Pergamon

Tetrahedron Letters 41 (2000) 1235–1240

TETRAHEDRON LETTERS

On the structure of intermediate adducts arising from dithionite reduction of pyridinium salts: a novel class of derivatives of the parent sulfinic acid

Vincenzo Carelli,[a,*] Felice Liberatore,[a] Luigi Scipione,[a] Roberta Musio [b] and Oronzo Sciacovelli [b]

[a] *Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi di Roma 'La Sapienza', Piazzale A. Moro, 5, 00185 Rome, Italy*

[b] *Centro CNR di Studi sulle Metodologie Innovative di Sintesi Organica, Dipartimento di Chimica, Università degli Studi di Bari, Viale E. Orabona, 4, 70126 Bari, Italy*

Received 19 October 1999; accepted 3 December 1999

Abstract

^{13}C and ^{17}O NMR spectroscopy show that adducts arising from dithionite reduction of 3- or 3,5-cyano- or carbamoyl-substituted pyridinium salts to the corresponding 1,4-dihydropyridines, are *S*-anions of esters of the simplest parent sulfinic acid. A pathway for formation of the 1,4-dihydropyridines, involving an intramolecular hydride transfer, is suggested. © 2000 Elsevier Science Ltd. All rights reserved.

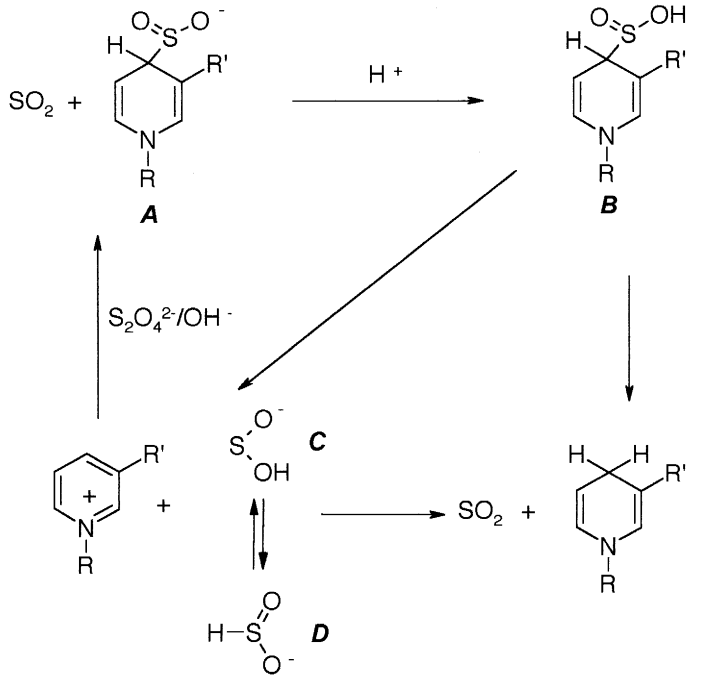
Keywords: pyridinium salts; dithionite reduction; parent sulfinic acid derivatives; ^{13}C and ^{17}O NMR spectroscopy.

Sodium dithionite is a versatile and powerful reducing agent, widely used in chemical and biochemical research. As a representative example of the use of dithionite, coenzyme NAD^+ can be converted to the reduced form NADH; indeed dithionite reduction appears to be applicable to all pyridinium salts bearing electron-withdrawing substituents (-CN or $-CONH_2$) in the 3- or 3,5-positions.[1] The reactions afford almost exclusively, as the final products, the corresponding 1,4-dihydropyridines.[2–8] In the course of the reduction, intermediate adducts are formed which have been identified as the sulfinate anions **A** (Scheme 1). These adducts are stable in alkaline solutions, whereas, in neutral or mildly basic solutions, they decompose into 1,4-dihydropyridines with elimination of SO_2. It has been suggested that, at lower pH, sulfinate anions should be protonated to sulfinic acids **B** which should be then converted directly to 1,4-dihydropyridines.[2,4–6] Otherwise, according to the Blankenhorn and Moore proposal,[9] the sulfinic acid adducts could be heterolytically dissociated into pyridinium and sulfoxylate ions **C**, from which sulfinate ions **D** could arise by tautomerization. Lastly, sulfinate ions, in view of their good hydride donor properties, should be able to reduce pyridinium ions to dihydropyridines (Scheme 1). From that reported

