Unique Charge-Separated Pyridinium-Barbituric Acid Zwitterions

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Abstract: A synthetic procedure for the preparation of the unusual charge-separated pyridinium barbiturate zwitterion **2** from 1,3-dimethylbarbituric acid and 2-pyridinecarbaldehyde in methanol was developed. The structure of the compound was confirmed with X-ray analysis to demonstrate the strong charge separation throughout the molecule. One would expect that this charge separation would increase its reactivity; however, contrary to this expectation, the compound is very stable in acidic media, and in the presence of a base, decarbonylation occurs on one barbituric acid while the zwitterionic moiety of the molecule stays intact.

Pyridinium zwitterions are widely used in organic synthesis.[1] Usually, these compounds are very reactive species that should be kept at low temperatures and in an inert atmosphere. The majority of these zwitterions are synthesized by first preparing the pyridinium salt, followed by the elimination of an acid in reaction with a base. However, there are some other routes that are one-step syntheses that utilize the capability of pyridine derivatives to add to reactive double bonds or to trap carbenes.[2] The 1,4-dihydropyridine addition to alkoxycarbene complexes of transition metals has been shown to produce pyridinium zwitterions whose negative charge resides on the transition metal, and as such, they are used for selective cyclopropanation.[3] In the majority of cases, the negative ion is on the carbon attached to the pyridinium nitrogen and delocalized by the presence of electron-withdrawing substituents.[1]

Pyridinium-cyclopentadienylide is probably the most theoretically explored pyridinium zwitterion with aromatic stabilization of a negative charge.[4] Yet, even in this case, the molecule has low stability and little is known about its reactivity.[5] To make pyridinium cyclopentadienylide sufficiently stable for structure determination in order to evaluate its reactivity, the cyclopentadienide moiety must have strong electron-withdrawing groups, as in the case of pyridiniotetrabromocyclopentadienides.[6]

Here we present our method for the preparation of a pyridinium zwitterion (**2**) with an aromatic stabilization of the negative charge[7] (Scheme 1). This compound was synthesized through controlled condensation between 1,3-dimethyl barbituric acid and 2-pyridinecarbaldehyde. There are previous data that suggest that if the reaction between the barbituric acid derivative and an electron-rich aromatic aldehyde is performed, then the Knoevenagel condensation[8] product **4** must be the major product isolated (Scheme 2).[9] However, there are some cases of unexpected condensation products, as in the case of electron-poor aromatic aldehydes like nitrobenzaldehyde, when the double addition product of type **1** is obtained (Scheme 1).[10] Considering the similarities in the electronic properties of 2-nitrobenzaldehyde and 2-pyridinecarbaldehyde, it should be expected that the isolated product of the condensation between 2-pyridinecarbaldehyde and substituted barbituric acids should be of type **1**. This, however, is not the case. In almost quantitative yield, the isolated product of this condensation is **2**.

Our attempt to actually isolate the Knoevenagel condensation product **4** in the reaction between 1,3-dimethyl barbituric acid and 2-pyridinecarbaldehyde was not successful, regardless of the nature of solvent or base and acid used in this reaction. From NMR spectra taken during the reaction, we know that intermediate **4** is formed and almost instantly consumed in nucleophilic addition of the barbituric acid (product **1**). When a better nucleophile is not present in the reaction mixture, then the nitrogen of the pyridine moiety of **4** acts as a nucleophile to another molecule of **4**, producing the pyridinium zwitterion **5**, which rearranges into the more stable pyridinium zwitterion **2**. Both of these zwitterions contain negatively charged barbituric acid rings.

Although we do not have direct evidence for the formation of pyridinium zwitterion **5**, we have indirect experimental information that strongly supports its existence. For instance, if the reaction is performed in acetic acid, then the practically insoluble polymeric product was obtained.[11] Another indication is that it was not possible to prepare type **2** zwitterions if 1-methyl, 1-phenyl, or

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(6) Figala, V.; Gessner, T.; Gompper, R.; Hädicke, E.; Lensky, S. *Tetrahedron Lett.* **1993**, *34*, 6375−6378.

(7) In barbituric acids, amide resonance dominates over the aromaticity. With a negative charge on the barbituric acid ring, it is reasonable to assume that p−p atomic orbital overlap between atoms in the ring should increase.

