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Novel peroxosolvates of quinolone antibiotics containing large hydrogen peroxide clusters

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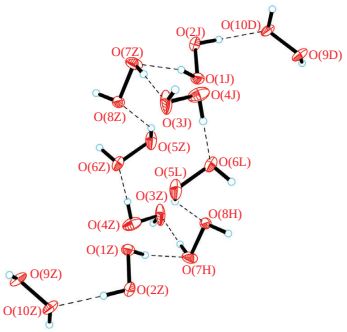
Novel class of multicomponent quinolone antibiotics, crystalline hydrogen peroxide adducts of nalidixic acid $C_{12}H_{12}N_2O_3 \cdot H_2O_2$ and ciprofloxacin $C_{17}H_{18}F_1N_3O_3 \cdot 5H_2O_2$, were prepared from highly concentrated hydrogen peroxide, and their structures were determined by X-ray crystallography. The second compound contains decameric H-bonded hydrogen peroxide clusters, which makes this substance one of the richest in hydrogen peroxide among organic peroxosolvates.



Keywords: peroxosolvates, hydrogen bonding, crystal packing, H-bonded clusters, multicomponent antibiotics, drug–drug cocrystals.

In the last decade, the development of drug–drug multicomponent crystals became one of the most promising areas in pharmaceutical chemistry[1–3] due to synergetic effect of their active ingredients[4–6] and increased bioavailability.[7–9] In this vein, peroxosolvates (crystalline adducts of hydrogen peroxide[10,11]) of pharmaceutic compounds look very promising since H_2O_2 exhibits wide spectrum of antimicrobial activity[12–14] and demonstrates unsurpassed hemostatic effect.[15–17] However, there are some evident restrictions on the choice of organic coformer. At first, it must be stable to the oxidizing action of hydrogen peroxide. Secondary, coformer molecules must be able to act as effective proton donor/acceptor in solid phases since the stability of peroxosolvates is governed by the strength, amount and topological organization of hydrogen bonds formed by H_2O_2 molecules.[18–20] Finally, hydrogen peroxide is not suitable for intravenous or gastroenteric use. Thus, only active pharmaceutical ingredients (APIs) employed for dermal, otorhinolaryngologic, and dental applications are of interest for perhydrate development. Despite these limitations, two relatively stable peroxosolvates of antimicrobial APIs, namely miconazole and nitrofurantoin, were obtained recently.[21,22]

Nalidixic acid (NA) and ciprofloxacin (CP) belong to the first and second generations of quinolone antibiotics, respectively.[23] Both compounds have a broad spectrum of antibacterial activity while CP is one of the most used antibiotics worldwide.[24] In this study, we prepared peroxoslovates of these compounds, namely, $NA \cdot H_2O_2 = C_{12}H_{12}N_2O_3 \cdot H_2O_2$ **1** and $CP \cdot 5H_2O_2 = C_{17}H_{18}F_1N_3O_3 \cdot 5H_2O_2$ **2**. Peroxosolvates **1** and **2** were obtained by low temperature crystallization from highly concentrated hydrogen peroxide solutions (danger of explosion!)[10,11] and their structures were established by X-ray diffractometry.†

Both substances **1** and **2** represent colourless crystalline solids stable for approximately half an hour without mother

† *Crystal data for* **1**. $C_{12}H_{14}N_2O_5$, $M = 266.25$, triclinic, $a = 7.1035(4)$, $b = 9.6341(6)$ and $c = 9.9683(6)$ Å, $\alpha = 106.911(2)$, $\beta = 104.324(2)$, and $\gamma = 102.288(2)°$, $V = 601.82(6)$ Å^3, space group $P\bar{1}$, $Z = 2$, $d_{calc} = 1.469$ g cm^{-3}, $F(000) = 280$, $\mu(MoK_\alpha) = 0.116$ mm^{-1}, colourless plate with dimensions *ca*. 0.30 × 0.15 × 0.02 mm. Total 8755 reflections (3198 unique, $R_{int} = 0.0215$). All hydrogen atoms were found from difference Fourier synthesis and refined with isotropic thermal parameters. The final residuals were: $R_1 = 0.0409$ for 2720 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.1039$ for all data and 228 parameters. GoF = 1.076. Largest difference peak/hole 0.34/–0.21 e Å^{-3}.

