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Inorganic Chemistry Communications 6 (2003) 819–822
INORGANIC CHEMISTRY COMMUNICATIONS
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A mononuclear complex of norfloxacin with silver(I) and its properties

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Received 11 March 2003; accepted 28 March 2003

Abstract

Reaction of norfloxacin (H-Norf) with $AgNO_3$ yields an unusual mononuclear complex $[Ag(H\text{-}Norf)_2]NO_3$ (**1**) in which the local coordination environment around Ag^+ ion is approximately linear with a N–Ag–N angle of 162.1(2)°. Larger concentration of Ag^+ ions was found in water solution of **1**. The unique bonding in **1** may lead to the readily release of Ag^+ ion from **1**, and leads to better antibacterial action in topical burn treatments. Strong blue fluorescent emission of **1** was also observed.

Keywords: Norfloxacin; Silver; Ag^+Release; Fluorescence; Crystal structure

1. Introduction

Silver complex of norfloxacin (1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid, H-Norf) was reported to prevent bacterial infection for humans during burn treatment [1], and its antibacterial property in topical applications is superior to those of silver and zinc sulfadiazine (AgSD and ZnSD) [2]. In both cases, the polymeric structures of these complexes are highly relevant to the slow release of the metal ions Ag^+ and Zn^{2+} as well as to their biological activity. Complexes of H-Norf with metal ions have thus attracted much attention lately due in part to H-Norf antibacterial action involving metal ion mediation [3]. Usually, the sites of bonding of metal ions with quinolones clearly involve the 4-oxo and 3-carboxyl oxygen atoms, and such bonding results in the formation of a stable six-membered chelate ring, even though the reaction takes place in weakly basic solutions [4]. To our surprise, the reaction of H-Norf with Ag^+ affords a monomeric $Ag(H\text{-}Norf)_2(NO_3)$ (**1**) in which H-Norf only acts as a monodentate ligand to bind to Ag^+ ion by the N atom of piperidyl ring (Scheme 1). To the best of our knowledge, **1** is the first example of the complexes of H-Norf with a metal ion involving only the coordination of N atom of piperidyl ring. Accordingly, the coordination mode of H-Norf in **1** provides a new insight into the understanding of H-Norf drug action mechanism. As a continuation of our work about the solid state structures of the complexes of H-Norf with metal ion [4g-I], we report herein synthesis, solid state structure, water solubility and fluorescent property of **1**.

2. Experimental section

2.1. *Preparation of* 1

A mixture of $AgNO_3$ (1.0 mmol, 0.17 g), H-Norf (2.0 mmol, 0.640 g), water (20 ml) and concentrated aqueous NH_3 (10 ml) was heated to reflux at 100 °C for 8 h. The resulting colorless precipitate was collected through filtration to give 0.323 g of **1** (0.4 mmol, 60% yield based H-Norf). The colorless block single crystals of **1** suitable for X-ray analysis were obtained from a solution of

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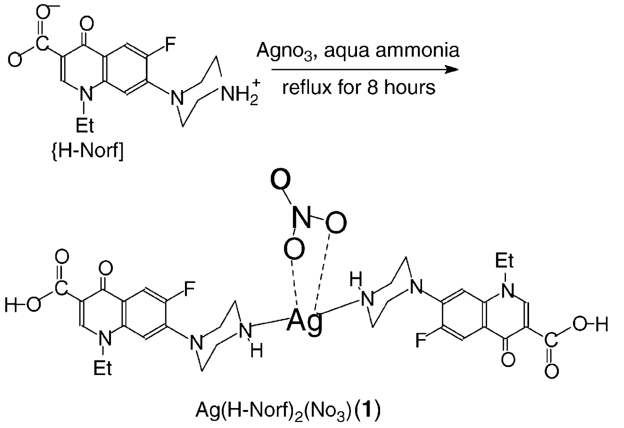
doi:10.1016/S1387-7003(03)00115-1



Scheme 1.

