Aromaticity

Synthesis of a Delocalized Azepinium Ion and Investigation of Its Electrophilic Character**

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The aromatic azepinium ion **1** is a topic of fundamental interest in connection to its isoelectronic hydrocarbon analogue, the tropylium ion **2** (Scheme 1). Theoretical investigations predict that azepinium ions should be a stable aromatic ion rather than a species with a triplet state,[1,2] however, to date, the synthesis of the heterocyclic ion has not been reported. So far, evidence for the azepinium ion is limited to the MS fragment ions of anilines,[3] isoquinoline derivatives[4] and phenyl azides.[5] The formation of the ion has also been deduced from the electrode reaction of a 3*H*-azepine derivative by inspection of its cyclic voltammogram.[6] On the other hand, cycloheptatriene (CHT; **2H**) was observed to react with an equivalent of bromine or a trityl cation to give **2**,[7] the high stability and low electrophilic reactivity of which has been rationalized by resonance energy.[8] Our similar approach using 3*H*-azepine derivatives to generate the azepinium ion by the action of bromine or trityl cation was unsuccessful. The result suggests that **1** is unstable compared to the hydrocarbon analogue **2**. In studying the chemistry of 3*H*-azepines, we established a new procedure for the synthesis of 2-methoxy-2*H*-azepine derivatives from 3*H*-azepine derivatives.[9] Since 2*H*-azepine is considered to be another good precursor for an azepinium ion, generation of the ionic species by acid-promoted ether bond cleavage was examined. Herein, we report evidence for the formation of an azepinium ion from the reaction between a 2-methoxy-2*H*-azepine derivative and titanium tetrachloride ($TiCl_4$).

1 **2**

Scheme 1. The azepinium ion **1** and the tropylium ion **2**.

When an excess of $TiCl_4$ was added to a $CDCl_3$ solution of 4,7-di-*tert*-butyl-2-methoxy-2*H*-azepine (**3a**, see Scheme 2) in an NMR sample tube, all the resonance signals attributed to **3a** vanished and new signals that indicate four ring protons ($\delta = 8.10$, 8.11, 8.78, and 9.24 ppm), two *tert*-butyl groups ($\delta =$ 1.48 and 1.55 ppm), and $[TiCl_4(OMe)]^-$ ($\delta = 4.8$ ppm) were observed. This spectral change suggests that all the ring

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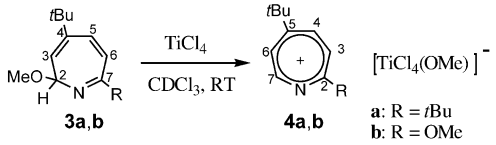
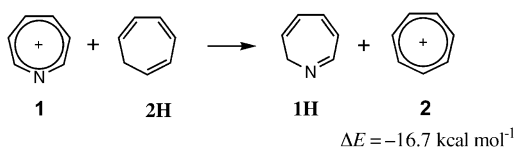
carbon atoms are sp^2 hybridized. This assumption was confirmed by the measurement of C–H coupling constants ($^1J_{C,H}$) for the ring carbon atoms resonating at $\delta = 133.1$ ($J =$ 169 Hz), 133.7 ($J = 166$ Hz), 150.0 ($J = 160$ Hz), and 158.6 ppm ($J = 191$ Hz). The NMR spectroscopic data supports the formation of the ionic species **4a** by Lewis acid promoted demethoxylation. Treatment of 4-*tert*-butyl-2,7-dimethoxy-2*H*-azepine (**3b**) with $TiCl_4$ showed a similar change in the NMR spectrum, which suggests the formation of ionic species **4b** (Scheme 2). Attempts to isolate the salt failed owing to its instability, thus detection of the ion was



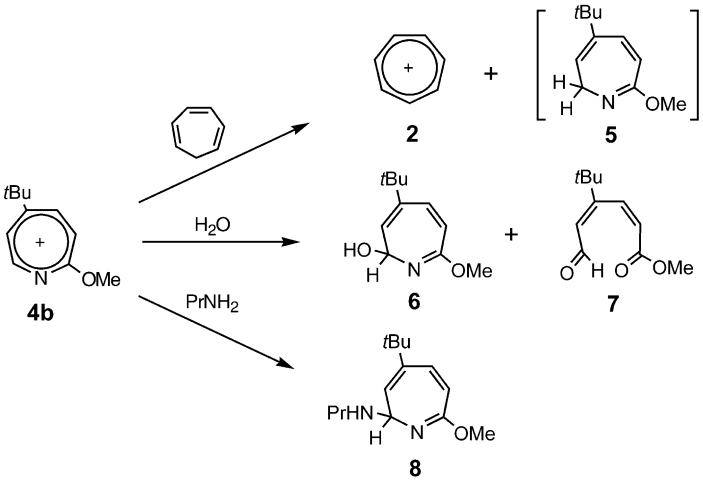
Scheme 2. Generation of azepinium ions (**4a,b**) from 2*H*-azepine derivatives (**3a,b**).

