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Relative Stabilities of Pyrylium Anhydrobases (α/γ-Methylenepyrans) and their N-Methylpyridinium Congeners

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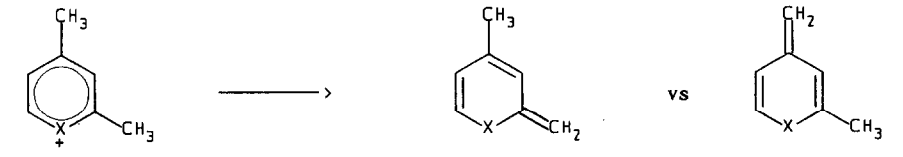
Summary: Semiempirical (MNDO, AM1 and PM3) as well as ab initio (MP2/6-31G*//6-31G*) calculations indicate that γ-methylenepyrans are more stable than their α-methylenepyran isomers (pyrylium anhydrobases). This provides an explanation for the higher rate of hydrogen isotope exchange of γ- over α-methyl substituted pyrylium salts in protic media, since transition states related in energy to these methylenepyran intermediates evidently are involved. Conversely, for substituted N-methylpyridinium salts, the calculations indicate the opposite α- vs γ-stability order and support a similar explanation for the lower rate of hydrogen isotopic exchange at the γ- than at the α-methyl groups.

Surprisingly, the side-chain deuterations of pyrylium salts[1-5] and of similarly substituted pyridinum salts[6] prefer different sites. As indicated in Scheme 1, H/D exchange occurs predominantly at the 4-methyl (γ-position) in **1** but at the 2- and 6-methyls (α-positions) in **2**. We have now examined the reasons for these opposite α vs γ-methyl deuteration preferences in pyrylium vs pyridinium cations computationally.

The exchange rates, followed by H-NMR spectroscopy on the pyrylium perchlorates **1** and **3**, were carried out in buffered deuterium oxide at pD 1 - 4[1-3] or in HCOOD + HCOONa.[4a] The reaction at the γ-methyl proceeds in non-buffered D_2O to completion at 80° in ten minutes, and with all methyls at 100° in one hour. The two different α-methyl groups in the 2,3,4,6-tetramethylpyrylium salt **3** do not undergo deuteration with equal rates (see Scheme 2)

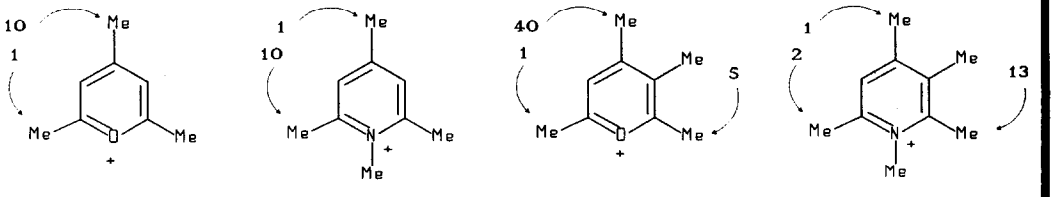
The H/D exchange reactions of the pyridinium salts[6] (1,2,4,6-tetramethyl-pyridinium **2** or 1,2,3,4,6-pentamethylpyridinium **4**) employed NaOD in D_2O.



X = O or NR preferred when X=NR preferred when X=O

Scheme 1

All these observations are in agreement with deprotonation mechanisms involving anhydrobases (α- or γ-methylenepyrans, **1-5**, X=O, or their pyridine analogues, X=NR) as intermediates. It is reasonable to assume that γ- methylenepyran is formed faster due to its greater stability than α-methylenepyran. Indeed, Our early MO computations indicated[7] lower energy for the γ- than for the α-methylenepyran. However, the energy differences were small and such simple levels of theory may not have given reliable results.



counterion: ClO_4^-

Relative rates of H/D exchange at the positions indicated. Note the differences in the α/γ reactivity ratios between corresponding pyrilium an pyridinium salts: **1** (1/10) vs **2** (10/1) and **3** (1 and S/40) vs **4** (2 and 13/1)

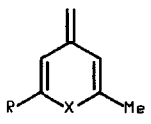
Scheme 2

Hence, we have now employed semiempirical MNDO, AM1 and PM3[9] as well as ab initio calculations[10] to reinvestigate this problem. While we focus on the α/γ-methylenepyrans which result from deprotonation of 2,4-di-, 2,4,6-tri-, and 2,3,4,6-tetramethyl-substituted pyrylium salts, our calculations have been extended to the NH- or NMe-pyridinium congeners of the O-heteroatom system. The MNDO, AM1 and PM3 enthalpies of formation are summarized in Table 1 for **5** - **9**. Although the heats of formation given by the three methods differ, the relative energies of the isomers are generally quite similar. The relative energies are our main interest.

