Vanderhoff, P. A., Thompson, H. W. & Lalancette, R. A. (1986). *Acta Cryst.* C**42**, 1766–1769.
Wasson, R. L. & House, H. O. (1963). *Org. Synth.* **4**, 552–553.
Webster, F. X., Rivas-Enterrios, J. & Silverstein, R. M. (1987). *J. Org. Chem.* **52**, 689–691.

Acta Cryst. (1997). C**53**, 106–108

3,5-Dicarboxy-2,6-dimethyl-4-(3-nitrophenyl)pyridinium Nitrate Monohydrate

KRISTIN R. ROWAN AND ELIZABETH M. HOLT

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078, USA. E-mail: chememh@osucc.bitnet

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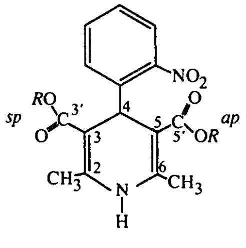
Abstract

Energy-minimization studies of the title compound, $C_{15}H_{13}N_2O_6^+.NO_3^-.H_2O$, suggest that the stable conformation of the molecule should be that in which the carboxyl groups are coplanar with the pyridine ring. Isolated in the solid as a pyridinium nitrate monohydrate, the significant rotation of these carboxyl groups from coplanarity with the aromatic ring may be attributed to networks of hydrogen bonding.

Comment

Derivatives of 1,4-dihydropyridine (DHP) are often prescribed as calcium-channel blockers, effective in the treatment of angina and hypertension (Triggle, Langs & Janis, 1989; Hurwitz, Partridge & Leach, 1991). Nifedipine [dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] is the lead compound of this family.



In the majority of the more than 30 reported crystal structures of members of the nifedipine family, the ester carbonyl groups are found to be almost coplanar with the nearest double bond in the DHP ring, with the carbonyl group oriented either *cis* (*sp*, synperiplanar) or *trans* (*ap*, antiperiplanar) with respect to that bond (Triggle, Langs & Janis, 1989).

Decomposition of this family of drugs involves aromatization of the 1,4-dihydropyridine ring to a pyridine moiety (Rowan & Holt, 1995) and is reported to diminish activity significantly in some cases (Loev, Goodman, Snader, Tedeschi & Macko, 1974).

The crystal structures of the decomposition products, *i.e.* dialkyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylates, routinely show the carbonyl groups at C3 and C5 to be rotated significantly from coplanarity with the aromatic ring. This rotation could be construed to inhibit the formation of strong hydrogen bonds on docking of the decomposition product with the purported calcium-channel receptor site (Rowan & Holt, 1996*a*,*b*) and thus to explain their lessened activity.

We have studied a series of derivatives of the nifedipine family, which vary in the identity of the esterification group, in order to understand the role played by the size and bulk of the ester groups in the activity of these compounds. We have also attempted to learn something about the activity of the derivatives by looking at the conformational changes arising upon aromatization of the heterocycle.

To assess whether the crystal structures of these decomposition materials represent stable molecular conformations as would be seen in solution, we have carried out molecular modeling studies on the parent diacid, 4-phenylpyridine-3,5-dicarboxylic acid, as representative of the group of diesterified molecules, and have completed a single-crystal X-ray analysis of this compound.

Molecular-modeling studies (*CS Chem3D Pro*; CambridgeSoft Corporation, 1995) show that there are three minimum-energy conformations of this molecule. All three show carboxyl groups close to coplanarity with the pyridine ring. The two carboxylic acid groups bound to the pyridine ring at C3 and C5 may adopt *sp*,*sp*, *ap*,*ap* or *sp*,*ap* conformations relative to the C2—C3 and C5—C6 bonds of the aromatic ring. The results of the energy-minimization studies show that the order of stability of these three conformations is *sp*,*sp* > *sp*,*ap* > *ap*,*ap*.

Furthermore, the three energy-minimized structures show near but not strict coplanarity of the carbonyl group with the aromatic ring; the C2—C3—C3′—O3′ and C6—C5—C5′—O5′ dihedral angles are 7.54 and 6.29, respectively, for *sp*,*sp*, 1.18 and −176.77 for *sp*,*ap*, and −171.26 and −170.42° for *ap*,*ap*.

