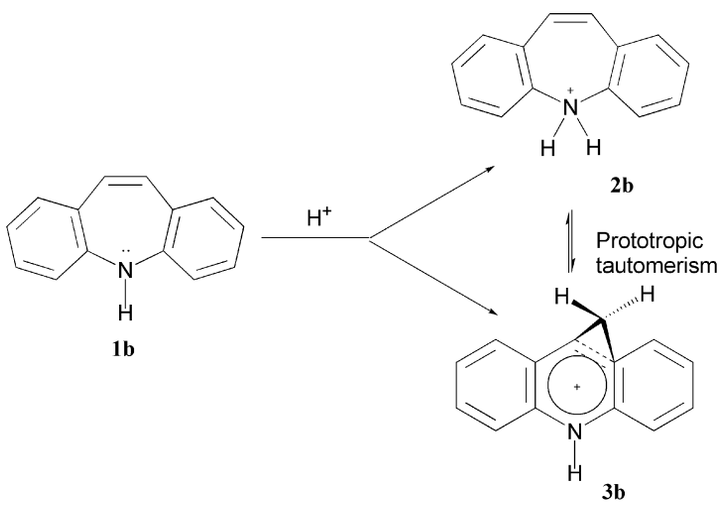
Table 1 Results of the theoretical calculations: energies (absolute values in hartrees, relative values and ZPE in kcal mol^{-1}) and dipole moments (in Debyes)

		B3LYP/6-31G*				B3LYP/6-311++G**		MP2/6-311++G**	
Compound	Charge	E_T	E_{rel}	ZPE	Dipole moment[a]	E_T	E_{rel}	E_T	E_{rel}
1a	0	−287.53629		73.07	1.66	−287.62183		−286.74679	
2a	1+	−287.90041	0.00	82.42	*3.29*	−287.97761	0.00	−287.10511	0.00
3a	1+	−287.92527	−15.60	82.08	*1.95*	−287.99910	−13.48	−287.12388	−11.78
4a	0	−288.76731		88.22	1.49	−288.85325		−287.95977	
5a	1+	−289.11435	—	97.05	*3.35*	−289.19384		−288.30296	
1b	0	−594.85884		132.76	0.91	−595.00963			
2b	1+	−595.22767	0.00	141.89	*2.98*	−595.37211	0.00		
3b	1+	−595.23016	−1.56	140.88	*1.81*	−595.37090	0.76		
4b	0	−596.08057		147.52	0.49	−596.23207			
5b	1+	−596.44250	—	156.68	*2.68*	−596.58920			

[a] The dipole moment of the cations in italics.



Scheme 2 Cations that could be formed by protonation of 5*H*-dibenz[*b*,*f*]azepine **1b**.

(−48.0°). In our case, the resulting geometries of the minimum are similar: B3LYP/6-311++G** [bond alternation ratio 0.916; C6C5C4C3 (0.0°), C5C4C3C2 (29.1°), C4C3C2N1 (−0.1°) and C3C2N1C7 (50.6°)] and MP2/6-311++G** [bond alternation ratio 0.930; C6C5C4C3 (0.0°), C5C4C3C2 (34.5°), C4C3C2N1 (−1.5°) and C3C2N1C7 (−62.8°)].

The most interesting structures are those of **3a** and **3b** (see Fig. 1). The C ··· C homoaromatic bond is 2.390 Å for **3a** (1.899 Å at the MP2/6-311++G** level) and 2.420 Å for **3b**. Distances of up to 2.284 Å have been reported for homotropylium cations,[1] thus **3a** and **3b** are at the limit of the geometrical definition of homoaromaticity. Note, nevertheless, that the distance is shorter in cation **3a** than in **3b** at the same level of calculations.

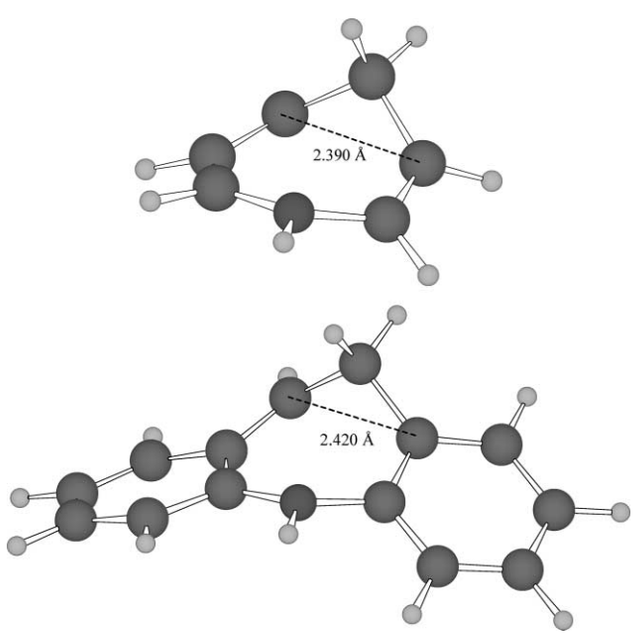


Fig. 1 Calculated molecular structures of **3a** and **3b**.