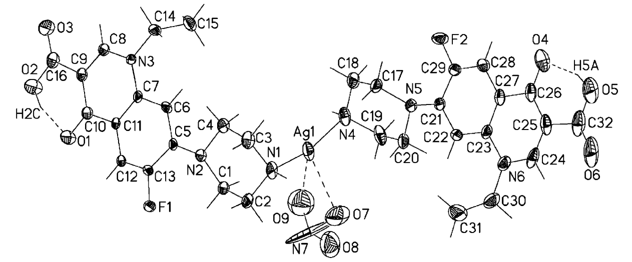


Fig. 1. ORTEP view of Ag(H-Norf)$_2$(NO$_2$) (**1**). The thermal ellipsoids are drawn at 30% probability level. Selected bond lengths (Å) and angles (°): Ag(1)–N(1) 2.182(5), Ag(1)–N(4), 2.188(5), F(1)–C(13) 1.363(5), F(2)–C(29) 1.366(6), O(1)–C(10) 1.280(6), O(2)–C(16) 1.343(8), O(3)–C(16) 1.209(7), O(4)–C(26) 1.259(8), O(5)–C(32) 1.298(12), O(6)–C(32) 1.199(11), N(1)–C(2) 1.465(8), N(2)–C(4), 1.467(7), N(2)–C(1) 1.477(7), N(3)–C(8) 1.345(6), N(3)–C(7) 1.394(6), N(3)–C(14) 1.478(6); N(1)–Ag(1)–N(4) 162.2(2), C(2)–N(1)–C(3) 107.6(5), C(18)–N(4)–C(19) 109.2(5), C(2)–N(1)–Ag(1) 113.7(4), C(18)–N(4)–Ag(1) 113.9(4), C(3)–N(1)–Ag(1) 111.7(4), C919)–N(4)–Ag(1) 112.6(4).

powdered **1** in water and ethanol heated for one day at 105 °C, followed by slow cooling to room temperature. Anal. Calc. for $C_{32}H_{36}F_2N_7O_9Ag$: C, 47.49; H, 4.45; N, 12.12. Found: C, 47.38; H, 4.50; N,12.07. IR of **1** (KBr, cm^{-1}): 3297(w), 1709(m), 1627(s), 1477(s), 1383(s), 1259(s), 1200(m), 1128(m), 1037(m), 928(w), 827(w), 750(m). **1** was also obtained from the reaction of $AgNO_3$, H-Norf, water in the absence of aqua ammonia, suggesting that pH has little influence on the reaction.

2.2. The measurement of equilibrium constants of 1

The composition and the stability constant of Ag^+ and H-Norf complex can be deduced from the following formula [8]:

$$M + nL = ML_n,$$

$$\log[F_0 - F] = n \log F + \log K + \log[M] + \log n, \qquad (1)$$

where M is the metal ion, L is H-Norf molecule, ML_n is the complex compound with a stability constant of K, F_0 is the fluorescence of the overall amount of the pharmaceutical molecule (bound and unbound), F is the fluorescence of unbound pharmaceutical molecule. When the concentration of metal [M] ion is fixed. A plot of log $[F_0 - F]$ versus log F will give straight line with a slope of n and y-axis intercept containing stability constant K (see Fig. 3).

Fig. 1 showed the data analysis of log $[F_0 - F]$ vs. log F. F_0 was determined in the solution of the same H-Norf concentration without presence of Ag^+. The correlation coefficient was 0.9987, suggesting the result was well fitted to Eq. (1). From the slope of 0.983 ± 0.015, the n value 1 was obtained. The stability constant, K, is calculated to be $1108 \pm 230\ M^{-1}$. The result indicates that the Norf can form a stable 1:1 complex with Ag^+.

2.3. The measurement of equilibrium constants of AgSD

Due to the fluorescent inactivity of SD, the composition and stability constant of Ag^+ and SD complex was determined by using potentiometry. A silver ion selective electrode was used for this performance. Upon addition of Ag^+ in the concentration range of 2×10^{-5} to 2×10^{-6} M to the solution containing 0.1 M KNO_3 and 5.05×10^{-5} M SD, the electrode potentials obtained increased. From the standard curve of the electrode potential vs. the logarithm of Ag^+ concentration, the concentrations of free Ag^+ in Ag^+–SD system were obtained. Thus, the stability constants could be calculated supposing the 1:1, 1:2 and 1:3 Ag^+–SD composition, respectively. When the Ag^+–SD composition was 1:1, the stability constant showed the lowest standard error. The average stability constant for six different Ag^+ concentration was calculated to be $2.43 \pm 0.98 \times 10^3\ M^{-1}$.

