Inorganic Drug Interactions: the Reaction between Thiobarbiturates and the Nitroprusside Ion

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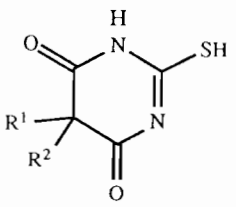
Abstract

The reaction between the hypotensive drug sodium nitroprusside ($Na_2[Fe(CN)_5NO]$; sodium pentacyanonitrosylferrate(2–)) and the anaesthetic drug thiopental has been modelled using as thiopental analogues both thiobarbituric acid and 5,5-diethylthiobarbituric acid. The thiobarbiturates do not react with nitroprusside as typical thiolates to form intermediates of type $[Fe(CN)_5N(O)SR]^{3-}$, but rather as thiones producing, either upon illumination or after basification/acidification, chromophores identical with those produced by either thiourea or thiocyanate. NMR evidence confirms that no oxidation of the thiobarbiturate occurs in the reaction with nitroprusside.

Introduction

Sodium nitroprusside, $Na_2[Fe(CN)_5NO]$ (sodium pentacyanonitrosylferrate(2–)), is a potent vasodilator widely used to effect a lowering of the blood pressure [1]: in particular, it is commonly employed to induce hypotension during surgery [2–4]. The anaesthetic thiopental (**1a**), usually as the sodium salt, is commonly used [5–7] as an anaesthetic at the same time as sodium nitroprusside is employed as a hypotensive.



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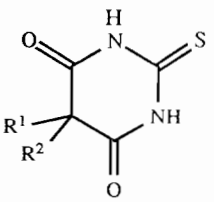

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a $R^1 = Et$
$R^2 = CH(CH_3)Pr$

b $R^1 = R^2 = Et$

c $R^1 = R^2 = H$

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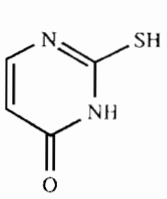
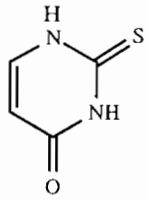
It has been reported [8] that thiopental reacts with nitroprusside to yield a 1:1 adduct. Many thiolate anions RS^- react with nitroprusside to form adducts of type $[Fe(CN)_5N(O)SR]^{3-}$ [9–13]; the final reaction products are, in general, RSSR, $[Fe(CN)_6]^{4-}$ and NO [13]. While the major reaction pathway proceeds via the paramagnetic intermediates $[Fe(CN)_5NO]^{3-}$ and $[Fe(CN)_4NO]^{2-}$, a minor pathway proceeds via the nitrosothiol RSNO [1, 13]. Whichever pathway is operative the net result is a redox reaction which effectively and quantitatively removes both RSH and $[Fe(CN)_5NO]^{2-}$ from the system. We have previously pointed out [1] that if the interaction of thiopental with nitroprusside proceeds along the same type of pathway as observed for other RSH species, then this would have the effect of simultaneously destroying both the anaesthetic drug thiopental and the hypotensive drug nitroprusside.

Although 2-thiouracil has been reported to occur as the thiol (**3a**), rather than as the thione isomer (**3b**) [14], the weight of evidence on thiobarbituric



3a



3b

acids [15–17] suggests that they exist in solution predominantly in the thione form. If, then, thiopental exists predominantly as **2a**, rather than as **1a**, its reactivity towards nitroprusside may be expected to resemble that of a thione, rather than of a thiolate. Thiourea, a thione clearly related to both **2** and **3b**, although not reacting with nitroprusside at neutral pH in the dark, upon photolysis, or upon acidification of a previously basified solution yields $[Fe(CN)_5SC(NH_2)_2]^{2-}$ [18, 19], eqns. (1) and (2)

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$$[Fe(CN)_5NO]^{2-} \xrightarrow[-NO, +H_2O]{h\nu} [Fe(CN)_5H_2O]^{2-} \xrightarrow{SC(NH_2)_2} [Fe(CN)_5SC(NH_2)_2]^{2-} \quad (1)$$