* Corresponding author. Fax: +390649913888; e-mail: v_carelli@uniroma1.it (V. Carelli)

PII: S0040-4039(99)02251-0

above, it is evident that considerable disagreement exists about the last step of the dihydropyridine formation pathway. Neither of the suggested mechanisms accounts fully for the experimental evidence and the main objections can be summarized thus: (i) the sulfinate anions **A** and not the protonated forms **B** should be converted directly into dihydropyridines, while the actual occurence shows the stability of dithionite adducts in basic solutions;[9] and (ii) intermolecular hydride transfer from sulfinate to pyridinium ions does not explain the high regioselectivity of dithionite reduction.[10]

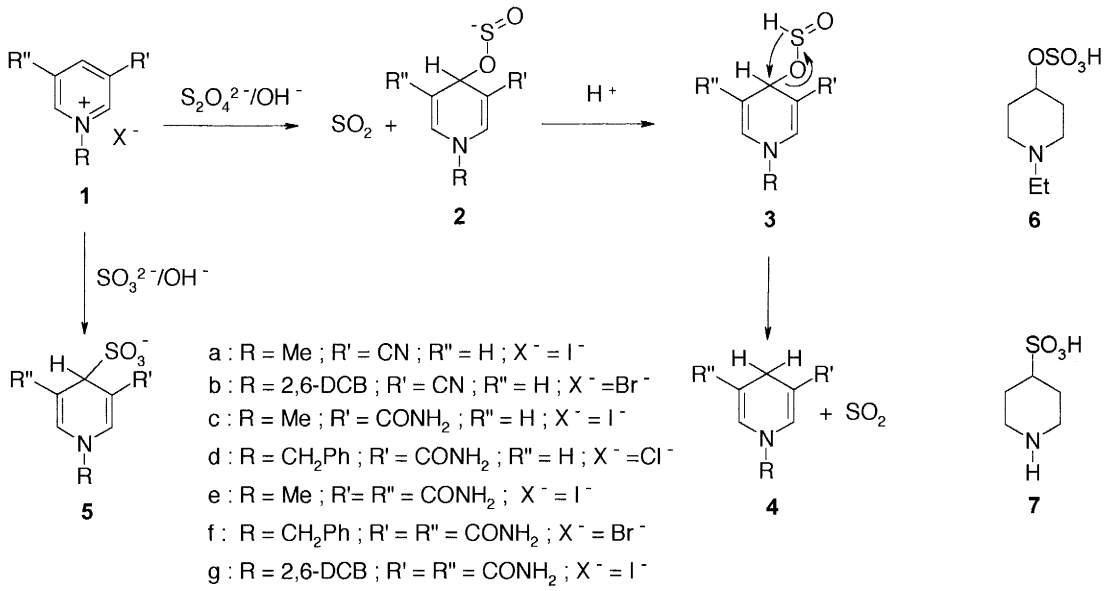


Scheme 1.

In this paper we present ^{13}C and ^{17}O spectroscopic evidence showing that the intermediate adducts are *S*-anions of esters of the simplest parent sulfinic acid (Scheme 2). To our knowledge, such compounds have not been reported previously. Furthermore, we suggest a reaction pathway which better accounts for the direct conversion of the protonated adducts to dihydropyridines as well as the high regioselectivity of the reduction.

During the course of our studies on the reduction of pyridinium salts, models of the coenzymes NAD^+ and $NADP^+$,[11] we have had occasion to acquire ^1H and ^{13}C NMR data concerning the intermediates arising from the reaction with dithionites of several 3- or 3,5-cyano- or carbamoyl-substituted pyridinium salts. We have also recorded ^1H and ^{13}C NMR spectra of the sulfonate derivatives obtained by reaction of the same pyridinium salts with sulfite ions.