Crystal data for **2**. $C_{17}H_{28}F_1N_3O_{13}$, $M = 501.42$, triclinic, $a = 7.6295(3)$, $b = 9.4504(4)$ and $c = 14.5004(6)$ Å, $\alpha = 90.7960(12)$, $\beta = 97.0169(14)$ and $\gamma = 90.1787(14)°$, $V = 1037.56(7)$ Å^3, space group $P\bar{1}$, $Z = 2$, $d_{calc} = 1.605$ g cm^{-3}, $F(000) = 528$, $\mu(MoK_\alpha) = 0.144$ mm^{-1}, colourless prism with dimensions *ca*. 0.20 × 0.17 × 0.07 mm. Total 17079 reflections (6043 unique, $R_{int} = 0.0220$). Two of five independent peroxide molecules were disordered over two or three positions with occupancy ratios 0.883(2)/0.117(2) and 0.539(3)/0.279(2)/0.182(2). All H atoms (except for disordered H_2O_2) were found from difference Fourier synthesis and refined with isotropic thermal parameters. Hydrogen atoms of disordered peroxide species were placed on the lines connecting hydrogen bonded oxygen atoms at distances 0.85 Å from O_{peroxo} positions and they were refined using a riding model (AFIX 3) with $U_{iso}(H) = 1.5U_{eq}(O)$. The final residuals were: $R_1 = 0.0436$ for 5299 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.1122$ for all data and 447 parameters. GoF = 1.029. Largest difference peak/hole 0.59/–0.64 e Å^{-3}.

Experimental data sets were collected on a Bruker D8 Venture machine using graphite monochromatized Mo$K\alpha$ radiation ($\lambda = 0.71073$ Å). Absorption corrections based on measurements of equivalent reflections were applied (SADABS). The structures were solved by direct methods and refined by full matrix least-squares on F^2 with anisotropic thermal parameters for all non-hydrogen atoms using SHELXTL software. Details of X-ray studies are given in Online Supplementary Materials, Table S3. The single-crystal X-ray diffraction experiments were performed at the Centre of Shared Equipment of IGIC RAS.

CCDC 2292623 and 2292624 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

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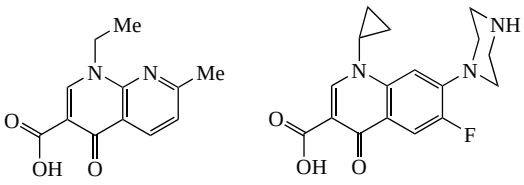

Nalidixic acid Ciprofloxacin

liquors. The structure **1** comprises one unique NA coformer and one H_2O_2 molecule lying on general positions (Figure 1). Fragment NA exhibits non-zwitterionic form with short intermolecular hydrogen bond between carboxy and keto groups (d[O(3)···O(1)] = 2.545(1) Å). This configuration is very typical for NA containing crystals (nine polymorphs hydrates, and cocrystals according to March 2003 version of CSD[25]). The hydrogen peroxide molecule adopts skew conformation with H–O–O–H torsion angle equal to 94(2)°. The O–O bond distance [1.461(1) Å] lies within normal range for solvent H_2O_2 molecules [1.442(7)–1.470(2) Å].[10]

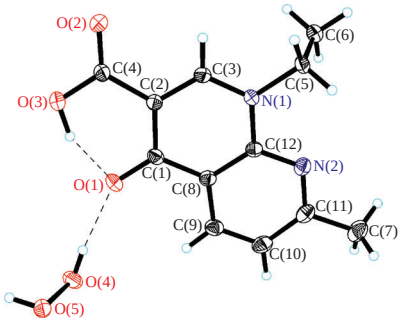

Figure 1 Asymmetric unit in the structure **1**. Displacement ellipsoids are shown at 50% probability level. Hydrogen bonds are drawn by dashed lines.