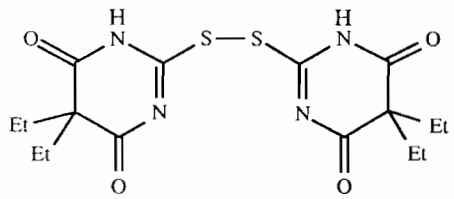
$$[Fe(CN)_5NO]^{2-} \xrightarrow{OH^-} [Fe(CN)_5NO_2]^{4-} \xrightarrow[-NO_2^-]{+SC(NH_2)_2} [Fe(CN)_5SC(NH_2)_2]^{3-} \xrightarrow[\text{by } HNO_2]{H^+;\text{oxidation}} [Fe(CN)_5SC(NH_2)_2]^{2-} \quad (2)$$

The reaction with thiocyanate to yield $[Fe(CN)_5SCN]^{3-}$ follows similar pathways [20, 21].

The fact that the same complexes, as judged spectrophotometrically [8], were formed by reaction of thiopental with both $[Fe(CN)_5NO]^{2-}$ and $[Fe(CN)_5NH_3]^{3-}$ suggests at once that thiopental is behaving towards nitroprusside not as a thiol, as suggested [8], but rather as a thione in a manner similar in fact to thiourea. As thiopental itself is a restricted substance, we have modelled its behaviour using the 5,5-diethyl analogue (**1b**) (or (**2b**)): here we present the results of a study of the reactions of **1b**/**2b** and **1c**/**2c** with nitroprusside.

Results and Discussion

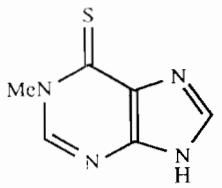
The ^{13}C NMR spectrum of 5,5-diethylthiobarbituric acid is extremely simple and indicates equivalence of the two carbonyl groups: in addition the carbon bound to sulphur resonates at δ 176.1. Oxidation to give compound **4** causes a shift in the C–S



4

resonance to δ 149.4. Such a shift is very similar to the difference observed between the C–S shifts in **5** and **6**, δ 171.7 and δ 150.2 respectively [22, 23], where no possibility exists of tautomerism involving sulphur.

On the basis of these NMR data, we conclude that 5,5-diethylthiobarbituric acid exists in solution as the thione (**2b**), rather than as the thiol (**1b**). MNDO calculations on the system **1c**/**2c** confirm that the thione tautomer (**2c**) is more stable than the thiol tautomer (**1c**) by some 45 kJ mol^{-1}, and



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6

show that even in the N-deprotonated form of **1c**/**2c** there is still considerable double bond character in the C–S bond. Accordingly it may be expected that the thione reaction with nitroprusside will be dominant at any physiologically significant pH.

We observed no reaction between nitroprusside and either **2b** or **2c** in the dark, in aqueous buffers in the pH range 4.0 to 9.2. On exposure to ordinary laboratory lighting (unfiltered light, pyrex glassware), equimolar solutions of **2b** and nitroprusside turned blue and gave a new absorption in the electronic spectrum, at 590 nm at pH 9.2 shifting to 610 nm at pH 6.9. Under identical conditions thiourea gave maxima at 590 (pH 9.2) or 585 (pH 6.9) nm while thiocyanate gave maxima at 590 and 580 nm respectively: these are identical with the values reported [18–21] for $[Fe(CN)_5SC(NH_2)_2]^{2-}$ and $[Fe(CN)_5SCN]^{3-}$ respectively. The solutions containing thiourea and thiocyanate both also showed weak absorption at 390 nm, which arises from $[Fe(CN)_5H_2O]^{2-}$, the primary photoproduct of nitroprusside [24, 25].

In a parallel series of experiments using **2b**, thiourea or thiocyanate, solutions containing equimolar quantities of nitroprusside and the sulphur ligand were, in the dark, firstly raised to pH 9.2 and then after 30 min the pH was reduced to 4.0. At pH 4.0 these solutions showed absorption maxima at 590, 590 and 585 nm, respectively. The spectra were not distinguishable from those of solutions which had previously been exposed to light, at the same pH. Hence, the same changes are occurring upon photolysis in the presence of the sulphur ligands (eqn. (1)), as upon basification followed by acidification (eqn. (2)). Moreover the same chromophore, $[Fe^{III}(CN)_5S{=}C<]$, is formed for each of **2b**, thiourea and thiocyanate.