limited to the solution in which it was generated. Complete assignment of ^1H and ^{13}C NMR spectra were performed by heteronuclear correlation spectroscopy using HMQC[10] and HMBC[11] techniques (Table 1). Interestingly, despite two asymmetrically located substituents, the β- and β′-positions (3- and 6-positions) of ion **4a** give rise to resonance signals with almost the same ^1H and ^{13}C NMR chemical shifts. If the positive charge is delocalized, these positions must be equivalent when the ring has no substituents. As the electronic perturbation of *tert*-butyl group is considered to be small, the NMR spectral data attained for **4a** suggests the induced positive charge is delocalized.

Displacement of an sp^2 carbon atom with a more electronegative sp^2 nitrogen atom is expected to destabilize the conjugated system. To rationalize this expectation, ab initio energy analysis of an isodesmic reaction (Scheme 3) between **1** and **2H** (CHT) was performed at a level of B3LYP[12] with the 6-31G(d) basis set using the Gaussian 98[13] program. Calculated energies for **1**, **1H**, **2**, and **2H** were −286.6891, −287.5468, −270.6786, and −271.5096 a.u., respectively. The hydride affinity of **1** is greater than that of **2** by 16.7 kcal mol^{-1} reflecting the decrease in the aromatic resonance energy, that is, the increase in electrophilicity. To confirm the relative hydride affinity between **4b** and **2**, demethoxylation of **3b** (→ **4b**) was performed in the presence of CHT in an NMR tube (Scheme 4). The reaction mixture showed a complex spectrum, however, a prominent singlet at $\delta = 9.38$ ppm was



Scheme 3. An isodesmic reaction between **1** and cycloheptatriene (**2H**) giving 2*H*-azepine (**1H**) and **2**.



Scheme 4. Observed reactions of 5-*tert*-butyl-2-methoxyazepinium (**4b**) with cycloheptatriene, water, and propylamine.

observed in place of the set of peaks attributed to **4b**, which suggests the formation of **2** based on the reported chemical shift of $\delta = 9.33$ ppm in CD_3CN.[14] This result explains that the azepinium **4b** is a stronger electrophile and has decreased resonance energy in comparison to **2**, however, clear spectral evidence for the expected product **5** was not found under these conditions. To obtain more evidence for the structure assignment of the azepinium ion, a GIAO ^{13}C chemical shift calculation[15] (B3LYP6-311 + G(2d,p)) based on the optimized geometry of **1** was performed. Calculated δ_C values for Cα, Cβ, and Cγ were 184.3, 148.1, and 164.0 ppm, respectively. Although overestimation of experimental δ_C values by 15–25 ppm resulted, this calculation and experimental data agree that the minimum shielding in the ring is at Cα and the maximum shielding is at Cβ.

The tropylium ion **2** typically reacts as an electrophile with basic nucleophiles to give the correspondingly substituted cycloheptatriene derivatives.[16] When freshly generated **4b** was quenched with an excess of water, 4-*tert*-butyl-7-

Table 1: Observed ^{13}C and ^1H chemical shifts, and selected coupling constants ($^1J_{C,H}$ and $^3J_{H,H}$) for the ring carbon atoms and ring protons of azepinium ion **4a** and **4b** in $CDCl_3$.

