Concave Reagents, 6[1b]

Can the Structure of Concave Reagents Determine Selectivities?[1a]

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The concave position of the proton in protonated concave pyridines **8**·H$^+$ or **9**·H$^+$ leads to increased selectivities in protonation reactions of nitronate anions **2a–d**. Thus, the reprotonation of the nitronate anion **2a** by the protonated concave pyridine **8**·H$^+$ selectively yields the nitro compound **1a** whereas the nitronate anions **2b–d** are transformed to the Nef products **4b–d**.

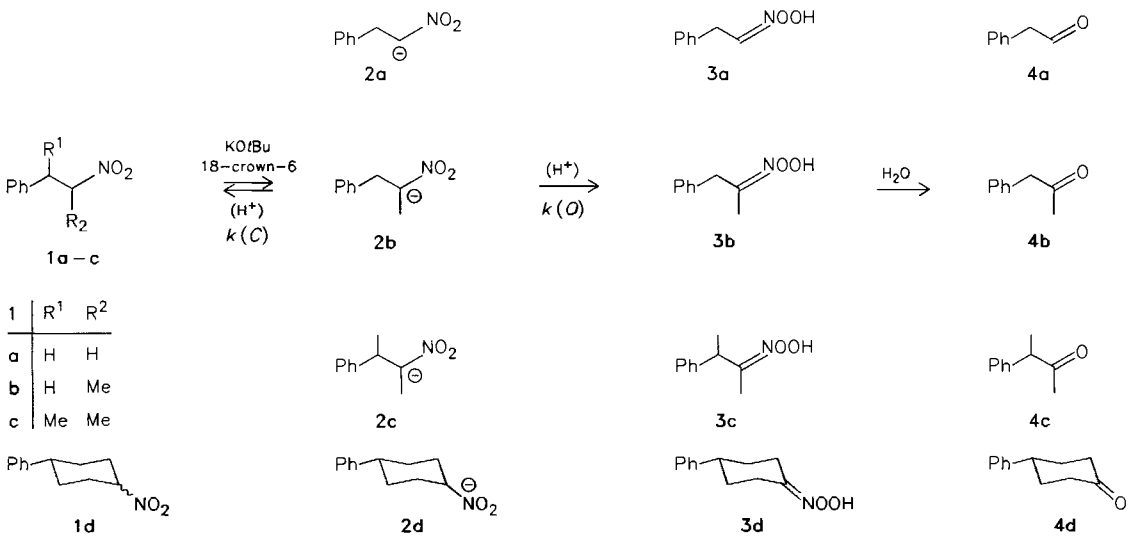
Concave reagents have been developed to improve the selectivities of standard reagents in organic chemistry (acids and bases, redox reagents)[2]. Bimacrocyclic concave pyridines show surprising regioselectivities in protonation reactions of the 1-nitro-4-phenylcyclohexyl anion[3].

In this work, the protonation of four different nitronate anions **2a–d** by different proton sources is investigated. Six protonating systems have been used: a *p*-toluenesulfonic acid solution (TosOH) and five buffers containing pyridines **5–9** and TosOH (two concave pyridines **8** and **9** and three pyridines **5–7** for comparison). Ethanolic nitronate solutions **2** have been prepared by deprotonating the four nitro compounds **1a–d** with potassium *tert*-butoxide in the presence of 18-crown-6. Aliquots of these solutions have been added to the buffer systems (see Scheme). The results of these experiments and from one-pot reactions of all four nitronate anions **2** in one solution are compiled in the Table.

While the use of TosOH and protonated 2,6-di-*tert*-butylpyridine[4] (**5**) yields the Nef products **4a–d** almost exclusively, protonated pyridine (**6**) and lutidine[4] (**7**) reprotonate the four anions **2a–d** nearly completely to **1a–d**. But when the concave pyridines **8** and **9**[4] are used the product distribution is different. The bimacrocyclic compound **8** is able to distinguish between the anions **2a–d**: **2a** is completely reprotonated to give **1a** whereas the other anions **2b–d** give predominantly the Nef products **4b–d**. With the concave pyridine **9** yet another product distribution has been found although **8** and **9** differ only by the basicity-increasing methoxy group in position 4 of the pyridine ring. When the bimacrocyclic compound **9** was used, mainly reprotonation of the anions **2** to **1** occurs.

By variation of the concentrations of the protonated pyridine and [$EtOH_2^+$] it has already been shown[5] that the direct proton transfer from the protonated pyridines to the nitronate anions **2** is responsible for the formation of the nitro compounds **1** (*C*-protonation) whereas the *O*-protonation leading to the Nef products **4** is determined by the concentration of [$EtOH_2^+$]. [$EtOH_2^+$] is a function of the basicity $K_{buff.}$ of the pyridines **5–9** in EtOH[6]. This leads to equations (1)–(4).