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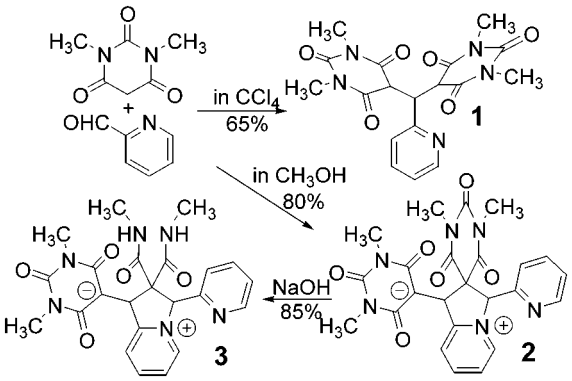
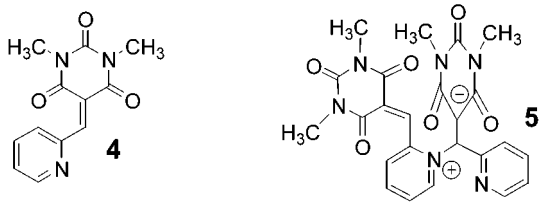
Scheme 1. Synthetic Path for Preparation of Two Pyridinium-barbituric Acid Zwitterions



Scheme 2. Proposed Reactive Intermediates



unsubstituted barbituric acid was used instead of the disubstituted 1,3-dimethyl barbituric acid in the condensation reaction with 2-pyridinecarbaldehyde.[12]

Pyridinium zwitterion **2** shows some interesting chemical properties. One would expect that due to the negative charge localized on the barbituric acid ring, zwitterion **2** would be very sensitive to protic solvents. Yet, it is stable in water, alcohol, and acetic acid. In fact, the compound is stable in hot acetic acid.[13] In long-term NMR experiments in acetic acid at room temperature (30 days), only proton−deuterium exchange products were observed. This proton exchange in a modest acid such as acetic acid is characteristic of an aromatic ring.[14]

Another surprise comes from the stability of the pyridinium zwitterion skeleton in basic solution. One would expect that in aqueous sodium hydroxide, the five-membered ring of **2** opens. Instead, the barbituric acid ring that is not part of the pyridinium zwitterion substructure is opened and the decarbonylation product **3** is isolated. This is a typical reaction for highly substituted barbituric acids.[15] If the reaction is performed in polar solvents such as DMSO and methanol, the formation of pyridinium zwitterions **2** and **3** should be favored. NMR

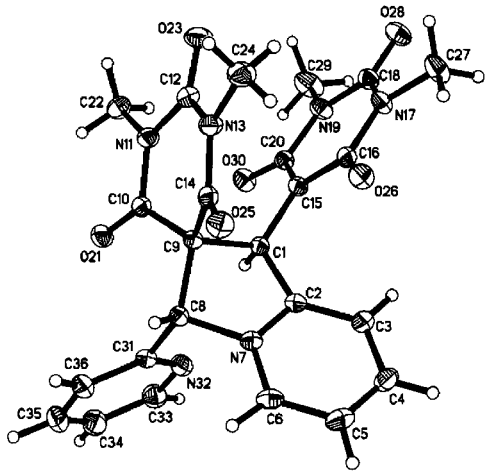


Figure 1. ORTEP drawing of X-ray-determined structure of **2**.

confirmed this. On the other hand, less polar solvents should inhibit the formation of pyridinium zwitterions **5** and **2** and the less polar product (**1**) should be expected. In the NMR experiment with chloroform as a solvent, formation of both **1** and **2** was detected in an approximate ratio of 7:3. If even less polar solvents such as carbon tetrachloride were used, then completion of the reaction was prolonged but the ratio of **1** to **2** became ~9:1.