Table 1 reports ^{13}C chemical shifts of carbons 4 in the dithionite adducts **2a**–**g** and in the corresponding sulfite adducts **5a**–**g**,[12] as well as in the model compounds 1-ethyl-4-piperidyl-hydrogen sulfate **6** and 4-piperidyl sulfonic acid **7**. It was found that the carbons 4 of the dithionite adducts are significantly deshielded relative to carbons 4 of the sulfite adducts. Starting from the carbon 4 chemical shifts in



Scheme 2.

the 1,4-dihydropyridine **4a**, **c** and **d** (22.6,[13] 21.7[14] and 22.3 ppm,[15] respectively), the magnitude of the substituent chemical shift (SCS) effect can be determined for both the **2** and **5** series. The SCS effect of the sulfonate group in **5a**, **c** and **d** ranges from 35.34 to 36.50 ppm, in reasonable agreement with the lowfield shift (31.53 ppm) observed in **7** relative to *N*-methyl-piperidine.[16] The SCS effect in the dithionite adducts **2a**, **c** and **d** ranges from 44.08 to 45.20 ppm. An SCS effect of such a magnitude suggests that carbons 4 are directly bonded to an oxygen atom. In fact, the substituent effect of an oxygen atom on the chemical shift of $^{13}C_{ipso}$ is 49 ppm in linear alkanes[17] and 42.4 ppm in cyclohexane derivatives.[17,18] The enhanced lowfield shift of carbon 4 in compound **6** (50.35 ppm relative to *N*-methyl-piperidine) could be due to the presence of three terminal oxygens which significantly reduce the electron density at the sulfur atom. To compensate for this, the electron density in the C–O–SO_3^- fragment is pulled away from the carbon atom, thus increasing the deshielding of carbon 4 in **6** with respect to the adducts **2**.

Table 1
^{1}H and ^{13}C chemical shift values (δ, referred to TMS) of H4 and C4 in compounds **2**, **5, 6** and **7**

Compounds	H 4	C 4	Compounds	H 4	C 4
2a [a]	3.68	66.68	**5a** [a]	4.49	59.10
2b [a]	3.49	67.25	**5b** [a]	4.32	58.90
2c [b]	3.98	65.90	**5c** [c]	4.28	57.10
2d [b]	3.85	67.50	**5d** [c]	4.44	57.64
2e [a]	4.27	64.49	**5e** [a]	4.98	56.34
2f [a]	4.21	65.12	**5f** [a]	4.99	56.33
2g [a]	4.09	65.56	**5g** [c]	4.67	56.43
6 [a]	4.24	76.75	**7** [a]	2.72	57.93

[a] 0.1M Na_2CO_3/D_2O ;
[b] 1M NaOD/D_2O ;
[c] 0.05M Na_2CO_3 / 1 : 1 D_2O / [D_6]-DMSO

In compounds **2**, hydrogens 4 resonate at higher field than in the corresponding compounds **5** (Table 1). This behavior cannot be accounted for on the basis of the SCS effect of the –O–S–O$^-$ and –SO_3^- groups, because in the literature no data are reported concerning the –O–S–O$^-$ group and those related to the –SO_3^- group are scarce. In addition, the chemical shift of hydrogen 4 depends also on the conformation of the dihydropyridine ring which could be influenced differently by the steric demands of the two groups. We have performed theoretical calculations, at the MNDO level of approximation, on adducts **2** and **5**. It was found that the optimized geometries are quite similar in both series of compounds and the magnetic anisotropy of substituents in the 3 and 5 positions do not affect hydrogen **4** chemical shifts. According to MNDO calculations,[19] in compounds **2** hydrogens 4 have electron densities higher than in the corresponding compounds **5** (Table 2). This could explain the hydrogen 4 upfield shifts observed for dithionite adducts with respect to sulfite adducts. It is worth noting that MNDO predicts a hydrogen 4 electron density difference (λ) between compounds **5** and **2** which is in reasonable agreement with the values calculated by the Lamb formula ($\delta_{\text{H4sulfite adduct}} - \delta_{\text{H4dithionite adduct}} = 17.8\lambda \times 10^{-6}$).[20]