Energies

The energetic results are reported in Table 1. To discuss the antiaromaticity of neutral molecules **1a** and **1b**, we have built up two homodesmotic reactions based on the use of saturated derivatives **4a** and **4b** (Scheme 3) [**4b** has the skeleton of tricyclic antidepressants].[14]

$$\mathbf{1a} + \mathbf{5a} \longrightarrow \mathbf{2a} + \mathbf{4a} \quad (1)$$

$$\mathbf{1b} + \mathbf{5b} \longrightarrow \mathbf{2b} + \mathbf{4b} \quad (2)$$

Using the data from Table 1 (B3LYP/6-31G* without ZPE correction), these equations lead to −10.72 kcal mol^{-1} for **a**, and −4.33 kcal mol^{-1} for **b** (the ZPE correction accounts for about 0.5 kcal mol^{-1}). With the larger basis set, these values become −9.51 (−9.49 kcal mol^{-1} at the MP2/6-311++G** level) and −4.05 kcal mol^{-1}. That is, saturated cations **5** transfer their proton to the more basic compounds **1** to yield cations **2** and neutral molecules **4**. In other words, destroying the antiaromaticity of **1a** results in a reward of 10.8 kcal mol^{-1} and that of **1b** only in a 4.2 kcal mol^{-1} effect, which can be taken as a measure of the antiaromaticity of 1*H*-azepine **1a** and 5*H*-dibenzo[*b*,*f*]azepine **1b**. Thus, our first conclusion is that neutral molecules related to **I** are antiaromatic, in agreement

Table 2 ^{1}H NMR chemical shifts (δ ppm) of compounds **4b**, **5b**, **1b** and **2b**

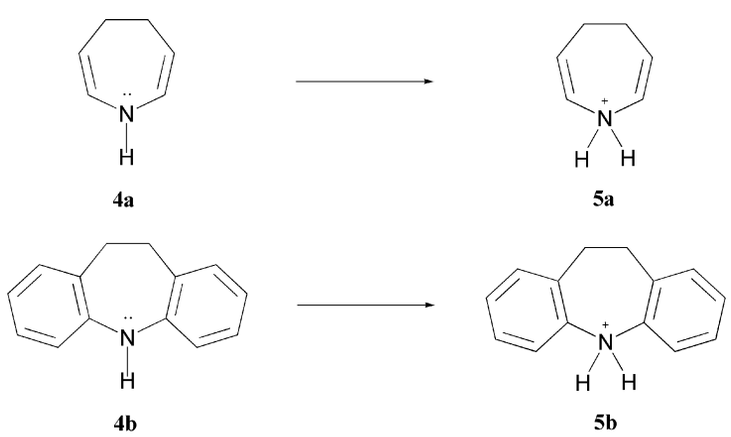
Compd.	Solv.	H1	H2	H3	H4	H10	NH
4b	DMSO	6.97	6.64	7.01	6.96	2.94 (CH_2)	8.25 (NH)
5b	H_2SO_4	6.71	6.58	6.68	6.57	2.52 (CH_2)	8.70 (N^+H_2)
Prot.[a]	—	−0.26	−0.06	−0.33	−0.39	−0.42 (CH_2)	+0.45
1b	DMSO	6.72	6.67	6.94	6.59	6.06 (CH)	6.91 (NH)
2b	TFAA	6.89	6.89	6.93	7.12	6.60 (CH)	—
Prot.[b]	—	0.17	0.22	−0.01	+0.53	+0.54 (CH)	—
2b[c]	H_2SO_4	6.77	6.75	6.82	6.90	6.48 (CH)	8.45 (N^+H_2)
2b[d]	—	−0.12	−0.14	−0.11	−0.22	−0.12 (CH)	—
Prot.[a]	—	0.05	0.08	−0.12	0.31	+0.42 (CH)	—

[a] $\delta(H_2SO_4) - \delta(DMSO)$. [b] $\delta(TFAA) - \delta(DMSO)$. [c] The product is not stable in this solvent and the data correspond to a spectrum recorded just after the solution has been prepared. [d] Solvent effect.