What is the source of this unique stability of pyridinium-barbituric acid zwitterion? The unique structure of zwitterion **2** allows direct comparison of the X-ray structural parameters. We have previously postulated that uniformity of the ring bond order is directly related to high stability.[16] This postulate can also be supported through X-ray data obtained for zwitterion **2**. The negative charge that mostly resides on the barbituric acid ring makes it more aromatic and adds to the bond order−bond distance uniformity. The barbituric acid ring with the negative charge becomes almost planar. Experimental dihedral angles are almost zero (Figure 1). The dihedral angles for C(16)−N(17)−C(18)−N(19) and C(20)−C(15)−C(16)−N(17) are −0.22 and −3.90°, respectively. Even the carbonyl oxygen and methyl carbon reside close to the plane of the negatively charged barbituric acid. For instance, the dihedral angle for C(27)−N(17)−C(18)−O(28) is −0.89° and that for O(26)−C(16)−N(17)−C(27) is 2.61°. It is quite obvious that the other barbituric acid ring is out of the plane. The dihedral angle for C(10)−C(9)−C(14)−N(13) is −40.64°.

Comparison of bond distances between two of the barbituric rings further indicates the aromatic character of the ring that bears the negative charge. For instance, bond distances in the nonaromatic barbituric acid ring for C(9)−C(10), C(10)−N(11), and N(11)−C(12) are 1.5128, 1.3934, and 1.3996 Å, respectively, while for the same kind of bonds in the aromatic barbituric acid moiety these distances for C(15)−C(16), C(16)−N(17), and N(17)−C(18) are 1.4138, 1.4220, and 1.3769 Å. On the other hand, structural changes regarding pyridine and pyridinium rings are not substantial.

An unusually charge-separated pyridinium barbiturate zwitterion was prepared in one-pot syntheses from 1,3-dimethylbarbituric acid and 2-pyridinecarbaldehyde in

(11) We were not able to determine the structure of this product. It is insoluble in solvents such as DMSO, CH_3OH, H_2O, $CHCl_3$, CH_3COOH, H_2O, CH_3NO_2, C_6H_6, and pyridine.

(12) It is reasonable to assume that with unsubstituted barbituric acids, as well as substituted barbituric acids in strong protic solvents like acetic acid, the nitrogen of the pyridine ring is involved in strong hydrogen bonding; therefore, the lone pair residing on this nitrogen is not free to participate in the nucleophilic addition necessary to dimerize compound **4** into zwitterion **5**.

(13) Acetic acid solution (2 mM) of **2** was heated at 80 °C for 3 h with no formation of decomposition products noticeable by TLC or ^1H NMR.

(14) For reviews of arenium ions formed by addition of a proton to an aromatic ring, see: Brouwer, D. M.; Mackor, E. L.; MacLean, C.; Olah, G. A.; Schleyer, P. v. *Carbonium Ions*; Wiley: New York, 1970; Vol. 2, p 837. Perkampus, H.-H. *Adv. Phys. Org. Chem.* **1966**, *4*, 195−304.

(15) We have recently reported very efficient synthetic procedures for base-assisted decarbonylation of tetrasubstituted barbituric acid into tetrasubstituted malonamides. Jursic, B. S. *Tetrahedron Lett.* **2000**, *41*, 5325−5328.

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high yield. High stability of the zwitterion can be attributed to the aromatic character of the barbituric acid moiety that bears a negative charge. The aromatic character of the barbituric acid ring with a negative charge makes this compound highly resistant to acetic media, and if a reaction is to be performed on the barbituric acid ring, the reaction will go to another barbituric acid ring that does not have a negative charge.

Experimental Section

All solvents and starting materials in this synthesis were obtained from Aldrich and used without further purification. Thin-layer chromatography was performed using plastic-based 0.25 mm thick silica gel 60 F-254 plates (E. Merc, Inc.) with 1:1 $CH_3COOH-CH_3OH$ as a solvent. All ^1H and ^{13}C NMR are recorded in DMSO-d_6 on a Gemini 2000 Varian instrument with the chemical shift of the solvent at 2.49 and 36.0 ppm as referenced in hydrogen and carbon NMR spectra. The ES-MS spectra of our product in CH_3OH-CH_3COOH solutions were acquired with a sector instrument with a mass of charge (m/z) range of 5000. A Micromass Autospec M mass spectrometer with an electrospray source was used. The ES-MS parameters (i.e., pressure, temperature, and voltage on the needle, etc.) were kept constant in each series of solutions. A flow rate of 10 μL/min was applied using 100 μL of sample solution. Elemental analyses were performed by Atlantic Microlab, Inc. X-ray structure determination was performed on a Bruker SMART 1KCCD automated diffractometer. Crystals of compound **2** were obtained by crystallization from methanol by allowing slow solvent evaporation.

