^{1}H NMR ($CDCl_3$): $\delta = 2.80$ (dd, $J = 7.4$, 5.0 Hz, 13-H), 4.92 (s, 21-H_2), 1.27 (s, 23-H_3), 1.35 (s, 26-H_3); ^{13}C NMR ($CDCl_3$): $\delta = 32.2$ (C-11), 61.3 (C-12), 61.5 (C-13), 170.0 (C-20), 62.2 (C-21).

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[1] G. Höfle, N. Bedorf, K. Gert, H. Reichenbach (GBF), DE-B 4138042, **1993** [*Chem. Abstr.* **1993**, *120*, 52841]; G.Höfle, N. Bedorf, H. Steinmetz, D. Schomburg, K. Gerth, H. Reichenbach, *Angew. Chem.* **1996**, *108*, 1671 – 1673; *Angew. Chem. Int. Ed. Engl.* **1996** *35*, 1567 – 1569; K.Gerth, N. Bedorf, G. Höfle, H. Irschik, H. Reichenbach, *J. Antibiot.* **1996**, *49*, 560 – 563.

[2] M. Bollag, A. Mc Queney, J. Zhu, O. Hensens, L. Koupal, J. Liesch, M. Goetz, E. Lazarides, C. M. Woods, *Cancer Research* **1995**, *55*, 2325 – 2333.

[3] S. B. Horwitz, J. Fant, P. B. Schiff, *Nature* **1979**, *277*, 665 – 667.

[4] E. ter Haar, R. J. Kowalski, E. Hamel, C. M. Lin, R. E. Longley, S. P. Gunasekera, H. S. Rosenkranz, B. W. Day, *Biochemistry* **1996**, *35*, 243 – 250.

[5] W. Fenical, P. R. Jensen, T. Lindel, US-A 5.437.057, **1995** [*Chem. Abstr.* **1998**, *124*, 194297]; T. Lindel, P. R. Jensen, W. Fenical, B. H. Long, A. M. Casazza, J. Carboni, C. R. Fairchild, *J. Am. Chem. Soc.* **1997**, *119*, 8744 – 8745; B. H. Long, A. M. Casazza, J. Carboni, C. R. Fairchild, T. Lindel, P. R. Jensen, W. Fenical, *Cancer Res.* **1998**, *58*, 1111 – 1115.

[6] J. Kowalski, P. Giannakakou, E. Hamel, *J. Biol. Chem.* **1997**, *272*, 2534 – 2541.

[7] A. Wolff, A. Technau, G. Brandner, *Int. J. Onc.* **1997**, *11*, 123 – 126.

[8] P. F. Mühlradt, F. Sasse, *Cancer Res.* **1997**, *57*, 3344 – 3346.

[9] A complete comprehensive summary can be found in the following review: K. C. Nicolaou, F. Roschangar, D. Vourloumis, *Angew. Chem.* **1998**, *110*, 2120 – 2153; *Angew. Chem. Int. Ed.* **1998**, *37*, 2015 – 2045.

[10] D.-S. Su, A. Balog, D. Meng, P. Bertinato, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *Angew. Chem.* **1997**, *109*, 2178 – 2180; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2093 – 2096; T.-C. Chou, X.-G. Zhang, A. Balog, D.-S. Su, D. Meng, K. Savin, J. R. Bertino, S. J. Danishefsky, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 9642 – 9647; T.-C. Chou, X.-G. Zhang, C. R. Harris, S. D. Kuduk, A. Balog, K. Savin, S. J. Danishefsky, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 15798 – 15802.

[11] H. Reichenbach, G. Höfle, K. Gerth, H. Steinmetz (GBF), WO-A 9822461, **1998** [*Chem. Abstr.* **1998**, *129*, 5346]; G. Höfle in *GBF Annual Report* (Ed: J.-H. Walsdorff), GBF, Braunschweig, **1997**, pp. 91 – 92; I. Hardt, H. Steinmetz, K. Gerth, H. Reichenbach, G. Höfle, unpublished results.