Table 2
H4 charges (millielectrons) in compounds **2** and **5**

Compounds	Charge	Compounds	Charge
2a	- 13	**5a**	+ 48
2b	- 7	**5b**	+ 49
2c	- 7	**5c**	+ 52
2d	- 10	**5d**	+ 53
2e	+ 7	**5e**	+ 64
2f	+ 9	**5f**	+ 63
2g	+ 10	**5g**	+ 64

It was decided to attempt to find conclusive evidence of the structure of the dithionite adducts by ^{17}O NMR spectroscopy. Indeed, ^{17}O NMR spectra of the sulfinate anions **A** should display a single resonance signal, while for the sulfinic esters **2** two signals should be found. ^{17}O NMR spectra of **2c**, **d** and **g** (Fig. 1) showed two partially overlapping signals in the chemical shift range found for S–O–C and S–O oxygens.[21,22] By deconvolution, the occurrence of two signals was confirmed, and their chemical shift, half height linewidth and integral values were determined (Table 3). This leads to the conclusion that in the compounds examined there are two different oxygen atoms as in structure **2**. The linewidth values observed are in agreement with this structure. Indeed, the ^{17}O spectra of other compounds containing the C–O–S–O sequence[22] (methyl and ethyl arenesulfinate,[23] methyl arenesulfonate[23] and sulfonyl-*exo*-2-norbornyl brosylate[24]) show that terminal S–O oxygens are always characterized by a linewidth narrower than bridge oxygens. This behavior is due to a different symmetry of the electron distribution, which is invariably lower around the bridge oxygen. As expected for sulfonate anions, the ^{17}O NMR spectra of **5b** and **g** [21] show a single broad signal whose chemical shift (158 and 164 ppm, respectively) is in good agreement with the values commonly found for sulfonate.[23,25]

In conclusion, the mechanism of reduction of pyridinium salts by dithionite appears to involve, as intermediates, the sulfinic ester *S*-anions **2** which originate from the attack on the electrophilic carbons 4 of the pyridinium salts by dithionite oxyanions, with simultaneous heterolysis of the S–S bond and elimination of SO_2 (Scheme 2). Indeed, it was shown that hard nucleophilic centers originate in dithionite anions from the localization, to a large extent, of the negative charges on the oxygen atoms.[26] Hence, the formation of C–O–S bonds can be the expected result of the reaction of dithionite with pyridinium

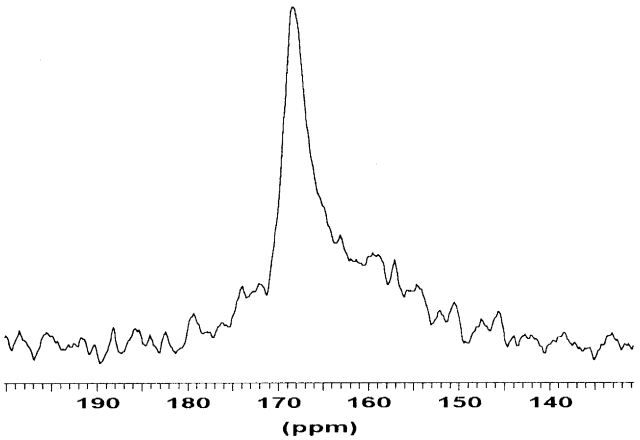


Fig. 1. ^{17}O NMR spectrum of compound **2g** at 11.7 tesla. The following operating conditions were used: 90° observing pulse; spectral width 41 700 Hz; acquisition time 0.05 s; number of scans 2.4×10^6

