The behavior of 5*H*-dibenz[*b*,*f*]azepine dissolved in sulfuric acid

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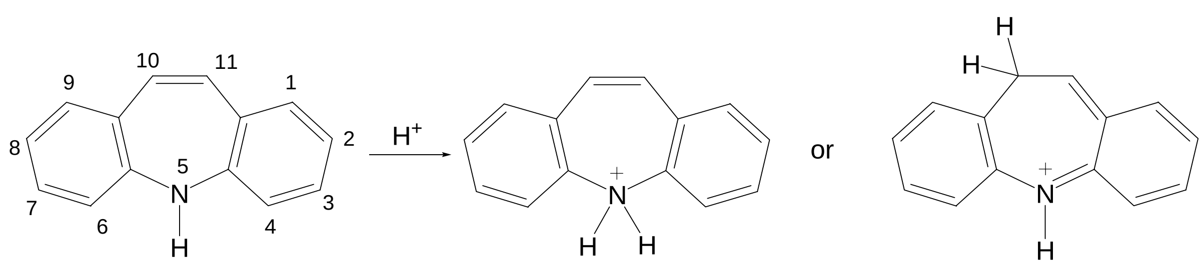
Dedicated to Professor Binne Zwanenburg on his 70th anniversary
(received 17 Dec 03; accepted 27 Mar 04; published on the web 08 Apr 04)

Abstract
When 5*H*-dibenz[*b*,*f*]azepine is dissolved in pure sulfuric acid it undergoes an oxidative dismutation into two acridine derivatives: 9-formylacridine and 9,9'-ethene-1,2-diyl-bis-acridine.

Keywords: Azepine, acridine, dismutation, rearrangement, NMR

The structure of 1*H*-azepines and their dibenzo derivatives, both neutral and protonated, is of interest being related to aromaticity and antiaromaticity.[1] To determine the protonation site of 5*H*-dibenz[*b*,*f*]azepine (**1**), either on the nitrogen, **2H**$^+$ (non aromatic), or on the carbon, **3H**$^+$ (homoaromatic) (Scheme 1) we dissolved it in an acid and observed, by ^{1}H and ^{13}C NMR, that the cation had the structure **2H**$^+$ (symmetry and absence of a CH_2).[1]

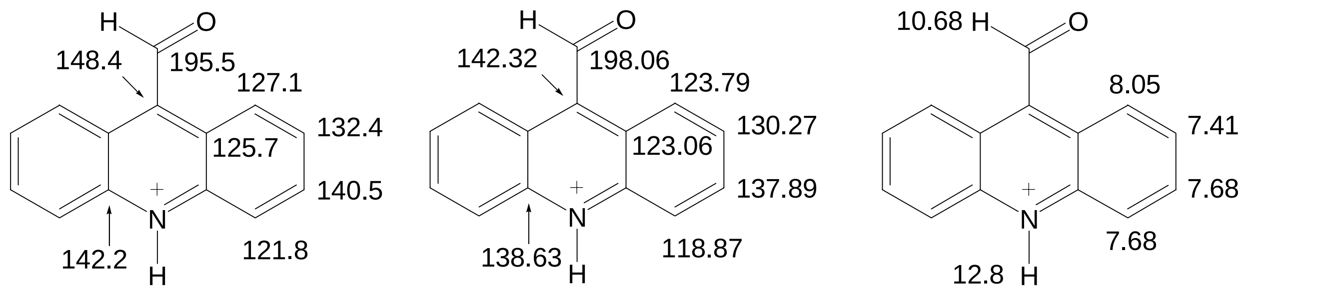


1 **2H**$^+$ **3H**$^+$

Scheme 1

We also observed that cation **2H**$^+$ underwent a rearrangement if H_2SO_4 was used (even after Ar has been bubbled through it). Thus, the signals corresponding to **2H**$^+$ disappeared and those of two new cations, **4H**$^+$ and **5H$_2$**$^{++}$, appeared. In contrast, the spectra remained unaltered when the solvent was pure CF_3CO_2H. Cations **4H**$^+$ and **5H$_2$**$^{++}$ were formed in a 1:1 mixture (by integration of the ^1H NMR signals at 7.32 and 7.41 ppm). This mixture seemed indefinitely stable (several months) in a stoppered NMR tube, suggesting that there was no interconversion between **4H**$^+$ and **5H$_2$**$^{++}$.