Preparation of 5,5′-(2-Pyrimidine)bis(1,3-dimethyl-barbituric acid) (1). A carbon tetrachloride solution (500 mL) of 1,3-dimethylbarbituric acid (780 mg; 5 mM) and 2-pyridinecarbaldehyde (270 mg; 2.5 mM) was stirred at room temperature for 7 days. The yellow precipitate was separated by filtration, washed with carbon tetrachloride (3 × 50 mL) and then ether (3 × 50 mL), and dried in air to afford 650 mg (65%) of product **1**: $R_f = 0.640$ in 1:1 $CH_3COOH-CH_3OH$. ^1H NMR (DMSO-d_6) δ 8.583 (1H, d, $J = 0.020$, pyridine 6-H), 8.402 (1H, t, $J = 0.022$, pyridine 5-H), 7.879 (1H, d, $J = 0.027$, pyridine 3-H), 7.811 (1H, t, $J = 0.022$, pyridine 4-H), 6.336 (1H, s, benzyl hydrogen), and 3.135 (12H, s, four methyl group hydrogens); ^{13}C NMR (DMSO-d_6) δ 159.355 and 156.005 (two different barbituric acid carbonyls), 147.891, 142.312, 137.607, 122.313, and 120.543 (five carbons from the pyridine ring), 80.576 (benzylic carbon), 32.067 (barbituric acid 5-carbon), 24.500 (barbituric methyl carbon). ES-MS (CH_3OH + NaCl) 424 (M + Na). Anal. Calcd For $C_{18}H_{19}N_5O_6$: C, 53.86; H, 4.77; N, 17.45. Found: C, 53.68; H, 4.85; N 17.32.

Preparation of Pyridinium-barbiturate Zwitterion 2. A methanol solution (100 mL) of 1,3-dimethylbarbituric acid (1.56 g; 10 mmol) and 2-pyridinecarbaldehyde (1.1 g; 10 mmol) was refluxed for 45 min. The solution was then transferred to an open 300 mL beaker and left to stand at room temperature until the solvent evaporated to approximately 1/10 of its original volume. The product slowly crystallized from the methanol solution during the course of evaporation. Crystals were separated by filtration, washed with cold methanol (3 × 20 mL) and then ether (3 × 20 mL), and dried at room temperature to give 2.1 g (80%) of product. If necessary, further purification should be repeated by dissolving the product in a larger amount of methanol (~100 mL) and by leaving it at room temperature in open air to crystallize from the reduced volume (1/10) of the solvent. $R_f = 0.505$ in 1:1 CH_3OH-CH_3COOH. ^1H NMR (DMSO-d_6) δ 9.003 (1H, d, $J = 0.022$, pyridinium 6-H), 8.415 (1H, t, $J = 0.026$, pyridinium 5-H), 8.340 (1H, d, $J = 0.017$, pyridine 6-H), 7.904 (1H, t, $J = 0.021$, pyridinium, 4-H), 7.852 (1H, t, $J = 0.026$, pyridine 5-H), 7.715 (1H, d, $J = 0.023$, pyridinium 3-H), 7.611 (1H, d, $J = 0.028$, pyridine 3-H), 7.362 (1H, d + d, $J_1 = 0.024$ Hz, $J_2 = 0.26$ Hz, pyridine 4-H), 6.940 (1H, s, pyridinium), 5.825 (1H, s, pyridinebenzyl), 2.996 (6H, 1H, CH_3), 2.909 (3H, s, CH_3), and 2.831 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 162.95, 161.21, 158.50, 154.32, 150.22, 148.94, 147.51, 145.09, 141.86, 141.29, 135.93, 132.90, 122.03, 121.80, 121.15, 120.13 (six signals for carbonyl carbons and 10 signals for two pyridine rings), 70.84, 59.04, and 51.15 (signals for carbons from a five-membered ring), 25.45, 25.12, and 23.32 (three different CH_3 carbons); MS-ES ($CH_3OH-CH_3COOH-NaCl$), 491 (M + 1), 492 (M + 2), and (M + 22). Anal. Calcd For $C_{24}H_{22}N_6O_6$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.71; H, 4.63; N 17.03.