Table 3 ^{13}C NMR chemical shifts (δ ppm) of compounds **4b**, **5b**, **1b** and **2b**

Compd.	Solv.	C1	C2	C3	C4	C4a	C9a	C10
4b	DMSO	130.30	118.29	126.57	117.90	142.88	127.71	34.92 (CH_2)
5b	H_2SO_4	130.94	130.17	127.25	120.30	132.90	131.79	27.60 (CH_2)
Prot.[a]	—	0.64	11.88	0.68	2.40	−9.98	4.08	−7.32 (CH_2)
1b	DMSO	130.42	121.90	129.54	119.05	149.48	129.03	132.06 (CH)
2b	TFAA	130.68	131.65	131.35	121.65	133.56	130.58	130.77 (CH)
Prot.[b]	—	0.24	9.75	1.81	2.60	−15.92	1.55	−1.29 (CH)
2b[c]	H_2SO_4	128.74	129.71	129.43	119.29	130.61	127.98	128.59 (CH)
2b[d]	—	−1.94	−1.94	−1.92	−2.36	−2.95	−2.60	−2.18 (CH)
Prot.[a]	—	−1.68	7.81	−0.11	0.24	−18.87	−1.05	−3.47 (CH)

[a] $\delta(H_2SO_4) - \delta(DMSO)$. [b] $\delta(TFAA) - \delta(DMSO)$. [c] The product is not stable in this solvent and the data correspond to a spectrum recorded just after the solution has been prepared. [d] Solvent effect.



Scheme 3 Saturated model compounds **4a** and **4b** and their *N*-protonated cations.

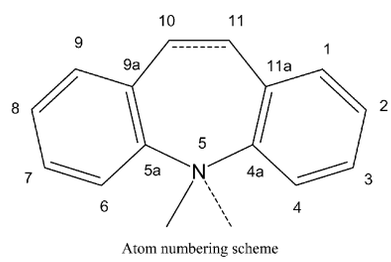
with Paquette, but that the annelated benzene rings partly remove it.[2]

From Table 1, it is possible to compare the stabilities of the non-aromatic cations **2a** and **2b** with those of the possible homoaromatic ones **3a** and **3b**. In the case of the **a** series, the homoaromatic structure is 15.6 kcal mol^{-1} (B3LYP/6-31G*) [13.5 (B3LYP/6-311++G**) and 11.8 kcal mol^{-1} (MP2/6-311++G**)] more stable than the non-aromatic one, while this difference is reduced to 1.6 kcal mol^{-1} for the **b** series (B3LYP/6-31G*) or even inverted, 0.8 kcal mol^{-1} (B3LYP/6-311++G**). The conclusion should be that **3a** is homoheteroaromatic but **3b** is a non-aromatic compound.

Combining these two conclusions, *i.e.*, **1** + **5** ⟶ **3** + **4**, it can be concluded that the protonation of the antiaromatic base **1a** to yield homoheteroaromatic cation **3a** results in an energy gain of about 25 kcal mol^{-1} while the protonation of the antiaromatic base **1b** to yield non-aromatic cation **3b** results in an energy gain of only about 4 kcal mol^{-1}.

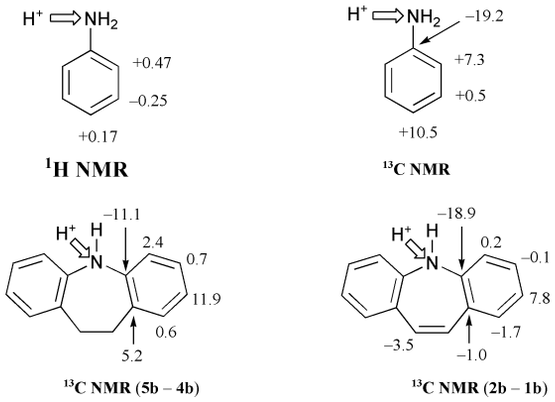
Solution NMR results

We have collected in Tables 2 (^{1}H) and 3 (^{13}C) the experimental results obtained for compounds **1b**, **2b**, **4b** and **5b**.



The first conclusion is that the cation has the structure **2b** and not **3b** (symmetry and absence of CH_2 signals, note also that in H_2SO_4, cation **2b** shows a signal at 8.45 ppm integrating for two protons that disappears with time). This corresponds to the result obtained with the larger basis set (0.8 kcal mol^{-1}); the calculated difference is rather weak but the dipole moment, with all the care that dipole moments of charged species need to be handled, is larger for **2b** than for **1b**.

Although the NMR spectra of aniline and the anilinium cation have been reported several times,[15,16] we have preferred to record them in DMSO-d_6 and H_2SO_4, to calculate the protonation effects (Scheme 4).



Scheme 4 Protonation effects in ppm, $\delta(H_2SO_4) - \delta$(DMSO).