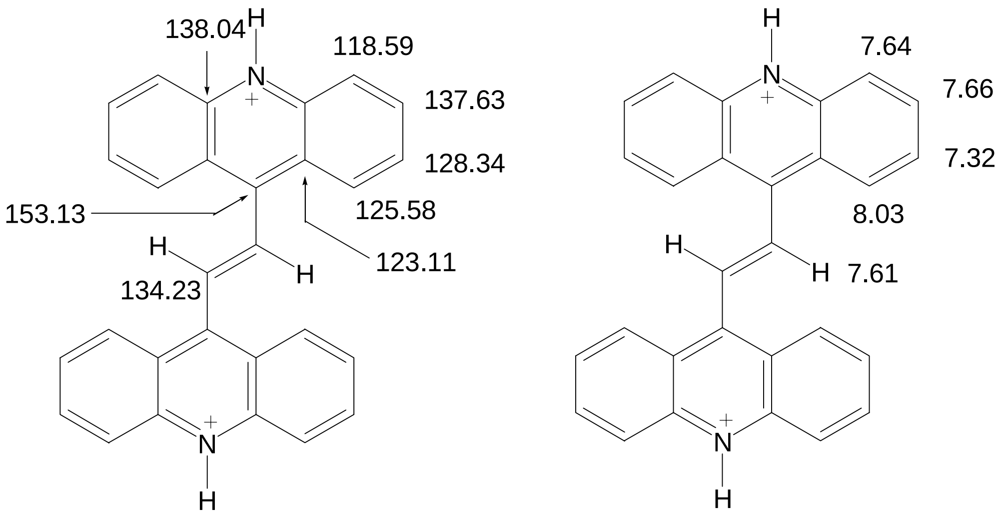
It is known that dibenz[*b*,*f*]azepines, depending on the experimental conditions, can undergo ring contraction yielding acridine,[2] 9-methylacridine,[3a] or 9-formylacridine.[3b] We identified the cation **4H**$^+$ as protonated 9-formylacridine (**4**) because we had, in another context, prepared **4** and recorded its NMR spectrum in CF_3CO_2H (Scheme 2).[4]



4H$^+$ (CF_3CO_2H)[3] ^{13}C NMR | **4H**$^+$ (H_2SO_4) ^{13}C NMR | **4H**$^+$ (H_2SO_4) ^1H NMR

Scheme 2

The analysis of the ^1H and ^{13}C NMR signals of the other cation (**5H$_2$**$^{++}$, see below) in H_2SO_4, suggested that it is also an acridine derivative. A series of 2D NMR experiments (HMQC, HMBC, NOESY, ROESY) allowed the determination of its structure as being the protonated form of 9,9'-ethene-1,2-diyl-bis-acridine (**5**) (Scheme 3). When a solution of the compound in sulfuric acid was poured into water, a yellow solid precipitated. This was the sulfate of **5 ($SO_4^=$ 5H$_2^{++}$)**, with a mass of 382 Da ($C_{28}H_{18}N_2$). Unfortunately, we have not been able to isolate **5**. This compound has been described only once, by Japanese authors[5] who obtained it as a by-product of the reaction of 9-bromomethylacridine with triethylphosphite (yield 9 %).