[12] G. Höfle, M. Kiffe (GBF), DE-A 19542986 A1, **1997** [*Chem. Abstr.* **1997**, *127*,50474]; G. Höfle, M. Kiffe (GBF), WO-A 97 19086, **1998** [*Chem. Abstr.* **1998**, *127*, 81289]; M. Sefkow, M. Kiffe, D. Schummer, G. Höfle, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3025 – 3030; M. Sefkow, M. Kiffe, G. Höfle, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3031 – 3036; M. Sefkow, G. Höfle, *Heterocycles* **1998**, *48*, 2485 – 2488.

[13] G. Höfle, K. Gerth, unpublished results.

[14] The use of 1.5 equivalents of *m*-chloroperbenzoic acid in chloroform for 8 d at $-20\,^\circ$C leads to a conversion of 40 and 90%, respectively. Based on the amount of **1c** and **1d** consumed, 40% of **1a** and 70% of **1b** are obtained.

[15] M. Begtrup, L. Bo L. Hansen, *Acta Chem. Scand.* **1992**, *46*, 372 – 383.

[16] Crystal structure data: $C_{26}H_{39}NO_7S$, crystals from methanol, monoclinic, space group $C2$; $a = 2089.0(3)$, $b = 926.8(1)$, $c = 1651.7(2)$ pm, $\beta = 106.20(1)^\circ$, $Z = 4$, $\rho_{calcd} = 1.241$ g cm^{-3}, $Cu_{K\alpha}$ radiation ($\lambda = 154.178$ pm), $\theta - 2\theta$ measurement, $0^\circ \le 2\theta \le 110^\circ$, $R = 0.0552$ ($F \ge 0$), max. residual electron density 0.532 e cm^{-3} Programs used: SIR92 (Giacovazzo, 1994) and Siemens-SHELXL-PLUS (Unix version). Crystallographic data (excluding structure factors) of the structure described in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-116610. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[17] An *S*-oxide proposed in a report of a total synthesis of epothilone A (K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, F. Roschanger, F. Sarabia, S. Ninkovic, Z. Yang, J. I. Frujillo, *J. Am. Chem. Soc.* **1997**, *119*, 7960 – 7973) was presumably the *N*-oxide **2a**.

[18] This conformational change cannot be deduced from the coupling constants since 2-H_2 and 3-H for **2** as well as for **1** are in a *trans* and *gauche* orientation, respectively.

[19] Total synthesis: K. C. Nicolaou, Y. He, F. Roschangar, N. Paul King, D. Vourloumis, T. Li, *Angew. Chem.* **1998**, *110*, 89 – 92, *Angew. Chem. Int. Ed.* **1998**, *37*, 84 – 87.

[20] See for example: A. R. Katritzky, J. M. Lagowski, *Chemistry of Heterocyclic N-Oxides*, Academic Press, New York, **1971**, pp. 288, 352.

[21] Also without precedent is the isomeric structure of the *N*-acetyl-*S*-oxide **II**. For structural proof, the reaction is to be applied to model compounds to possibly obtain crystalline compounds of type **II** or **III**.

[22] H. J. Anderson, D. J. Barnes, Z. M. Khan, *Can. J. Chem.* **1964**, *42*, 2375 – 2380.

Molecular Beside Ionic: Crystal Structures of a 1/1 and a 1/4 Adduct of Pyridine and Formic Acid**

Dirk Wiechert and Dietrich Mootz*

Dedicated to Professor Heinz Dieter Lutz on the occasion of his 65th birthday

In the context of longstanding work in this laboratory on binary adducts composed of a neutral (uncharged) selected Brønsted base and acid, two such phases have recently been identified in the system pyridine/formic acid and their crystal structures determined. With rare reported precedence in analogous systems, one is molecular and the other ionic. Phase analysis of the system has been done by differential thermal analysis (DTA) and differential scanning calorimetry (DSC) as well as temperature-dependent X-ray powder diffraction. The adducts have stoichiometries $C_5H_5N \cdot HCOOH$ and $C_5H_5N \cdot 4\,HCOOH$ and melt at 219 and 233 K, respectively. The structures have been determined at 173 and 183 K.[1]

The results are visualized in Figure 1. In the 1/1 compound, a neutral molecule of the base and one of the acid form an O–H···N hydrogen-bonded heterodimer. The 1/4 compound is a pyridinium salt, $[C_5H_5NH][HCOO(HCOOH)_3]$. In the complex anion, reported here in a crystal for the first time, a central formate ion is coordinated, through rather strong O–H···O hydrogen bonds, by the three extra molecules of the acid. In these, the conformation of the carboxylic group is twice synplanar and once antiplanar. A hydrogen bond