Table 3
^{17}O chemical shifts (δ, referred to $H_2{}^{17}O$) and linewidths (LW, Hz) of bridge and terminal oxygens in compounds **2**

Compounds	δ (LW) C-O-S [a]	δ (LW) S-O [a]
2c [b]	161 ± 3 (530 ± 50)	162 ± 1 (170 ± 15)
2d [c]	161 ± 3 (660 ± 50)	162 ± 1 (200 ± 15)
2g [d]	161 ± 3 (740 ± 50)	168 ± 1 (220 ± 15)

[a] Integral values ratio of corresponding signals is 1:1;
[b] prepared directly in the NMR sample tube (0.6 and 1.2 M in 1M NaOD D_2O);
[c] 0.02 M in 2M NaOD D_2O;
[d] 0.02 M in 1:1 [D_6]-DMF / D_2O made alkaline with NH_3(pH ca. 9).

salts. The ambident sulfite ions stand in considerable contrast; sulfur can expand its valence shell to produce a soft nucleophilic center,[27] which is highly reactive in bond formation to electrophilic carbons.[28] Therefore, *S*-nucleophilicity accounts for the formation of sulfonates by the reaction of sulfite ions with pyridinium salts.

The structure we propose for dithionite adducts better accounts for the experimental evidence. According to the reaction pathway depicted in Scheme 2, protonation of the alkali-stable *S*-anions **2** gives rise to labile esters **3**, which quickly decompose into 1,4-dihydropyridines with elimination of SO_2. This lability is likely to be due to a hydride induced intramolecular displacement of the sulfinic substituent, aided by the good leaving group properties of SO_2. Thus an intramolecular regioselective hydride transfer from the sulfinic SH group to the adjacent carbon atom can take place.

Acknowledgements

This work was financially supported by 60% M.U.R.S.T. funding.