The structural literature contains information about two appropriate dicarboxy compounds. Two single-crystal studies of isophthalic acid (1,3-dicarboxybenzene) show the carboxylic acid groups to lie close to the plane of the aromatic ring (Alcala & Martinez-Carrera, 1972; Derissen, 1974), with the deviation of the O atoms from that plane reported to be in the range −0.006 to 0.125 Å and only small rotations from coplanarity being observed for the carboxyl groups (2.8 and 4.7°). Similarly, dinicotinic acid (3,5-dicarboxypyridine) (Takusagawa, Hirotsu & Shimada, 1973) has an approximately planar conformation of all the atoms, with a maximum deviation of 0.229 Å from this mean plane.

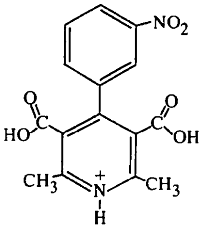
In these structures, each carboxyl group serves both as hydrogen-bond donor and hydrogen-bond acceptor to a neighboring carboxyl group in classic fashion. The crystal structures of both isophthalic and dinicotinic acid are apparently in the *ap*,*ap* conformation.

Thus, both energy minimization studies and literature examples lead to the expectation that the carboxyl groups are more stable when coplanar with the aromatic ring.

2,6-Dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylic acid shows the carboxyl groups to be considerably rotated from coplanarity with the pyridine ring [O5′—C5′—C5—C6 −114.4 (6) and O3′—C3′—C3—C2 −88.5 (7)°]. One carbonyl group is rotated upward and the other downward relative to the plane of the pyridine ring. The nitrophenyl ring rotates away from the polar carbonyl groups and subtends an angle of 55.8 (3)° to the pyridine ring.

Thus, despite expectations that these carbonyl groups might experience increased stability from orbital overlap with the aromatic pyridine ring, they are not found in this position in the crystal structure.

In the solid state, 3,5-dicarboxy-2,6-dimethyl-4-(3-nitrophenyl)pyridinium nitrate monohydrate, (I), displays hydrogen bonding of a complicated nature involving the NO_3^- anion and water molecules. The H1*A* atom of the pyridinium cation is 1.74 (6) Å from a nitrate O atom (O4). The carboxylic acid H atom (H3″*A*) is 3.14 (6) Å from a nitro O atom [O2^{ii}; symmetry code: (ii) $1-x$, $1-y$, $2-z$]. The H5″*A* atom is 1.86 (6) and 2.05 (6) Å from two nitrate O atoms. The water H atoms, H6*A* and H6*B*, are within reasonable hydrogen-bonding distances of the carbonyl O3′ and nitrate O3 and O7 atoms. There is no classic double hydrogen bond between neighboring carboxyl groups.



(I)

Thus, coplanarity of the carboxyl groups with the aromatic ring appears to be the conformation of lowest energy as evaluated from energy-minimization studies and this is confirmed from comparable crystal structures.

The title compound presents different patterns of hydrogen bonding from those seen for the comparable crystal structures. The stability gained from this hydrogen bonding leads to non-coplanarity in the solid.

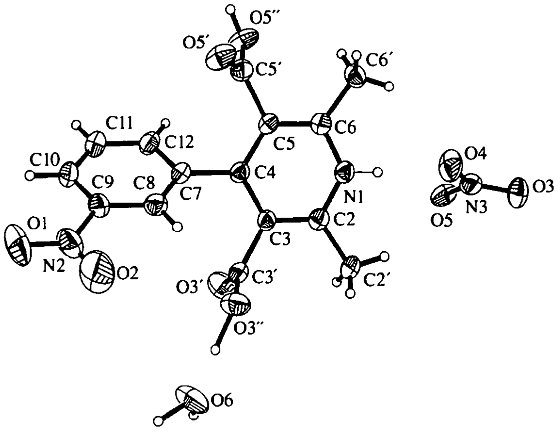


Fig. 1. A projection view of 3,5-dicarboxy-2,6-dimethyl-4-(3-nitrophenyl)pyridinium nitrate monohydrate, with ellipsoids shown at 50% probability.

One may suspect, on the basis of energy-minimization studies which do not involve hydrogen bonding, that the ester carbonyl group conformations of decomposition products which are not coplanar in the crystal are coplanar in solution and that if decomposition-product docking with the receptor site is not energetically favored, it is probably not due to the ester group conformations, which appear likely to match those of the carbonyl groups in the nifedipine family parent compounds.

Experimental

Di-*tert*-butyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,4-dicarboxylate (2 g, 4.65 mmol) was mixed with 30 ml 2 *N* HNO_3. The resulting solution was extracted with $CHCl_3$. The organic layer was washed twice with water and once with 5% $NaHCO_3$. The aqueous layer yielded transparent crystals suitable for diffraction studies.