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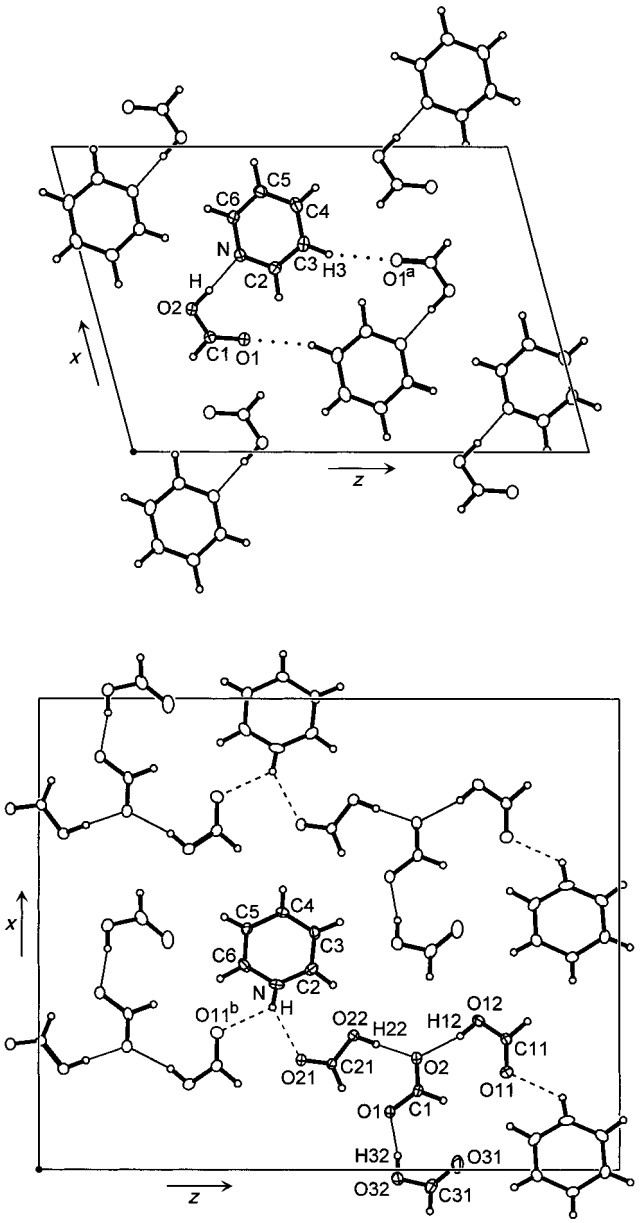

Figure 1. Projections of the molecular 1/1 adduct (top) and ionic 1/4 adduct (below) on the x,z planes of their unit cells; 25% ellipsoids for the non-hydrogen atoms; symmetry code a and b for $-x+1, -y+1, -z+1$ and $-x+0.5, y, z-0.5$, respectively.

N–H($\cdots$O)$_2$—that is, of yet another type and bifurcated—links the pyridinium cation with two complex anions and vice versa along a one-dimensional array parallel to the crystallographic z direction.

Some parameters of the covalent and hydrogen-bonding geometry, with H atom positions not corrected for the systematic errors of the X-ray method, are given in Tables 1 and 2. The above assignment of molecular or ionic to structures and species is not only based on which of the alternative positions for the proton in a hydrogen bond has been found occupied in each case, but is substantiated by the particular pattern of distances C–O and angles C-N-C.

With angles of 9 to 51° between the (best) planes through the two molecular or ionic species each involved in a hydrogen bond, the heterodimer as well as the one-dimensional array are not as close to planar as their projections in Figure 1 may infer. In the 1/1 compound, very weak further hydrogen bonding of the unconventional type C–H$\cdots$O[2] leads to a heterodimeric cyclic pair around an inversion center of the space group. Additional interactions of this type, not detailed in this account, can be perceived in either structure.

Table 1. Selected bond lengths [Å] and bond angles [°].