Table 1
Crystal data and structure refinement for **1**

Empirical formula	$C_{32}H_{36}F_2N_7O_9Ag$
Fw	808.55
T (K)	293(2) K
Crystal system	Triclinic
Space group	P-1(No. 2)
a (Å)	9.7100(2)
b (Å)	13.3498(2)
c (Å)	14.0331(1)
α (deg)	75.869(1)
β (deg)	78.338(1)
γ (deg)	72.277(1)
V (Å^3)	1664.13(5)
Z	2
ρ (cald) (g/cm^3)	1.614
μ(Mo-Kα) (cm^{-1})	6.83
F(000)	828
$R1$, $wR2$ [$I > 2\sigma(I)$]	0.0765, 0.1851
(All data)	0.1527, 0.2256

$R1 = \sum ||F_o| - |F_c|| / \sum |F_o| wR2 = \left[\sum w(F_0^2 - F_c^2)^2 / \sum w(F_0^2)^2\right]^{1/2}$

2.4. X-ray crystallographic determinations of **1**

Data were collected at room temperature using epoxy-coated crystals mounted on glass fiber. All measurements were made on a CCD Smart diffractometer with graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Empirical absorption corrections were applied in each case. Relevant crystallographic data are presented in Table 1. The structure was solved with Direct methods using the program SHELXTL (Sheldrick, 1997) [9]. All the nonhydrogen atoms were located from the trial structure and then refined anisotropically with SHELXTL using full-matrix least-squares procedure. The hydrogen atom positions were fixed geometrically at calculated distances and allowed to ride on the parent carbon atoms. The final difference Fourier map was found to be featureless.

3. Results and discussion

Colorless powdered solids of **1** were prepared in 60% yield by refluxing of a 1:2 mixture of $AgNO_3$ and H-Norf in NH_3/water at 100 °C for 8 h (Scheme 1). NH_3 may play an important role in protecting Ag^+ decomposition and slowly releasing of Ag^+ from the complex of $[Ag(NH_3)_2](NO_3)$ to get good crystals suitable for X-ray analysis because in the abstract of NH_3 we also can get powdered compound **1** in the same conditions. The IR spectrum of compound **1** shows distinct bands of $v(COOH)$ and $v(C–O_{keto})$ which are similar to those of free norfloxacin, indicating the presence of uncoordinated $O_{carboxylate}$ and O_{keto} in **1**.

The molecular structure of **1** (Fig. 1) consists of cationic mononuclear units of $[Ag(H\text{-}Norf)_2]^+$ and weekly coordinated anionic NO_3^-. The H-Norf ligand in **1** acts as a neutral monodentate to coordinate to Ag atom by N atom of piperidyl ring, and 4-oxo and 3-carboxylate oxygen atoms do not take part in the coordination. Unlike in other known complexes of H-Norf ligand [4], only N of the piperidyl ring in H-Norf coordinates to the silver ion in **1**. This bonding mode was unexpected and, to our knowledge, unprecedented in quinolone drug interactions toward metal ions. The local coordination environment around Ag^+ ion is approximately linear [N(1)–Ag(1)–N(4) = 162.1(2)°]. The deviation from the linear geometry is probably a result of a weak interaction between Ag^+ ion and NO_3^- anion [Ag(1)–O(7) 2.661 Å and Ag(1)–O(9) 2.841 Å. O7 and O9 link to Ag^+ by dotted line in Fig. 1]. The silver atom may be considered to be 4-coordinated. Two neutral H-Norf ligands locate in the *trans*-position around axis of N(1)–Ag–N(4), and the Ag atom is in a symmetric center. H-Norf ligand basically maintains the structure of uncoordinated molecule as observed in $Nof \cdot 2DCl \cdot D_2O$ [5]. However, the strong intramolecular hydrogen bonds (2.532–2.534 Å) were observed between O1 and O2 as well as between O4 and O5. The hydrogen bonds may have prevented the carboxylate groups from coordinating to the Ag^+ ion. The bond distances such as Ag–N, C–C, C–N, C–O and C–F are unexceptional.

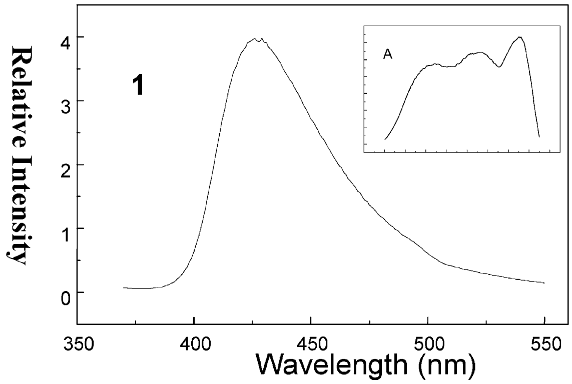


Fig. 2. Fluorescent spectrum of **1** in the solid state at room temperature. A: exciting spectrum, $\lambda_{max} = 390$ nm, **1**: emission spectrum $\lambda_{max} = 426$ nm.