References

1. Warburg, O.; Christian, W.; Griese, A. *Biochem. Z.* **1935**, *282*, 157.
2. Yarmolinsky, M. B.; Colowick, S. P. *Biochim. Biophys. Acta* **1956**, *20*, 177.
3. Sutter-Kostic, K.; Carrer, P. *Helv. Chim. Acta* **1956**, *39*, 677.
4. Wallenfels, K.; Schüly, H. *Justus Liebig Ann. Chem.* **1959**, *621*, 178.
5. Kosower, E. M.; Bauer, S. *J. Am. Chem. Soc.* **1960**, *82*, 2191.
6. Caughey, W. S.; Shellenberg, K. A. *J. Org. Chem.* **1966**, *31*, 1978.
7. Biellmann, J. F.; Callot, H. J. *Tetrahedron Lett.* **1966**, *7*, 3991.
8. Biellmann, J. F.; Callot, H. J. *Bull. Soc. Chim. Fr.* **1968**, 1154.
9. Blankenhorn, G.; Moore, E. G. *J. Am. Chem. Soc.* **1980**, *102*, 1092.
10. Roberts, R. M. G.; Ostovic, D.; Kreevoy, M. M. *J. Org. Chem.* **1983**, *48*, 2053.
11. (a) Carelli, V.; Liberatore, F.; Tortorella, S.; Micheletti-Moracci, F. *Gazz. Chim. Ital.* **1983**, *113*, 569. (b) Carelli, V.; Liberatore, F.; Casini, A.; Di Rienzo, B.; Tortorella, S.; Scipione, L. *New J. Chem.* **1996**, *20*, 125. (c) Carelli, V.; Liberatore, F.; Scipione, L.; Impicciatore, M.; Barocelli, E.; Cardellini, M.; Giorgioni, G. *J. Control Release* **1996**, *42*, 209.
12. Compound **7** was purchased from Sigma. According to a typical procedure, dithionite adducts were obtained by reaction of the corresponding pyridinium salts with $Na_2S_2O_4$ in 1 M NaOH or Na_2CO_3 solution, under nitrogen. Sulfite adducts were similarly obtained from the corresponding pyridinium salts and Na_2SO_3 in 0.1 M Na_2CO_3. Adducts **2d** and **2g**, poorly soluble in the reaction medium, were isolated by centrifugation and washed with a little cold water. Furthermore, **2g** was recrystallized from 0.1 M NaOH and washed with ethanol. Adducts **5b** and **5g**, poorly soluble in the reaction medium, were separated by filtration and washed with a little cold water. Compound **6** was obtained by prolonged reaction, at room temperature, of *N*-ethylpiperidinyl-4-ol with chlorosulfonic acid in $CHCl_3$; the solvent was then removed and the residue washed with acetone. For ^1H and ^{13}C NMR studies the adduct preparation was carried out directly in NMR tubes. All spectra were recorded at 11.4 tesla on a Bruker AM 500 spectrometer.
13. Butt, G. L.; Deady, L. W. *J. Heterocycl. Chem.* **1984**, *21*, 981.
14. Bossaert, J. D.; Domisse, R. A.; Alderweireldt, F. C.; Gerlings, P. *J. Chem. Res. (Miniprint)* **1987**, 2360.
15. Micheletti-Moracci, F.; Liberatore, F.; Carelli, V.; Arnone, A.; Carelli, I.; Cardinali, M. E. *J. Org. Chem.* **1978**, *43*, 3420.
16. Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tabellen zur Strukturaufklärung Organischer Verbindungen mit Spektroskopichen Methoden*; Springer: Berlin, Heidelberg, 1976; C45.
17. Breitmeir, E.; Bauer, G. *^{13}C NMR Spectroskopie*; Georg Thieme: Stuttgart, 1977; pp. 52–54.
18. Schneider, H. J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866.
19. (a) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899. (b) Thiel, W. *QCPE* **1982**, 438. (c) Musio, R. *QCPE Bulletin* **1997**, *17*, 41.
20. Pople, J. A.; Schneider, W. G.; Bernstein, H. J. *High-Resolution Nuclear Magnetic Resonance*; McGraw-Hill: New York, 1959; p. 175.
21. Spectra were recorded at 11.4 tesla on a Bruker AM 500 spectrometer and were obtained at ^{17}O natural abundance by a 15 mm selective probe using different experimental conditions in order to assess that the observed signals were not artifacts. Both RIDE and single pulse sequences were used, with different values of the pre-acquisition delay (20–100 μs) and carrier offset. In all cases no significant changes in the spectra were observed. Analysis of **2c**, **2d** and **2g**, was carried out as indicated in footnotes of Table 3; compounds **5b** and **5g** were analyzed in 0.02 M D_2O and 0.02 M 1:1 [D_6]-DMSO/D_2O respectively.
22. (a) Barbarella, G. *J. Mol. Struct.* **1989**, *186*, 197. (b) Hellier, D. G.; Liddy, H. G. *Mag. Res. Chem.* **1988**, *26*, 671. (c) Hellier, D. G.; Liddy, H. G. *Mag. Res. Chem.* **1989**, *27*, 431. (d) *O-17 NMR Spectroscopy in Organic Chemistry*; Boykin, D. W., Ed.; CRC Press: Boca Raton, FL, 1991.
23. Dahn, H.; Van Toan, V.; Ung-Truong, M. N. *Mag. Res. Chem.* **1991**, *29*, 897.
24. Chang, S.; Le Noble, W. J. *J. Am. Chem. Soc.* **1983**, *105*, 3708.
25. (a) Bugner, D. E. *J. Org. Chem.* **1989**, *54*, 2580. (b) Musio, R.; Sciacovelli, O. *J. Org. Chem.* **1997**, *62*, 9031.
26. Dunitz, J. D. *Acta Cryst.* **1956**, *9*, 579.
27. Horner, D. A.; Connick, R. *Inorg. Chem.* **1986**, *25*, 2414.
28. Meek, J. S.; Fowler, J. S. *J. Org. Chem.* **1958**, *33*, 3422.