$C_5H_5N \cdot HCOOH$, molecular:					
C2-N-C6	117.7(2)				
C1–O1	1.198(3)	C1–O2	1.315(3)	O2–H	0.98(4)
$C_5H_5N \cdot 4\,HCOOH$, ionic:					
C2-N-C6	123.0(2)				
C1–O1	1.239(3)	C1–O2	1.266(3)	N–H	0.88(4)
C11–O11	1.194(3)	C11–O12	1.296(4)	O12–H12	0.84(4)
C21–O21	1.214(3)	C21–O22	1.290(3)	O22–H22	0.96(5)
C31–O31	1.197(5)	C31–O32	1.314(4)	O32–H32	0.84(4)

Table 2. Distances [Å] and angles [°] of hydrogen bonds.

D–H$\cdots$A	D–A	H–A	D-H-A
1/1 adduct:			
O2–H$\cdots$N	2.664(3)	1.69(4)	173(4)
C3–H3$\cdots$O1^a	3.308(3)	2.37(3)	160(2)
1/4 adduct:			
N–H$\cdots$O11^b	3.020(4)	2.38(4)	130(4)
N–H$\cdots$O21	2.871(3)	2.14(4)	141(4)
O12–H12$\cdots$O2	2.557(3)	1.74(4)	167(4)
O22–H22$\cdots$O2	2.542(3)	1.59(5)	170(5)
O32–H32$\cdots$O1	2.590(3)	1.76(4)	167(4)

The few other proven cases, known to the authors, of an adduct with a molecular and another one with an ionic crystal structure in one and the same Brønsted acid/base binary system have all originated in this laboratory. One of them is given by pyridine and hydrogen fluoride instead of formic acid. The respective system contains again a molecular 1/1 and, among several others, an ionic 1/4 adduct, the latter with a complex anion similar to that described above.[3] Formic acid and hydrogen fluoride, on the other hand, combine in a 1/1 and a 1/3 cocrystal, of which the former was found molecular and the latter at least argued to be ionic, with the proton transfer from the inorganic to the organic acid.[4]

The remaining examples are those of acid hydrates beside (hydrated) oxonium salts. Trifluoroacetic acid forms a molecular mono- and an ionic tetrahydrate.[5] Furthermore, the deuterated tetrahydrate is isotypic, that is also ionic, only up to 230 K, whereas a here existing high-temperature form, though in some ways structurally related, is again clearly molecular.[6] For dichlorofluoroacetic acid, there is a hemi- and a hexahydrate, and also in this case the lower is a true hydrate and the higher an oxonium salt.[7] Finally, in both the nondeuterated[8] and the deuterated[9] system water/hydrogen fluoride there are three adducts, pairwise isotypic and all of them ionic, whereas a singular further phase[9] of composition $2\,D_2O \cdot 3\,DF$ was found to be molecular.