Molecules H_2O_2 are involved in only two moderate hydrogen bonds forming insular centrosymmetric $R_6^6(18)$ motif (Figure 2). It should be noted that hydrogen peroxide participates at least in two hydrogen bonds as proton donor in crystalline adducts[10,11] while the maximal possible number of H-bonds is six (two as proton donor and four as proton acceptor).[10,19] It is of note that all peroxide species are weak donors of electron lone pairs.[26]

Structure **2** contains one independent CP zwitterion and five hydrogen peroxide molecules (Figure 3). In contrast to NA, ionic form for neutral CP species is preferable in crystalline state (nine polymorphs hydrates, and cocrystals[25]) with the only exception for second polymorph of unsolvated CP.[27] Two of five

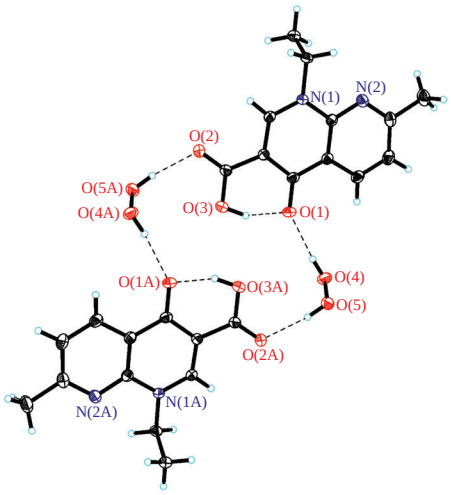

Figure 2 Hydrogen bonded cycles in the structure **1**.

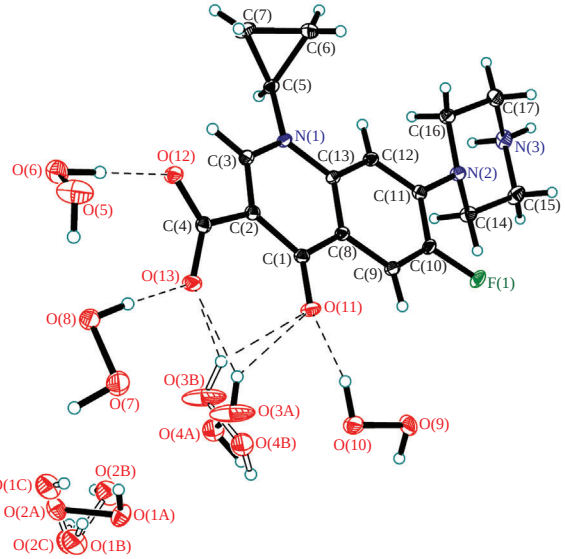

Figure 3 Asymmetric unit in the structure **2**. Displacement ellipsoids are shown at 50% probability level. Hydrogen bonds are drawn by dashed lines. Minor components of disorder are depicted by open lines.

hydrogen peroxide molecules are disordered over two or three positions (see Online Supplementary Materials, Figures S1–S5). All of them represent skew geometry (H–O–O–H angles vary within 87–154°) and are involved in three or five H-bonds. Two-positional disorder of H_2O_2 is well-known,[28–30] but the structure exhibiting three-positional disorder of peroxide species was reported just once.[31] In crystal of **2**, the H(7)–O(7)–O(8)–H(8) molecule is the second known example of proton-donor peroxide moiety involved in bifurcated hydrogen bonding HOOH···2(O).[22]