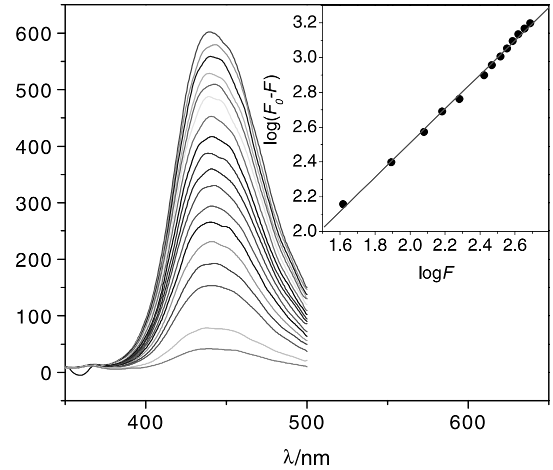


Fig. 3. Fluorescence emission spectra of H-Norf with the concentration of 3.33×10^{-7} to 6.00×10^{-6} mol/l (from lower to higher) in the presence of 4.96×10^{-3} mol/l Ag^+. Inset: plot of log $[F_0 - F]$ vs. log F.

To evaluate the solubility of **1** in water and the slow release of Ag^+, we have measured the equilibrium concentration of Ag^+ in water at room temperature and the equilibrium constant ($1.108 \pm 0.230 \times 10^3$ M^{-1}). In comparison, the equilibrium constant of AgSD was measured to be $2.43 \pm 0.98 \times 10^3$ M^{-1}. Thus, the larger concentration of Ag^+ of **1** in water, compared to that of AgSD probably is responsible for better antibacterial action of the former in topical burn applications.

Similar to $Zn(Norf)_2(H_2O)$ and $Zn(H\text{-}Norf)_2(NO_3)_2(H_2O)_2$ [4h], the fluorescent emission intensity of **1** in the solid state was about 2 times larger than that of free H-Norf, as shown in Fig. 2. The enhancement may be due to the coordination of H-Norf to Ag^+ increasing the ligand conformational rigidity, thereby reducing the nonradiative decay of the intraligand $^1(\pi\text{–}\pi^*)$ excited state. Similar enhancement of the intraligand fluorescence has also been reported for $[Zn(terpyridine)_2]^{2+}$ and $[Zn(L)_2(OAc)_2]$ ($L = N,N'$-bisbenzyl-2,7-diamino-1,8-naphthyridine) [6]. The solid state diffuse reflectance UV–Vis spectrum of **1** shows two intense bands at 335 and 283 nm which are ascribed to intraligand $\pi\text{–}\pi^*$ transition of H-Norf (329.9 and 278.1 nm) and match well with excitation spectrum of **1** and free ligand ($\lambda_{max} = 350$ nm). The emission of **1** [$\lambda_{max} = 426$ nm ($\tau = 1.1$ ns, $\Phi_{em} \approx 0.23$)] (τ is the lifetime, Φ is the quantum efficiency) is neither metal-to-ligand charge transfer (MLCT) nor ligand-to-metal charge transfer (LMCT) in nature, and can be tentatively assigned to the intraligand fluorescent emission since a weak similar emission [$\lambda_{max} = 440$ nm($\tau = 1.0$ ns, $\Phi_{em} \approx 0.11$)] is also observed for free H-Norf. It is worthy noting that a blue shift (14 nm) occurred for **1** from that of free H-Norf, probably as a result of decreased $\pi\text{–}\pi$ stacking interactions in **1** [7].

In conclusion, silver salt of H-Norf having better antibacterial action in topical burn treatments may be the result of unique bonding between the ligand and Ag^+ and its mononuclear structure. Such bonding may have result in the larger concentration and fast release of Ag^+.

Supporting Information Available

X-ray crystallographic files in CIF format for compound **1** is available from Prof. Dr. Ren-Gen Xiong.

Acknowledgements

This work was funded by The Major State Basic Research Development Program (Grant No. G2000077500), National Natural Science Foundation of China (Grand No. 20028101).

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