Scheme



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$$\mathbf{5-9} + EtOH_2^+ \xrightarrow[k(O)]{2} \mathbf{3} \xrightarrow{H_2O} \mathbf{4} \quad (1)$$

$$\mathbf{5-9}\cdot H^+ \xrightarrow[k(C)]{2} \mathbf{1} \quad (2)$$

$$K_{buff.} = \frac{[\mathbf{5-9}]\cdot[EtOH_2^+]}{[\mathbf{5-9}\cdot H^+]\cdot[EtOH]} \quad (3)$$

O-protonation: $r(O) = k(O)\cdot[\mathbf{2}]\cdot[EtOH_2^+]$
C-protonation: $r(C) = k(C)\cdot[\mathbf{2}]\cdot[\mathbf{5-9}\cdot H^+]$

$$\frac{r(O)}{r(C)} = \frac{k(O)\cdot[\mathbf{2}]\cdot([\mathbf{5-9}\cdot H^+]/[\mathbf{5-9}])\cdot[EtOH]\cdot K_{buff.}}{k(C)\cdot[\mathbf{2}]\cdot[\mathbf{5-9}\cdot H^+]} \quad (4)$$

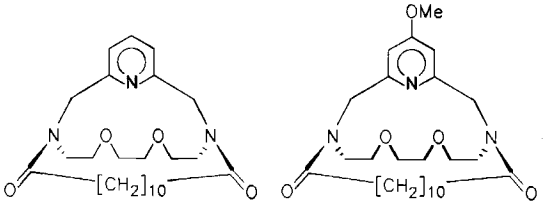
Because all reactions have been carried out in buffers of the same concentration with a large excess of **5–9** and **5–9**·H^+, [**5–9**] and [**5–9**·H^+] remain constant. If one assumes that in all buffer systems the O-protonation occurs always in the same way via the protonated solvent, $k(O)$ is a constant, too. Then, the equation for the competition $r(O)/r(C)$ can be simplified to equation (5).

$$\frac{r(O)}{r(C)} = \text{const.}\ \frac{K_{buff.}}{k(C)} \quad (5)$$

In equation (5), the C-protonation is only determined by $k(C)$ whereas the basicity $K_{buff.}$ of the pyridines **5–9** determines the O-protonation[7]. Thus, the results compiled in the Table may be explained as follows:

The [$EtOH_2^+$] concentration of a non-buffered *p*-toluenesulfonic acid is so high that only Nef reaction yielding the carbonyl compounds **4** is observed. In the 2,6-di-*tert*-butylpyridine buffer (**5**), the [$EtOH_2^+$] concentration is lowered but the rate of the C-protonation is also slowed down by the bulky *tert*-butyl groups in positions 2 and 6 of the pyridine ring. Therefore, only in the case of the smallest nitronate anion **2a** a small amount of C-protonation product **1a** has been found.

Table. Yield (in %)[a] of nitro compounds **1** (C-protonation) in reprotonation experiments of nitronate anions **2** with different proton sources (TosOH, **5–9**·H^+)[b]



8 **9**

	TosOH	2,6-Di-*tert*-butylpyridine (**5**)	Pyridine (**6**)	Lutidine (**7**)	**8**	**9**
1a	≤5	25	100	100	>90	100
1b	0	0	100	100	0	100
1c	0	0	100	90	15–20	(50)[c]
1d	0	0	ca. 75	90–95	25–30	90

[a] Combined yields of the nitro compounds **1** and the Nef products **4**: >90%. The results of the one-pot reaction of all four anions **2a–d** in one solution did not differ from the results of the individual experiments by more than ±10%. — [b] The pyridines **5–9** were used in buffers (0.11 M **5–9**, 0.03 M TosOH·H_2O); TosOH·H_2O was used as a 0.11 M solution. — [c] The difference between the individual protonation experiments and the one-pot protonation of all four anions **2a–d** was up to ±20%.

In the pyridine and lutidine buffers (**6** and **7**), however, the [$EtOH_2^+$] concentration is drastically diminished. Furthermore, there is no marked sterical hindrance in pyridine (**6**) and lutidine (**7**). Therefore, the C-protonation is dominant. Only in the case of the less basic pyridine (**6**) (increased [$EtOH_2^+$] concentration), the sterical hindrance between the cyclic anion **2d** and the protonated pyridine (**6**·H^+) seems to be large enough that the higher [$EtOH_2^+$] concentration leads to some Nef product **4d** by O-protonation.

But with the concave pyridines **8** and **9**, the sterical interactions between the protonated pyridines and the nitronate anions **2a–d** vary with the anions **2**. Thus, **2a** is C-protonated by **8**·H^+ almost completely to form **1a**, whereas for the anions **2b–d** O-protonation is observed. But also in this case, a change in the [$EtOH_2^+$] concentration (use of the more basic[9] concave pyridine **9** instead of **8**) leads to C-protonation as the main reaction.