Not so long ago, it has been suggested that the directed design of new crystal architectures containing large clusters of H_2O_2 molecules can lead to new peroxosolvates with high active oxygen content.[32] Recently, insular hydrogen peroxide dodecameric and pentameric clusters in the structures of 2-aminonicotinic acid and lidocaine *N*-oxide peroxosolvates have been reported.[31] Substance **2** contains large decameric H-bonded hydrogen peroxide clusters (Figure 4), which makes it one of the richest in hydrogen peroxide content among organic peroxosolvates.[33] The topology of these clusters may be treated as D2(1)R6(1)D2(1) according to the Infantes–Motherwell notation.[34]

In conclusion, two novel peroxosolvates of widely used quinolone antibiotics were prepared and their structures were explored by X-ray crystallography. Despite the fact that, due to

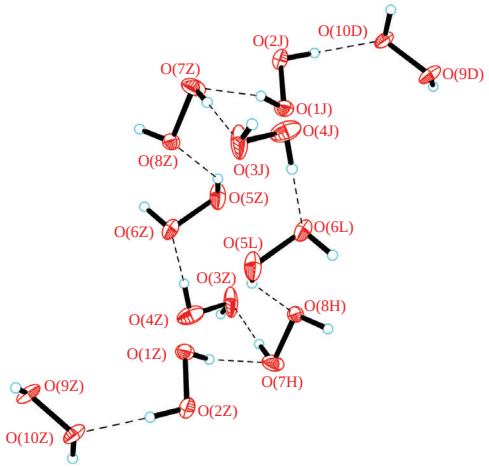

Figure 4 Centrosymmetric decameric H-bonded peroxide clusters in the structure **2**. Minor components of disorder are not shown.

insufficient stability, these compounds will not find application in medical practice, their preparation opens up a wide field for research. Quinolone antibiotics represent a large group of APIs whose molecules contain significant amounts of proton-donor and proton-acceptor sites. The latter makes them very promising for studying the possibilities of their cocrystallization with hydrogen peroxide.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.01.008.