Compound	^{13}C Chemical shifts [ppm] ($^1J_{C,H}$ [Hz])						^1H Chemical shifts [ppm]				$^3J_{H,H}$ [Hz]		
	C2	C3	C4	C5	C6	C7	C3-H	C4-H	C6-H	C7-H	$J_{3,4}$	$J_{4,6}$	$J_{6,7}$
4a	187.5	133.1	150.0	180.0	133.7	158.6	8.11	8.78	8.10	9.24	11.1.	2.4	4.7
	–	(168.5)	(160.4)	–	(166.2)	(190.7)							
4b	176.0	131.0	150.8	181.2	134.5	170.2	7.81	8.61	8.19	9.36	11.7	2.1	6.0
	–	(170.7)	(161.4)	–	(163.8)	(185.6)							

methoxy-2*H*-azepin-2-ol (**6**)[17] was isolated in 45% yield along with hydrolyzed methyl 4-*tert*-butyl-6-oxo-hexa-2Z,4E-dienoate (**7**)[18] in 24% yield (see Scheme 4). A pattern of signals for four ring protons similar that of **3b** and the appearance of a new signal attributed to an alcoholic proton (D_2O exchangeable) at $\delta = 2.65$ ppm supports the 2-hydroxy-2*H*-azepine structure of **6**. When propylamine was used in place of water, 4-*tert*-butyl-7-methoxy-2-propylamino-2*H*-azepine (**8**)[19] was obtained in 85% yield as a single product. The highfield shift of the resonance signal of C2-H by 0.93 ppm compared to **6** indicates the replacement of the hydroxy by the propylamino group connected to the 2-position of the 2*H*-azepine ring. Regioslectivity of the reaction can be explained by the frontier molecular orbital interaction[20] between a nucleophile and the ion **4b**. The most important orbital is considered to be the π_{LUMO} of **4b**, for which AM1[21] calculated orbital profiles are illustrated in Figure 1. Selective formation of 2-substituted 2*H*-azepine can be explained by an effective mutual interaction between the nucleophile and the carbon atom with the largest orbital coefficient.

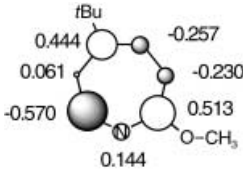


Figure 1. AM1 calculated π_{LUMO} for azepinium ion **4b**. Values indicate the orbital coefficients of each ring atom.

Proposed NMR spectral data and the results of nucleophilic reactions suggest the formation of a hitherto unknown azepinium ion, which is less stable than tropylium.

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[17] Selected data for **6**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.11$ (s, 9H), 2.65 (brs, 1H), 3.70 (s, 3H), 4.68 (d, $J = 4.2$ Hz, 1H), 5.79 (dd, $J = 4.2$, 1.0 Hz, 1H), 6.47 (d, $J = 12.0$ Hz, 1H), 6.96 ppm (dd, $J = 12.0$, 1.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 29.5$, 34.4, 53.8, 80.6, 124.6, 130.4, 139.6, 144.9, 158.5 ppm; IR (neat): $\tilde{\nu} = 3370$ cm^{-1} (O-H); UV/Vis (EtOH): λ_{max} (log ε) 277 nm (3.03); MS (FAB): *m*/*z* 196 $[M+H]^+$.
[18] Selected data for **7**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.19$ (s, 9H), 3.66 (s, 3H), 6.05 (dd, $J = 7.5$, 1.5 Hz, 1H), 6.23 (d, $J = 12.5$ Hz, 1H), 6.74 (dd, $J = 12.5$, 1.5 Hz, 1H), 9.69 ppm (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 28.8$, 37.5, 51.5, 125.1, 125.4, 139.1, 165.0, 168.0, 193.1 ppm; IR (neat): $\tilde{\nu} = 1734$, 1676 cm^{-1} (C=O); UV/Vis (EtOH): λ_{max} (log ε) 236 nm (4.02); MS (FAB): *m*/*z* 197 $[M+H]^+$.
[19] Selected data for **8:** m.p. 75.5–77.0°C; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.95$ (t, $J = 7.2$ Hz, 3H), 1.07 (s, 9H), 1.50–1.60 (m, 2H), 1.70 (brs, 1H), 2.51–2.57 (m, 1H), 2.93–2.99 (m, 1H), 3.66 (s, 3H), 3.75 (d, $J = 4.8$ Hz, 1H), 5.62 (d, $J = 4.8$ Hz, 1H), 6.46 (d, $J = 12.0$ Hz, 1H), 6.92 ppm (d, $J = 12.0$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 12.0$, 23.4, 29.6, 34.5, 48.0, 53.4, 70.3, 124.5, 128.9, 139.0, 145.8, 159.5 ppm; IR (KBr): $\tilde{\nu} = 3260$ cm^{-1} (N-H); UV/Vis (EtOH): λ_{max} (log ε) 276 nm (3.07); MS (FAB): *m*/*z* 237 $[M+H]^+$.
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