In contrast to the standard reagents [e.g. TosOH, protonated lutidine (**7**·H^+)], which transform all nitronate anions **2** in the same way [either Nef reaction to **4** *or* reprotonation to **1**], the protonated concave pyridine **8**·H^+ is able to distinguish between different nitronate anions **2a–d**. In a mixture, the protonated concave pyridine **8**·H^+ can convert the anions **2** into different products **1** and **4**. The fine-tuning of this *selectivity* is possible by variation of the [$EtOH_2^+$] concentration in the buffer, either by the use of different concave pyridines **8** or **9** (see above) or by variation of the concentrations in the buffer[5].

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Experimental

General remarks see also ref.[3].

To a mixture of 0.11 mmol of each of the four nitro compounds **1a–d**[10] in 2 ml of dry ethanol, 6.6 mg (33 µmol) of *n*-$C_{14}H_{30}$ as GLC standard and 286 mg (1.08 mmol) of 18-crown-6 were added. For GLC comparison, four 80-µl samples were taken. Then, the nitro compounds **1** were deprotonated by the addition of 90 mg (0.80 mmol) of potassium *tert*-butoxide in 2 ml of dry ethanol. For the reprotonation experiments, 160-µl aliquots of this solution were added to buffer systems containing 0.44 mmol of pyridine **5–9** and 0.12 mmol of TosOH·H_2O (0.44 mmol TosOH·H_2O in the case of the non-buffered TosOH experiments) in 4 ml of dry ethanol (each experiment was done at least twice). After 15 h, the mixture was diluted with 10 ml of diethyl ether; 4 ml of 2 N HCl was added, and after 1 min the layers were separated. The HCl layer was extracted with 5 ml of diethyl ether. The combined ether layers were washed with 2 ml of water and dried with $MgSO_4$. After concentration, the samples were investigated by GLC (Carlo-Erba GC 6000 Vega, splitless injection by autosampler, SE 30/15 m capillary column, 5 min 70°C, 10°C/min up to 250°C).

CAS Registry Numbers

2a: 128575-87-1 / **2b**: 83705-50-4 / **2c**: 128575-88-2 / **2d**: 29916-50-5 / **5**·H^+: 62907-61-3 / **6**·H^+: 16969-45-2 / **7**·H^+: 128575-89-3 / **8**·H^+: 124177-57-7 / **9**·H^+: 124177-55-5

[1] [1a] Dedicated to Professor *Christoph Rüchardt* on the occasion of his 60th birthday. — [1b] Concave Reagents, 5: U. Lüning, M. Müller, *Chem. Ber.* **123** (1990) 643.

[2] U. Lüning, *Liebigs Ann. Chem.* **1987**, 949. — See also ref.[1b] and ref. cited therein.

[3] U. Lüning, R. Baumstark, M. Müller, C. Wangnick, F. Schillinger, *Chem. Ber.* **123** (1990) 221.

[4] The protonation of the nitronate anions **2** always takes place via the conjugated acids of the pyridines **5**–**9**, when a protonation by pyridines is discussed.

[5] See ref.[3], Table 2, variation of the [$EtOH_2^+$] and the [concave pyridine · H^+] concentration, and ref. cited therein.

[6] Relative basicities log *K* of concave pyridines have been measured (see ref.[9]). But note the comment on absolute pK_a values in ethanol: ref.[12] in U. Lüning, M. Müller, *Liebigs Ann. Chem.* **1989**, 367.

[7] The *O*- and *C*-protonation can also be discussed in terms of specific and general acid catalysis[8]. But for the *C*-protonation (general acid catalysis) the Brönsted relation [log $k = f(pK_a)$][8] is not valid, because concave (sterical) and not electronic factors determine the *C*-protonation.

[8] See for instance: R. A. V. Jones, *Physical and Mechanistic Organic Chemistry*, 2nd ed., p. 72ff., Cambridge University Press, Cambridge, 1985.

[9] U. Lüning, R. Baumstark, K. Peters, H. G. von Schnering, *Liebigs Ann. Chem.* **1990**, 129.

[10] **1a**–**c**: Syntheses via the 2-nitrostyrenes[11] with reduction by $NaBH_4$ in DMSO[12] or methylation by MeMgI followed by chromatographic isolation of **1c** from the reaction mixture. – **1d**: H. E. Zimmerman, P. S. Mariano, *J. Am. Chem. Soc.* **90** (1968) 6091.

[11] C. B. Gairaud, G. R. Lappin, *J. Org. Chem.* **18** (1953) 1.

[12] G. B. Bachman, R. J. Maleski, *J. Org. Chem.* **37** (1972) 2810.

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