The two anhydrobases (**5** and **6**) are obtained by deprotonating heterocyclic six-membered cationic systems with one heteroatom X (X=O, NH or NMe) with two (R=H) or with three (R=Me) carbon-bonded methyl groups in the α- and γ-positions. The data in Table 1 and 2 show that the pyran γ-anhydrobases **5**, X=O are generally more stable (lower in energy) than the isomeric α-anhydrobases **6**, X=O (the energy difference for the various semiempirical methods averages 0.5 kcal/mol for R=H, and 0.8 kcal/mol for R=Me). However, the reverse is true for the pyridinium anhydrobases: the γ- anhydrobases **5** are less stable than the α-anhydrobases (the energy differences average 0.8 kcal/mol for X=NH, R=H, and 1.0 kcal/mol for X=NMe, R=Me). This agrees with the relative order of deuteration rates observed experimentally (Scheme 2).

From the 2,3,4,6-tetramethyl-substituted systems, three different anhydrobases **7-9** may be obtained on deprotonation. The semiempirical results (Table 1 and 2) for the tetrasubstituted pyranic systems **7-9** (X=O) also agree with the experimental observation that the γ-methyl group is deuterated faster than α-methyl groups: **7** (X=O) is more stable than **8** (X=O) and **9** (X=O) by 1.0-1.1 kcal/mol. However they fail to discriminate between the two α-methylenepyrans: **8** and **9**, X=O. The calculated energy difference is too small (**8** is about 0.2 kcal/mol more stable than **9**) to be significant, while the experimental deuteration rates indicate that **9** ought to be slightly lower in energy than **8**.

With regard to the pentamethylpyridinium compounds **7-9**, X=NMe, the calculations predict rather more preference for **9** than is observed experimentally. Although the lower energy of **9** than of its isomers **7** and **8** agrees with the experimental data, the rate ratios are much smaller than the MNDO energy differences indicate. In addition, the experimental order for the two α-methyl groups is opposite to that found by MNDO (but the energy difference is only 0.5 kcal/mol between **7** and **8**). The calculations may overemphasize the steric effects present in the pyridinic



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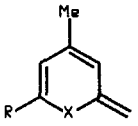

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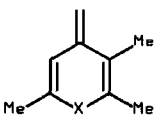

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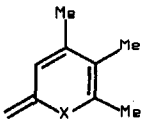

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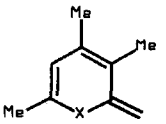

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Table 1a: Semi-empirical (MNDO,AM1, and PM3) heats of formation (kcal/mol) for 5 - 6

Compound/Method		X= O R= H	X= O R= Me	X= NH R= H	X= NH R= Me	X= NMe R= Me
5	MNDO	-4.8	-13.0	+36.7	+28.7	+38.4
	AM1	+4.6	- 1.6	+38.9	+31.9	+39.8
	PM3	+0.8	+ 0.4	+34.0	+24.2	+26.8
6	MNDO	-4.1	-12.0	+36.4	+28.4	+37.0
	AM1	+5.8	0.0	+38.3	+31.3	+39.3
	PM3	-4.2	- 7.3	+33.1	+23.2	+24.7

Table 1b: Semi-empirical (MNDO,AM1, and PM3) heats of formation (kcal/mol) for 7 - 9

Compound/Method		X= O	X= NH	X= NMe
7	MNDO	-16.1	+26.3	+34.7
	AM1	- 7.5	+28.0	+35.8
	PM3	-15.0	+17.2	+18.9
8	MNDO	-15.3	+26.1	+35.0
	AM1	- 6.3	+25.8	+34.6
	PM3	-14.7	+16.4	+17.5
9	MNDO	-15.0	+26.1	+32.9
	AM1	- 6.1	+26.5	+33.9
	PM3	-15.8	+15.1	+17.2

systems **7-9** (X=NMe): systems **7** and **8** (but not **9**) have four vicinal methyl groups. The same reasoning applied to the pyranic anhydrobases **7-9** (X=O) would suggest that the 6-methylenepyran **8** should have the highest energy: unlike **7** and **9**, **8** has three vicinal methyl groups. Indeed, the 6-methyl group undergoes the slowest deuteration. The importance of buttressing and steric effects in 6-membered heterocyclic systems has been documented recently.[8] Due to the small energy differences and the possible limitations in the accurracy of semiempirical methods, the relative energies the unsubstituted α- and γ-methylenpyrans and pyridine analogues **10** - **13** also were calculated at adequate ab initio levels.[10]