Crystal data

$C_{15}H_{13}N_2O_6^+.NO_3^-.H_2O$
$M_r = 397.3$
Triclinic
$P\bar{1}$
$a = 8.813\ (1)$ Å
$b = 9.597\ (1)$ Å
$c = 12.805\ (2)$ Å
$\alpha = 70.12\ (1)°$
$\beta = 84.45\ (1)°$
$\gamma = 67.87\ (1)°$
$V = 942.9\ (3)$ Å^3
$Z = 2$
$D_x = 1.399$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 56 reflections
$\theta = 12.18–12.48°$
$\mu = 0.120$ mm^{-1}
$T = 298$ K
Chunk
0.2 × 0.1 × 0.1 mm
Colorless

Data collection

Syntex *P*4 four-circle diffractometer

$R_{int} = 0.0208$
$\theta_{max} = 22.5°$

$\theta/2\theta$ scans
Absorption correction: none
3002 measured reflections
2416 independent reflections
1314 observed reflections [$F > 5\sigma(F)$]

$h = -9 \rightarrow 9$
$k = -9 \rightarrow 9$
$l = 0 \rightarrow 13$
3 standard reflections
frequency: 97 min
intensity decay: negligible

Refinement

Refinement on F
$R = 0.0460$
$wR = 0.0561$
$S = 1.19$
2426 reflections
267 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F) + 0.0008F^2]$
$(\Delta/\sigma)_{\max} = 0.23$
$\Delta\rho_{\max} = 0.19$ e Å^{-3}
$\Delta\rho_{\min} = -0.19$ e Å^{-3}

Extinction correction: *SHELXS*86 (Sheldrick, 1990)
Extinction coefficient: 0.0015 (6)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
N1	0.2679 (4)	0.7166 (4)	0.5522 (3)	0.049 (2)
C2	0.2498 (5)	0.6383 (5)	0.6613 (4)	0.050 (2)
C2′	0.2588 (7)	0.4669 (5)	0.6896 (4)	0.067 (3)
C3	0.2226 (5)	0.7185 (5)	0.7388 (3)	0.045 (2)
C3′	0.1889 (8)	0.6346 (6)	0.8575 (4)	0.057 (3)
O3′	0.0503 (6)	0.6446 (5)	0.8879 (3)	0.089 (2)
O3″	0.3235 (5)	0.5485 (4)	0.9230 (3)	0.080 (2)
C4	0.2151 (5)	0.8789 (5)	0.7036 (4)	0.045 (2)
C5	0.2309 (5)	0.9547 (5)	0.5887 (4)	0.044 (2)
C5′	0.2310 (6)	1.1258 (6)	0.5472 (4)	0.053 (3)
O5′	0.3349 (5)	1.1596 (4)	0.5783 (3)	0.075 (2)
O5″	0.1065 (4)	1.2270 (4)	0.4756 (3)	0.076 (2)
C6	0.2575 (5)	0.8737 (5)	0.5118 (4)	0.048 (2)
C6′	0.2793 (6)	0.9421 (6)	0.3884 (3)	0.060 (3)
C7	0.1837 (6)	0.9671 (5)	0.7868 (4)	0.049 (2)
C8	0.2869 (6)	0.9062 (5)	0.8820 (4)	0.058 (3)
C9	0.2510 (7)	0.9899 (6)	0.9580 (4)	0.062 (3)
C10	0.1192 (8)	1.1331 (7)	0.9421 (5)	0.072 (3)
C11	0.0168 (7)	1.1931 (6)	0.8474 (5)	0.072 (3)
C12	0.0483 (6)	1.1132 (5)	0.7700 (4)	0.061 (3)
N2	0.3609 (9)	0.9206 (8)	1.0593 (4)	0.093 (4)
N3	0.2988 (8)	0.4817 (5)	0.3740 (4)	0.063 (3)
O1	0.3279 (7)	0.9918 (7)	1.1268 (4)	0.143 (4)
O2	0.4768 (9)	0.7994 (8)	1.0727 (4)	0.171 (4)
O3	0.3711 (7)	0.3783 (5)	0.3268 (3)	0.083 (3)
O4	0.3754 (5)	0.5554 (5)	0.3960 (4)	0.091 (3)
O5	0.1501 (6)	0.5092 (4)	0.4036 (3)	0.075 (2)
O6	0.2617 (5)	0.3902 (5)	1.1216 (3)	0.104 (3)
O7	0.255 (11)	0.398 (8)	0.324 (6)	0.05 (2)
O8	0.310 (10)	0.616 (9)	0.281 (7)	0.10 (4)
O9	0.324 (8)	0.464 (7)	0.463 (6)	0.05 (2)