Comparison of protonation effects (Scheme 4 and Tables 2 and 3) shows that the three compounds behave quite differently. We will not discuss the weak effects measured in ^{1}H NMR and concentrate instead on those observed by ^{13}C NMR. The differences between **1b** and **4b** could be related to the fact that when **1b** is protonated its antiaromaticity is destroyed. Both compounds behave, in some respects, similarly to aniline: a very large negative *ipso* effect (C4a) and a large positive *para* effect (C2). However, the large positive *ortho* effect (+7.3 ppm) is not observed on C4 or C11a.

Absolute shieldings and NICS

We have calculated within the GIAO methodology, the absolute shieldings of the different nuclei of compounds **1b**, **2b**, **4b** and **5b** (see Supplementary Material †). The ^{1}H chemical shifts are too sensitive to solvent effects and cannot be used to compare with those obtained in polar solvents (the calculations correspond to isolated molecules *in vacuo*). The ^{13}C chemical shifts of Table 3 (neutral molecules in DMSO, cations in H_2SO_4) can be compared with the absolute shieldings of Table 4 (eqn. 3).

$$\delta_{exp} = (175.8 \pm 0.9) - (0.98 \pm 0.02)\,\sigma_{calcd},\ n = 28,\ r^2 = 0.993 \quad (3)$$

This satisfactory result indicates that the assignments of the signals and the structures are correct (TMS was not included in the regression, its calculated σ = 184.75 ppm).

Experimental protonation effects [$\Delta\delta = \delta(H_2SO_4) - \delta$(DMSO)] compare well with calculated protonation effects [$\Delta\delta = \delta$(cation) − δ(neutral)]. Eqn. 4 has been calculated using only the sp^2 carbon atoms of Scheme 4.

$$\Delta\delta_{exp} = -(1.9 \pm 0.4) + (0.70 \pm 0.04)\Delta\delta_{calcd},\ n = 17,\ r^2 = 0.963 \quad (4)$$

As a magnetic criterion of aromaticity, we have calculated NICS (nuclear independent chemical shifts) values in the geometrical centre of the seven-membered ring.[9,17] The results (Table 4), taking into account that NICS(0) of benzene at the same level is 9.6 ppm, show: i) non-aromatic compounds **4a**, **5a**, **4b** and **5b** have NICS(0) values < |1.9| ppm; ii) a compound **2b** (0.1 ppm) which is clearly non-aromatic; iii) two antiaromatic compounds, **1a** and **1b**, the second less antiaromatic, in agreement with the isodesmic calculations (−9.5 and −4.1 kcal mol^{-1}); iv) two homoaromatic compounds **2a**, **3a**; and v) a borderline compound **3b** between non-aromatic and homoaromatic. The homoaromaticity of **2a** is probably related to its folded structure with a C2 ··· C7 homoaromatic distance of 2.429 Å.

Conclusions

1*H*-Azepines and their cations cover the whole range of aromatic situations, from aromatic cations to antiaromatic neutral molecules to non-aromatic compounds like **2b**. Noteworthy is the fact that **3b**, although never observed, is the intermediate proposed for the oxidation of **1b** in acidic medium.[18]

Table 4 NICS(0)[a] values in ppm (B3LYP/6-311++G**//B3LYP/6-311++G**)

Compound	NICS(0)	Compound	NICS(0)
1a	−11.12	**1b**	−8.10
2a	4.93	**2b**	0.12
3a	4.78	**3b**	3.25
4a	−0.76	**4b**	−1.49
5a	−1.23	**5b**	−1.90

[a] Calculated at 0 Å of the ring center.

Experimental

Materials

Compounds 5*H*-dibenz[*b*,*f*]azepine **1b** and 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (iminodibenzyl) **4b** are commercial (Aldrich) and were used without further purification.

NMR spectroscopy

The ^{1}H and ^{13}C spectra in solution were recorded on a Varian Unity 500 instrument working at 499.88 MHz (^{1}H) and 125.71 MHz (^{13}C) using standard conditions. Chemical shifts (δ) in ppm are referred to external TMS. When using H_2SO_4 as solvent, a capillary containing DMSO-d_6 was introduced in the NMR tube both as lock and reference.

Computational details

Initially, the geometry optimisation as well as the frequency calculations were carried out at the B3LYP/6-31G* level of the theory.[19,20] Afterwards, the structures were optimised at the B3LYP/6-311++G** level.[21] For compounds of the **a** series, supplementary calculations were carried out at the MP2/6-311++G** level.[22] The absolute shieldings and NICS were calculated over the second geometry within the GIAO approximation at the B3LYP/6-311++G** computational level.[23] All these calculations were carried out using the Gaussian 98 facilities.[24]

Acknowledgements

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