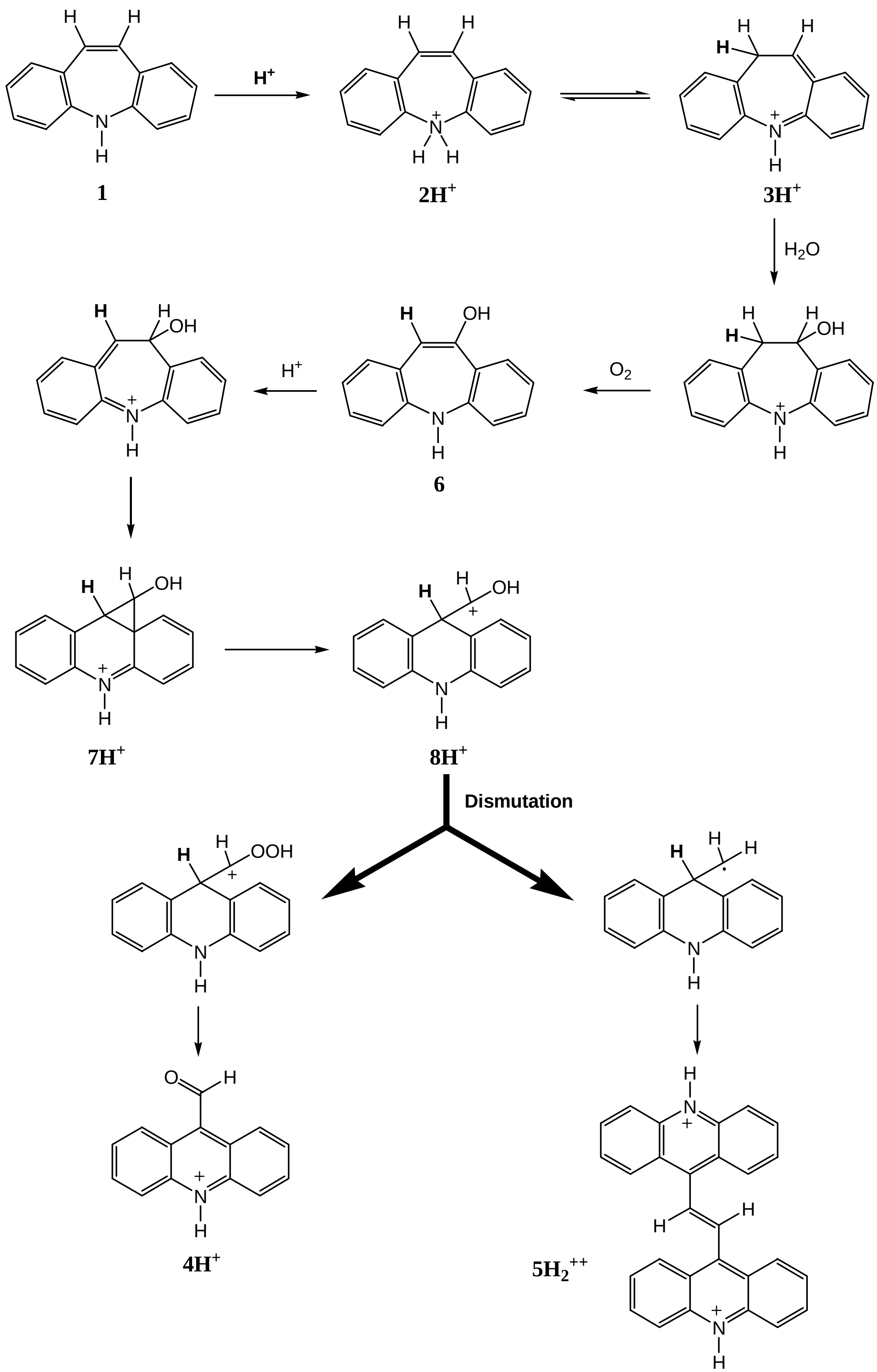
$5H_2^{++}$ (H_2SO_4) ^{13}C NMR

$5H_2^{++}$ (H_2SO_4) ^{1}H NMR

Scheme 3

Taking into account that **$5H_2^{++}$** contains two equivalent acridine moieties, the ratio calculated by integration of the ^1H NMR signals at 7.32 (**$5H_2^{++}$**) and 7.41 ppm (**$4H^+$**), corresponds to a 1:2 ratio of **$5H_2^{++}$**/**$4H^+$**. When the sulfate of **$5H_2^{++}$** was dissolved in H_2SO_4**,** it was stable and no formation of **$4H^+$** was observed. Finally, when 5*H*-dibenz[*b*,*f*]azepine **1** was dissolved in D_2SO_4, the same mixture of **$4H^+$** and **$5H_2^{++}$** was formed. Neither **$4H^+$** (no D in the CHO group) nor **$5H_2^{++}$** (no D in the olefin part) incorporated deuterium atoms (as shown by integration in ^1H NMR).

Based on our results and on previous mechanistic studies for the acid catalyzed rearrangements of 5*H*-dibenz[*b*,*f*]azepine,[3] we propose a simplified scheme for the formation of cations **$4H^+$** and **$5H_2^{++}$** (Scheme 4). First, the *N*-protonation of **1** affords **$2H^+$** that isomerize to the quinone imonium ion **$3H^+$**.[6] This cation (**$3H^+$**) is less stable than the *N*-protonated one (**$2H^+$**) and suffers a hydration followed by an oxidation process leading to the enol **6** (neither this enol nor its more stable keto tautomer were observed in the NMR spectra). Another C-protonation and a Wagner-Meerwein rearrangement lead to an acridine derivative **$7H^+$**. Finally, the cyclopropyl ring opens to the carbenium **$8H^+$** which suffers a dismutation leading to an oxidized aldehyde **$4H^+$** and a reduced olefin **$5H_2^{++}$**. With this sequence, the deuterium atom incorporated with the use of D_2SO_4 would disappear in the last steps, which is in agreement with the experimental results (vide supra). However, this mechanistic proposal needs further experimental confirmation.



Scheme 4

In an attempt to determine whether the structure of **5** in sulfuric acid corresponds to a mono- (**5H**$^+$) or a diprotonated cation (**5H**$_2^{++}$), we have calculated, assuming free rotation about the C(9)-C(11) bond, the ^{13}C absolute shieldings (σ, ppm, see Computational details) of **4**, **4H**$^+$, **5H**$^+$ and **5H**$_2^{++}$ and compared them to the experimental results (Table 1). To this aim, we have optimized the geometries of the compounds at the B3LYP/6-311++G** level of the theory. Over these geometries, the absolute shieldings were calculated with the GIAO method (for details see after the Experimental Part).