Confirmation of the intermediacy of $[Fe(CN)_5H_2O]^{2-}$ in these reactions was obtained by reaction of each of **2b**, thiourea and thiocyanate with preformed [26] $[Fe(CN)_5H_2O]^{2-}$ in the dark at pH 4.0. In each case the spectral changes were identical to those observed with nitroprusside. On the other hand, we at no stage observed any absorption in the range 520–525 nm, characteristic [13] of adducts of nitroprusside with thiolates, of type $[Fe(CN)_5N(O)SR]^{3-}$.

Further confirmation of the lack of any typical thiolate reaction of **1b**/**2b** whith nitroprusside was obtained from ^{13}C NMR observations. When a solu-

tion comprising equimolar quantities of sodium nitroprusside and **2b** in aqueous methanol was sealed under vacuum and kept in the dark, no change in the ^{13}C NMR spectrum was apparent over many months. In particular no new resonances appeared which were assignable either to the oxidation product **4** or to $[Fe(CN)_6]^{4-}$ both of which would have been produced if (**2b**) had taken part in a typical [13] thiolate reaction with nitroprusside.

Conclusions

We conclude from these experiments firstly that, on the basis of ^{13}C NMR evidence, thiobarbiturates exist in solution at physiologically pHs in the thione form (**2**), rather than the thiol form (**1**): secondly, that there is no reaction between thiobarbiturates (**2**) and nitroprusside in the dark, but that when **2** interacts with a nitroprusside solution which has been exposed to even moderate illumination, complexation by **2** of $[Fe(CN)_5]^{2-}$ results. We have pointed out on previous occasions [1, 27, 28] the hazards which arise from exposure of sodium nitroprusside infusion solutions to light before administration to patients: the present study indicates that an additional problem with such solutions is their ready reactivity with thiobarbiturate anaesthetics, involving not only destruction of the hypotensive drug but simultaneous sequestration and complexation of the anaesthetic drug. As we have shown previously [29], complexation of a pharmacologically active drug to an electrophilic metal centre can have a drastic impact on the pharmacodynamics of the drug.

Experimental

^{13}C NMR spectra were measured at ambient temperature and 75.47 MHz, using a Brüker AM-300 spectrometer. Electronic spectra were measured using a Pye-Unicam SP8-150 spectrophotometer.

$Na_2[Fe(CN)_5H_2O]$ was prepared by the literature method [26]. $Na_2[Fe(CN)_5NO]2H_2O$ was A.C.S. Reagent grade, and was used as received: all manipulations involving solutions of sodium nitroprusside were carried out with exclusion of light, except where stated otherwise in the text.

Preparation of Compound 1b

The compound was prepared by base-induced condensation of dimethyl diethylmalonate, $Et_2C(COOMe)_2$ with thiourea [30]. *Anal.* Found: C, 47.6; H, 6.1; N, 13.8. Calc. for $C_8H_{12}N_2O_2S$: C, 48.0; H, 6.0; N, 14.0%. NMR: δ(H), $CDCl_3$: 0.90 (t, *J* 8 Hz, 6H, 2 × CH_3), 2.10 (q, *J* 8 Hz, 4H, 2 × CH_2, 9.2 (s, br, 2H, 2 × N*H*); δ(C), $CDCl_3$: 9.5 (q, 2 × CH_3), 32.1 (t, 2 × CH_2), 58.3 (s, $Et_2C<$), 170.5 (s, 2 × *C*=O), 176.1 (s, *C*=S). Infrared, ν_{max} (cm^{-1}): 3280, 3190 (NH). Mass spectrum, *m/z*: 200 (M^+), 172 $(M - CO)^+$, 157 $(M - HNCO)^+$, 129 $(Et_2CNHCS)^+$.

Preparation of Compound 4

Dissolution of **1b** in aqueous base, followed by titration with elemental bromine afforded **4**. NMR: δ(H), CD_3COCD_3: 0.72 (t, *J* 8 Hz, 12H, 4 × CH_3), 1.82 (q, *J* 8 Hz, 8H, 4 × CH_2), 10.2 (s, br, 2 × N*H*); δ(C), CD_3COCD_3: 9.0 (q, 4 × CH_3), 31.8 (t, 4 × CH_2), 57.4 (s, $Et_2C<$), 149.4 (s, *C*–S), 172.8 (s, 2 × *C*=O).

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