References

1 X. Wang, S. Du, R. Zhang, X. Jia, T. Yang and X. Zhang, *Asian J. Pharm. Sci.*, 2021, **16**, 307.
2 R. K. Bandaru, S. R. Rout, G. Kenguva, B. Gorain, N. A. Alhakamy, P. Kesharwani and R. Dandela, *Front. Pharmacol.*, 2021, **12**, 780582.
3 M. Karimi-Jafari, L. Padrela, G. M. Walker and D. M. Croker, *Cryst. Growth Des.*, 2018, **18**, 6370.
4 F. Liu, Y. Song, Y.-N. Liu, Y.-T. Li, Z.-Y. Wu and C.-W. Yan, *Cryst. Growth Des.*, 2018, **18**, 1283.
5 N. K. Duggirala, M. L. Perry, Ö. Almarsson and M. J. Zaworotko, *Chem. Commun.*, 2016, **52**, 640.
6 L. Liu, Y. Lia, M. Zhang, Y. Zhang and B. Lou, *J. Pharm. Sci.*, 2022, **111**, 82.
7 M. Guo, X. Sun, J. Chen and T. Cai, *Acta Pharm. Sin. B*, 2021, **11**, 2537.
8 K. V. Drozd, A. N. Manin, A. V. Churakov and G. L. Perlovich, *CrystEngComm*, 2017, **19**, 4273.
9 F. Martin, M. Pop, I. Kacso, I. G. Grosu, M. Miclăuş, D. Vodnar, I. Lung, G. A. Filip, E. D. Olteanu, R. Moldovan, A. Nagy, X. Filip and I. Bâldea, *Mol. Pharmaceutics*, 2020, **17**, 919.
10 I. Yu. Chernyshov, M. V. Vener, P. V. Prikhodchenko, A. G. Medvedev, O. Lev and A. V. Churakov, *Cryst. Growth Des.*, 2017, **17**, 214.
11 A. G. Medvedev, A. V. Churakov, P. V. Prikhodchenko, O. Lev and M. V. Vener, *Molecules*, 2021, **26**, 26.
12 E. Le Toquin, S. Faure, N. Orange and F. Gas, *Front. Microbiol.*, 2018, **9**, 2295.
13 K. Nakamura, M. Shirato, T. Kanno, U. Örtengren, P. Lingström and Y. Niwano, *Int. J. Antimicrob. Agents*, 2016, **48**, 373.
14 J. Mills, K. M. Horváth and G. Brightwell, *Meat Science*, 2018, **143**, 69.
15 J. Weiss, F. J. Winkelman, A. Titone and E. Weiss, *Dermatol. Surg.*, 2010, **36**, 1601.
16 C.-Y. Hsieh, C.-J. Hsu, H.-P. Wu and C.-H. Sun, *J. Clin. Med.*, 2022, **11**, 2723.
17 F. M. Hankin, S. E. Campbell, S. A. Goldstein and L. S. Matthews, *Clin. Orthop. Relat. Res.*, 1984, **186**, 244.
18 C. R. Hilliard, N. Bhuvanesh, J. A. Gladysz and J. Blümel, *Dalton Trans.*, 2012, **41**, 1742.
19 A. V. Churakov, D. A. Grishanov, A. G. Medvedev, A. A. Mikhaylov, M. V. Vener, M. A. Navasardyan, T. A. Tripol'skaya, O. Lev and P. V. Prikhodchenko, *CrystEngComm*, 2020, **22**, 2866.
20 L. M. Foroughi and A. J. Matzger, *Cryst. Growth Des.*, 2021, **21**, 5873.
21 K. M. Kersten, M. E. Breen, A. K. Mapp and A. J. Matzger, *Chem. Commun*., 2018, **54**, 9286.
22 M. V. Vener, A. V. Churakov, A. P. Voronin, O. D. Parashchuk, S. V. Artobolevskii, O. A. Alatortsev, D. E. Makhrov, A. G. Medvedev and A. Filarowski, *Molecules*, 2022, **27**, 717.
23 M. I. Andersson and A. P. MacGowan, *J. Antimicrob. Chemother.*, 2003, **51**, S1.
24 S. Heeb, M. P. Fletcher, S. R. Chhabra, S. P. Diggle, P. Williams and M. Cámara, *FEMS Microbiol. Rev.*, 2011, **35**, 247.
25 C. R. Groom, I. J. Bruno, M. P. Lightfoot and S. C. Ward, *Acta Crystallogr.*, 2016, **B72**, 171.
26 A. G. Medvedev, M. Yu. Sharipov, D. A. Grishanov, A. V. Eshtukov, A. V. Churakov, I. A. Buldashov, P. A. Egorov, O. Lev and P. V. Prikhodchenko, *Mendeleev Commun.*, 2022, **32**, 57.
27 S. Mahapatra, K. N. Venugopala and T. N. G. Row, *Cryst. Growth Des.*, 2010, **10**, 1866.
28 A. V. Churakov, A. V. Medved'ko, P. V. Prikhodchenko, D. P. Krut'ko and S. Z. Vatsadze, *Mendeleev Commun.*, 2021, **31**, 352.
29 L. G. Kuz'mina and A. V. Churakov, *Russ. Chem. Bull.*, 2022, **71**, 283.
30 F. F. Arp, N. Bhuvanesh and J. Blümel, *Dalton Trans.*, 2019, **48**, 14312.
31 D. A. Grishanov, M. A. Navasardyan, A. G. Medvedev, O. Lev, P. V. Prikhodchenko and A. V. Churakov, *Angew. Chem., Int. Ed.*, 2017, **56**, 15241.
32 M. A. Navasardyan, D. A. Grishanov, P. V. Prikhodchenko and A. V. Churakov, *Acta Crystallogr.*, 2020, **E76**, 1331.
33 P. V. Prikhodchenko, A. G. Medvedev, T. A. Tripol'skaya, A. V. Churakov, Y. Wolanov, J. A. K. Howard and O. Lev, *CrystEngComm*, 2011, **13**, 2399.
34 L. Infantes and S. Motherwell, *CrystEngComm*, 2002, **4**, 454.

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