Preparation of Amide 3. Sodium hydroxide (80 mg; 2 mM) in water (1 mL) and compound **3** (245 mg; 0.5 mmol) was kept at room temperature for 4 h with occasional stirring. In the beginning, the reaction mixture was a suspension that became a clear solution after ~10 min. Progress of the reaction was followed by TLC chromatography and ^1H NMR spectroscopy (D_2O as a solvent). After approximately 2 h, zwitterion **3** was fully converted into amide **4**. The R_f of the soluble product in ethanol is 0.295 in 1:1 $CH_3COOH-CH_3OH$. Into the water solution was added ethanol (200 mL), and the solution was dried over anhydrous calcium chloride. The solid was separated by filtration, and ethanol was evaporated in vacuo at room temperature. The oily residue was slurried in anhydrous 1:1 alcohol−benzene, and the solvent was again evaporated. This procedure was repeated several times. The solid residue left after evaporation of the solvent was slurried in dry ether, filtered, and dried in a vacuum to give 198 mg (85%) of amide. ^1H NMR (D_2O-KOH) δ 8.450 (1H, d-d, $J = 0.020$, $J_2 = 0.004$ Hz), 8.218 (1H, t, $J = 0.024$ Hz), 7.840 (1H, t-d, $J_1 = 0.024$ Hz, $J_2 = 0.004$ Hz), 7.642 (1H, t, $J = 0.022$ Hz), 7.605 (1H, d-d, $J_1 = 0.024$ Hz, $J_2 = 0.004$ Hz), 7.532 (1H, d-d, $J_1 = 0.024$ Hz, $J_2 = 0.004$ Hz), 7.498 (1H, t, $J = 0.026$ Hz), 7.389 (1H, d-d-d, $J_1 = 0.024$ Hz, $J_2 = 0.020$ Hz, $J_3 = 0.04$ Hz), 3.046 (6H, s), and 2.461 (6H, s). ^{13}C NMR (D_2O-KOH) δ 171.749, 170.438, 163.810, 157.416, 120.835, 120.784, 120, 048, 118.635, 85.761, 53.156, 43.616, 23.239, and 21.993; MS-ES (CH_3OH-H_2O-KOH), 502 (M + 38).

X-ray Single-Crystal Structure Determination of Compound 2 at 155(2) K. Crystal Data: $C_{24}H_{22}N_6O_6$, $M_r = 490.48$, monoclinic, space group $P2_1/n$, $a = 11.6777(6)$ Å, $b = 13.4416(7)$ Å, $c = 15.0367(8)$ Å, $\alpha = 90°$, $\beta = 111.630(1)°$, $\gamma = 90°$, $V = 2194.1(2)$ Å^3, $Z = 4$, ρ_{calcd} 1.485 Mg/m^3, $F_{000} = 1024$, wavelength (λ) = 0.71073 Å, absorption coefficient (μ) = 0.110 mm^{-1}. **Data Collection and Reduction**: crystal size = 0.4 × 0.5 × 0.6 mm; theta range, 2.10−30.00°; index ranges, $-16 \le h \le 16$, $-18 \le k \le 18$, $-21 \le l \le 20$; reflections collected, 30679; independent reflections, 6390 [$R_{int} = 0.0284$]; refinement method, full-matrix least-squares on F^2; data/restraints/parameters, 6390/0/413; final R indices [$I > 2\sigma(I)$]: $R1 = 0.0370$, w$R2 = 0.1041$, GOF on $F^2 = 1.035$. R indices (all data) $R1 = 0.0486$, w$R2 = 0.1067$; largest difference peak and hole: 0.388 and −0.241 eÅ^{-3}. **Measurement, Computing, and Graphics**: *SMART 1K CDD* (Bruker, 2000); cell refinement, *SMART*; data reduction, *SAINT-Plus* (Bruker, 2000); programs(s) used to solve structure, *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure, *SHELX97* (Sheldrick, 1997); molecular graphics, *SHELXTL97* (Sheldrick, 1997); software used to prepare material for publication, *SHELXTL97*.[17]

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Supporting Information Available: Tables of crystal data for **2** (structure solution, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters). This material is available free of charge via the Internet at http://pubs.acs.org.

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