Table 2. *Selected geometric parameters (Å, °)*

N1—C2	1.370 (6)	C5′—O5′	1.217 (8)
N1—C6	1.387 (6)	C5′—O5″	1.333 (5)
C2—C2′	1.532 (7)	C6—C6′	1.515 (6)
C2—C3	1.403 (8)	C7—C8	1.409 (7)
C3—C3′	1.519 (6)	C7—C12	1.421 (6)
C3—C4	1.426 (7)	C8—C9	1.405 (8)
C3′—O3′	1.225 (9)	C9—C10	1.390 (7)
C3′—O3″	1.333 (7)	C9—N2	1.495 (8)
C4—C5	1.422 (6)	C10—C11	1.400 (9)
C4—C7	1.518 (8)	C11—C12	1.396 (9)
C5—C5′	1.545 (7)	N2—O1	1.225 (9)
C5—C6	1.403 (8)	N2—O2	1.195 (8)

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···A	H···A	D—H···A
N1—H1A···O4	1.74 (6)	161 (1)
N1—H1A···O4$^{\rm i}$	3.13 (6)	83 (1)
O3″—H3″A···O2$^{\rm ii}$	3.14 (6)	77 (1)
O5″—H5″···O5$^{\rm iii}$	1.86 (6)	176 (1)
O5″—H5″···O7$^{\rm iii}$	2.05 (6)	129 (1)
O5″—H5″···O9$^{\rm iii}$	2.74 (6)	141 (1)
O5″—H5″···O3$^{\rm iii}$	2.76 (6)	125 (1)
O5″—H5″···O5$^{\rm iii}$	3.17 (6)	99 (1)

Symmetry codes: (i) $1-x, 1-y, 1-z$; (ii) $1-x, 1-y, 2-z$; (iii) $x, 1+y, z$.

A variable scan rate was used and a $\theta/2\theta$ scan mode with a scan width of 0.6° below $K\alpha_1$ and 0.6° above $K\alpha_2$ to a maximum 2θ value of 50°. Refinement was completed using full-matrix least-squares methods. The methyl groups, C2′ and C6′, display rotational disorder of the H-atom positions. The nitrate group has two sets of O atoms about the central N atom, *i.e.* O3, O4 and O5, which refine to 95.0% occupancy, and O7, O8 and O9, which show 5% presence.

Data collection: *XSCANS* (Siemens, 1991). Cell refinement: *XSCANS*. Data reduction: *XSCANS*. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXS*86. Molecular graphics: *XP* (Siemens, 1990).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: PA1241). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Alcala, R. & Martinez-Carrera, S. (1972). *Acta Cryst.* **B28**, 1671–1677.

CambridgeSoft Corporation (1995). *CS Chem3D Pro*. Version 3.2. CambridgeSoft Corporation (Cambridge Scientific Computing Inc.), Cambridge, Massachusetts, USA.

Derissen, J. L. (1974). *Acta Cryst.* **B30**, 2764–2765.

Hurwitz, L., Partridge, L. D. & Leach, J. K. (1991). *Calcium Channels: Their Properties, Functions, Regulation and Clinical Relevance*. Boca Raton, Florida: CRC Press.

Loev, B., Goodman, M. M., Snader, K. M., Tedeschi, R. & Macko, E. (1974). *J. Med. Chem.* **17**, 956–965.

Rowan, K. R. & Holt, E. M. (1995). *Acta Cryst.* **C51**, 2554–2559.

Rowan, K. R. & Holt, E. M. (1996*a*). *Acta Cryst.* **C52**, 1565–1570.

Rowan, K. R. & Holt, E. M. (1996*b*). *Acta Cryst.* **C52**. Submitted.

Sheldrick, G. M. (1990). *Acta Cryst.* **A46**, 467–473.

Siemens (1990). *XP. Molecular Graphics Program*. Version 4.1. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Siemens (1991). *XSCANS Users Manual*. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Takusagawa, F., Hirotsu, K. & Shimada, A. (1973). *Bull. Chem. Soc. Jpn*, **46**, 2292–2299.

Triggle, D. J., Langs, D. A. & Janis, R. A. (1989). *Med. Res. Rev.* **9**, 123–180.