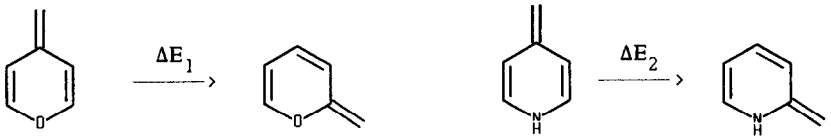
Table 2: Calculated and estimated experimental relative energies (kcal/mol) for 5 - 9.

	Comp.	MNDO	AM1	PM3	Exp.[a]
X = O, R = H	5 / 6	+ 0.7	+ 1.0	- 0.4	--
X = O, R = Me	5 / 6	+ 1.0	+ 1.6	+ 0.4	+ 1.6
X = NH, R = H	5 / 6	- 0.3	- 0.6	- 0.9	--
X = NH, R = Me	5 / 6	- 0.3	- 0.6	- 1.0	--
X = NMe, R = Me	5 / 6	- 1.4	- 0.5	- 2.1	- 1.6
X = O	7 / 8	+ 0.8	+ 1.2	+ 0.3	+ 2.6
	7 / 9	+ 1.1	+ 1.4	- 0.8	+ 1.5
	8 / 9	+ 0.3	+ 0.2	- 1.1	- 1.1
X = NH	7 / 8	- 0.2	- 2.2	- 0.8	--
	7 / 9	- 0.2	- 1.5	- 2.1	--
	8 / 9	0.0	+ 0.7	- 1.3	--
X = NMe	7 / 8	+ 0.3	- 1.2	- 1.4	- 0.5
	7 / 9	- 1.8	- 1.9	- 1.7	- 1.8
	8 / 9	- 2.1	- 0.7	- 0.3	- 1.3

a) Estimated from the experimental data for T = 353 K

The ab initio results , presented in Table 3, confirm the semiemipirical findings nicely. At the highest level employed (MP2/6-31G*//6-31G*), γ-methylenepyrane **10** is less stable than the α-methylenepyrane **11** by 2.3 kcal/mol. For the NH-pyridinium congeners, the α-picoline tautomer **13** is 0.14 kcal/mol more stable than the γ-picoline tautomer **12** . Note that all levels of theory predict the same stability order, **10** < **11** and **12** **13**,in Table 3. These differences can be ascribed to the preference for a smaller angle at oxygen, which is accomodated better in the more symmetrical **10**.

Table 3: MNDO/AM1/PM3 and ab initio calculations of the energy differences of the parent compounds.



10 11 12 13

	10	11	ΔE_1	12	13	ΔE_2
MNDO	+ 3.5	+ 4.1	+ 0.6	+ 45.4	+ 44.0	- 1.4
AM1	+ 10.8	+ 13.9	+ 3.1	+ 45.9	+ 45.8	- 0.1
PM3	+ 8.8	+ 10.3	+ 1.5	+ 43.8	+ 42.8	- 1.0
3-21G//3-21G	-303.80770	-303.78290	+ 0.48	-284.09896	-284.10120	- 1.40
6-31G*//3-21G	-305.45719	-305.45410	+ 1.94	-285.68685	-285.68724	- 0.25
MP2/6-31G*//3-21G	-306.41889	-306.41564	+ 2.04	-286.63282	-286.63313	- 0.20
6-31G*//6-31G*	-305.50790	-305.50457	+ 2.09	-285.68701	-285.68741	- 0.25
MP2/6-31G*//6-31G*	-306.46452	-306.46092	+ 2.25	-286.59971	-286.59993	- 0.14

All absolute energies are in kcal/mol for semiempirical methods and in Hartrees for the ab initio calculations. The energy differences, ΔE_1 and ΔE_2, are given in kcal/mol.

We speculate that a gradual transition between the contrasting influence of O vs. NR (R = H or Me) might be achieved by attaching acceptor groups to the nitrogen heteroatom in pyridinium salts, eg. R'=CN, SO_3^-, NO_2 or 2,4-dinitrophenyl. Indeed, all such pyridinium salts readily undergo ring-opening on nucleophilic attack, just like pyrylium salts, and unlike N-alkylpyridinium salts or pyridine-N-oxides. It will be interesting to investigate relative rates of α/γ-methyl deuteration in such pyridinium salts with acceptor N-bonded groups.

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