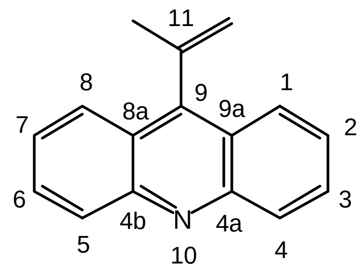


Table 1. ^{13}C Absolute shieldings of compounds **4**, **4H**$^+$, **5H**$^+$ and **5H**$_2^{++}$. Neutral aldehyde (δ, ppm, solvent: acetone-d_6)

Atom	**4**	**4** (exp.)[4]	**4H**$^+$	**5H**$^+$	**5H**$_2^{++}$
C(1)	53.86	123.6	48.34	52.02	50.53
C(2)	48.00	128.3	45.35	47.74	45.68
C(3)	49.15	130.0	34.07	42.14	33.42
C(4)	44.20	129.8	60.42	51.03	58.52
C(4a)	27.28	148.9	37.87	33.58	39.04
C(8a)	53.50	123.2	54.37	54.34	53.80
C(9)	50.44	132.7	26.99	51.03	19.50
C(11)	−15.55	194.2	−13.99	35.48	36.54

A statistical treatment of these data showed that molecule **5** was diprotonated in H_2SO_4 (the most discriminating signal is that of C(9), Δσ = 31.5 ppm]. Using the σ values of the dication **5H**$_2^{++}$ the following equation was obtained:

$$\delta(\text{ppm}) = (176.7\pm1.7) - (1.02\pm0.44)\ \sigma(\text{ppm}),\ n = 24,\ r^2 = 0.97$$

In conclusion, this study reports an unprecedented example of dismutation of the parent 5*H*-dibenz[*b*,*f*]azepine that could be extended to other compounds and, since the transformation is complete, could even have preparative interest.

Experimental Section

General Procedures. Melting points were determined with a Gallenkamp apparatus and are uncorrected. Electrospray mass spectra were recorded on an MSD-Serie 1100 Hewlett Packard apparatus. High resolution mass spectrum was recorded using FAB ionization and NOBA matrix on a VG AutoSpec apparatus.

Reaction of 5*H*-dibenz[*b*,*f*]azepine (1) with H_2SO_4. argon was bubbled into a solution of **1** (350 mg) in concentrated H_2SO_4 95-98% (10 mL). The reaction mixture was allowed to stand at room temperature under an argon atmosphere for two weeks. The crude reaction mixture was poured into crushed ice and the resulting mixture was allowed to stand overnight. The precipitated solid was collected by filtration and rinsed successively with water, EtOH and Et_2O to afford a mixture of $\mathbf{4H}^+$ and $\mathbf{5H_2}^{++}$. Part of the crude sample was heated in a mixture of CH_3CN/H_2O/EtOH and filtered hot. The mother liquor was allowed to stand in the fridge for two days. The solid was collected by filtration and rinsed successively with EtOH and Et_2O to afford $\mathbf{5H_2}^{++}$ as its sulfate salt. Brown solid; mp > 350 °C; LRMS (ES^+) *m/z* 383 [M+H]; HRMS (FAB) *m/z* 383.1559 ($C_{28}H_{19}N_2$ requires 383.1548).

Isolation of 9-formylacridine (4) from the crude sample. the crude mixture was stirred with aqueous K_2CO_3 (20 mL) and toluene (20 mL) for 2 days. The aqueous phase was extracted with toluene. Combined toluene extracts were dried ($MgSO_4$) and concentrated to give **4** as a yellow solid; mp 148-149 °C [Litt.[7] 149-150 °C].

Materials. 5*H*-Dibenz[*b*,*f*]azepine **1** is commercial (Aldrich) and was used without further purification.

NMR spectroscopy. The ^1H and ^{13}C spectra in solution were recorded on a Varian Unity 500 instrument working at 499.88 (^1H) and 125.71 (^{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.[8,9] Afterwards, the structures were optimised at the B3LYP/6-311++G** level.[10] The absolute shieldings and NICS were calculated over the second geometry within the GIAO approximation at the B3LYP/6-311++G** computational level.[11] All these calculations were carried out using the Gaussian 98 facilities.[12]

Acknowledgements

Thanks are given to the DGI/MCyT of Spain for financial support (project number BQU-2000-0645), and to the European Community for a Marie Curie individual Fellowship (program: “Improving Human Research Potential and the Socio-economic Knowledge Base”, contract number: HMPF-CT-2001-01120). CD thanks the Spanish MECD for a grant (SB2001-0174).

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