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[1] Crystal growth by miniature zone-melting[10] with the samples of stoichiometric composition in glass capillaries of 0.3 mm inner diameter. $C_5H_5N \cdot HCOOH$: monoclinic, space group $P2_1/n$, $a = 10.954(6)$, $b = 3.817(3)$, $c = 15.842(7)$ Å, $\beta = 104.96(5)^\circ$, $V = 639.9(7)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.30$ g cm^{-3}, $\mu = 0.10$ mm^{-1}; $2\theta_{max} = 50^\circ$, 1120 independent reflections with $F_o^2 > -3\sigma_{F^2}$, 986 of them with $|F_o| > 4\sigma_F$ observed; direct methods, 111 variables refined on F^2, $R(F)(obsd) = 0.047$, $wR(F^2)(all) = 0.167$, residual electron density between -0.22 and $+0.16$ e Å^{-3}. $C_5H_5N \cdot 4HCOOH$: orthorhombic, $Pca2_1$, $a = 16.35(1)$, $b = 3.702(3)$, $c = 20.23(1)$ Å, $V = 1225(1)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.43$ g cm^{-3}, $\mu = 0.13$ mm^{-1}; $2\theta_{max} = 60^\circ$, 1835 independent reflections with $F_o^2 > -3\sigma_{F^2}$, 1551 of them with $|F_o| > 4\sigma_F$ observed; direct methods, 216 variables refined on F^2, $R(F)(obsd) = 0.041$, $wR(F^2)(all) = 0.114$, residual electron density between -0.24 and $+0.22$ e Å^{-3}. Siemens Stoe AED 2 diffractometer adapted for low-temperature work, graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å); computer programs SHELXS-86, SHELXL-93 and SHELXTL PLUS.[11] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-112269 and CCDC-112270. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[2] For a recent discussion of C-H ··· O hydrogen bonding see: T. Steiner, *Chem. Commun.* **1997**, 727 – 734, and references therein.
[3] D. Boenigk, D. Mootz, *J. Am. Chem. Soc.* **1988**, *110*, 2135 – 2139.
[4] D. Wiechert, D. Mootz, T. Dahlems, *J. Am. Chem. Soc.* **1997**, *119*, 12665 – 12666.
[5] D. Mootz, D. Boenigk, *Z. Naturforsch. B* **1984**, *39*, 298 – 304.
[6] D. Mootz, M. Schilling, *J. Am. Chem. Soc.* **1992**, *114*, 7435 – 7439.
[7] T. Dahlems, D. Mootz, M. Schilling, *Z. Naturforsch. B* **1996**, *51*, 536 – 544.
[8] D. Mootz, W. Poll, *Z. Anorg. Allg. Chem.* **1982**, *484*, 158 – 164; D. Mootz, U. Ohms, W. Poll, *Z. Anorg. Allg. Chem.* **1981**, *479*, 75 – 83.
[9] W. Poll, M. Lohmeyer, D. Mootz, *Z. Naturforsch. B* **1989**, *44*, 1359 – 1364.
[10] D. Brodalla, D. Mootz, R. Boese, W. Osswald, *J. Appl. Crystallogr.* **1985**, *18*, 316 – 319.
[11] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467 – 473; G. M. Sheldrick, Program for the Refinement of Crystal Structures, Universität Göttingen, **1993**; SHELXTL PLUS, Structure Determination System Revision 4.21/V, Siemens Analytical X-Ray Instruments, Inc., Madison, WI, **1990**.

New Advances in the Biosynthesis of Glycopeptide Antibiotics of the Vancomycin Type from *Amycolatopsis mediterranei***

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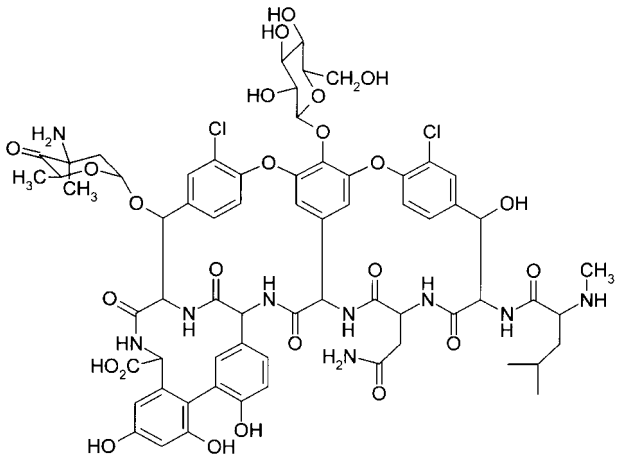
The glycopeptide antibiotic vancomycin was isolated in the mid 1950s,[1] and its structure was conclusively determined with spectroscopic methods and by means of crystal structure analysis.[2] As a drug of last resort, vancomycin is the most important agent after penicillin against Gram-positive bacteria, such as methicillin-resistant staphylococci (MRS).[3] It is employed in enantiomer analytics as a chiral selector.[4] The total synthesis of vancomycin is especially challenging owing to the synthetically demanding biphenyl ether and biphenyl bridges.[5] Although vancomycin has been known for more than 40 years, little is known about the biosynthesis and the intermediates of the aglycon.

Recently the DNA sequence of a gene cluster of the chloroeremomycin producer was described[6] which is assumed to encode enzymes for glycopeptide biosynthesis. Functional proof by means of expression studies or mutant analysis has so far not been reported. However, an understanding of the biosynthesis on a genetic and on a structural level is important for the development of novel glycopeptide analogs by combinatorial biosynthesis.

Amycolatopsis mediterranei, the producer of balhimycin (Scheme 1),[7] a glycopeptide antibiotic identical with vanco-



Scheme 1. Structure of balhimycin, an antibiotic of the vancomycin type.

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