

Ab initio structure determination of bethanechol chloride

A. Le Bail^{a)}

Laboratoire des Oxydes et Fluorures, CNRS UMR 6010, Université du Maine, Ave. O. Messiaen, 72085 Le Mans Cedex 9, France

(Received 3 February 2010; accepted 7 April 2010)

The structure of bethanechol chloride $C_7H_{17}ClN_2O_2$ is solved from conventional X-ray powder diffraction data in direct space [monoclinic unit cell with $a=8.8749(3)$ Å, $b=16.4118(7)$ Å, $c=7.1373(3)$ Å, $\beta=93.803(1)^\circ$, $V=1037.29(7)$ Å³, $Z=4$, and space group $P2_1/n$]. The existence of a second orthorhombic closely related form is discussed. © 2010 International Centre for Diffraction Data. [DOI: 10.1154/1.3478380]

Key words: bethanechol chloride, carbamyl- β -methylcholine chloride, acetylcholine, powder diffraction, crystal structure, *ab initio*, polymorphism

I. INTRODUCTION

Many pharmaceutical compounds in daily use have a well defined molecular formula but were never completely characterized crystallographically (or results stay unpublished), so the question of a possible polymorphism has no answer, opening some place for industrial competition. A typical example is bethanechol chloride, also called carbamyl- β -methylcholine chloride (Major and Bonnett, 1943), a quaternary amine which is a cholinergic agent. This compound is a synthetic ester structurally and pharmacologically related to acetylcholine. It acts principally as stimulant of the parasympathetic nervous system. It has been used for a long time in urology and gastroenterology, and more recently it has found new applications in the treatment of Alzheimer's disease (Cummings and Kaufer, 1996) and cerebral palsy (Carter, 2008). The PDF contains two entries (00-043-1748 and 00-046-1964), both are unindexed and show some discrepancies. The aim of the present work is to provide more in depth results, in spite of the absence of single crystal, by solving the structure from the powder data by using methodologies which continuously have demonstrated their efficiency during repeated blind tests (Le Bail *et al.*, 2009).

II. STRUCTURE DETERMINATION AND RIETVELD REFINEMENTS

Various samples, as received from the SERATEC company (www.serateclab.com), showed powder diffraction patterns with large discrepancies at first sight (Figure 1), but they all evolved with time (weeks) into one unique stable state. As the bethanechol chloride is said to be hygroscopic, this suggested that the final formula could be, in fact, $C_7H_{17}ClN_2O_2 \cdot nH_2O$. However, no mass loss was detected on the thermogravimetric analysis before decomposition,

leading to a hypothesis of polymorphism, one of the polymorphs being possibly unstable at ambient conditions, transforming slowly into the final stable form. The powder pattern of this latter form could be indexed in a monoclinic cell by the MCMAILLE software (Le Bail, 2004), the figures of merit (FoMs) for the pattern selected for this study being $M_{20}=84.4$ (de Wolff, 1968), $F_{20}=192.0$ (0.0035, 30) (Smith and Snyder, 1979), and $McM_{20}=198.0$ (Le Bail, 2008). Indeed, a series of ten data sets were proposed to be used as indexing benchmarks for the comparison of computer programs during an indexing round robin (Bergmann *et al.*, 2004), including a synchrotron pattern which was the easiest to index, leading to FoMs: $M_{20}=168.0$, $F_{20}=888.2$ (0.0008, 30), and $McM_{20}=540.0$. This synchrotron pattern, limited to 2θ max = 28° at $\lambda=0.6995$ Å, is not used at the final Rietveld stage in this work because the corresponding sample either was not completely transformed into the stable polymorph or more probably suffered from its airplane low-pressure and low-temperature trip [such effects were observed for a vanadium hypophosphite (Le Bail *et al.*, 1994)], and the line profiles show anisotropic broadening, contrarily to the sample se-

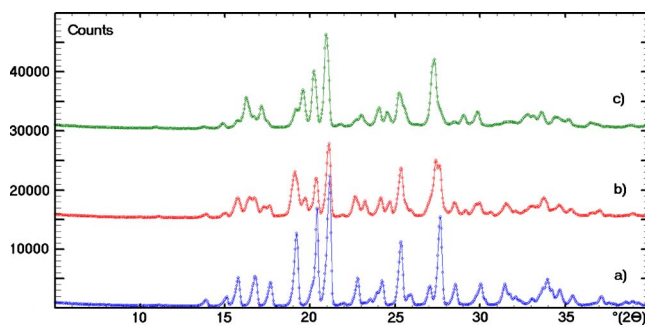


Figure 1. (Color online) Three representative bethanechol chloride samples as received from the SERATEC (www.serateclab.com). Samples b and c finally evolved slowly, without mass gain nor loss, into a powder pattern identical to that of sample a which could be indexed. The transformation has already started for sample c which contains the largest proportion of probably another still undefined and unstable polymorph.

^{a)} Author to whom correspondence should be addressed. Electronic mail: armel.le_bail@univ-lemans.fr

TABLE I. Experimental and Rietveld refinement details for bethanechol chloride.

Diffractometer	Panalytical MPD PRO
Geometry	Bragg-Brentano
Goniometer	horizontal
Radiation type	Cu $K\alpha$
Wavelengths (\AA)	1.540 56, 1.544 33
Detector	X'Celerator
Pattern range (2θ)	9 to 70
Step size (2θ)	0.017°
Chemical formula	$C_7H_{17}ClN_2O_2$
Space group	$P2_1/n$
Cell parameter (\AA and deg) a	8.8749(3)
b	16.4118(7)
c	7.1373(3)
β	93.803(1)
Volume (\AA^3)	1037.28(7)
Z	4
No. of contributing reflections	570
No. of refined parameters	116 (total)
No. of atomic coordinate parameters	87
No. of restraints	31
No. of isotropic thermal parameters	4
No. of background parameters (interpolated from a set of points)	14
Profile shape	Pseudo-Voigt
η	0.323(7)
U	0.036(2)
V	0
W	0.0107(1)
Conventional Rietveld reliability factors	(Rietveld, 1969)
$R_p(\%)$	7.49
$R_{wp}(\%)$	7.07
$R_{exp}(\%)$	4.10
$R_B(\%)$	3.58
$R_F(\%)$	5.10

lected here, prepared in conditions so as to obtain directly the stable polymorph.

The cell volume suggested $Z=4$. Using the Le Bail fitting (Le Bail, 2005) for evaluating the reliability of the indexing and for intensity extraction, the $P2_1/n$ space group was determined unambiguously. The first structure solution attempts were done in direct space from the Cu $K\alpha$ conventional laboratory data using the ESPOIR software (Le Bail, 2001) moving in the cell by a Monte Carlo process, a NC_4 tetrahedron, a CO_2N triangle, and the chlorine and two carbon atoms at random (for a total of 21 degrees of freedom), expecting to complete the bethanechol molecule. This led to $R=16\%$ on the first 200 extracted hkl . Refinements were undertaken by the Rietveld (1969) FULLPROF software (Rodríguez-Carvajal, 1993). Some ambiguity for the NH_2 position in the CO_2NH_2 group was removed by consideration on the Cl-N interatomic distances, the Cl atom being expected to point towards the direction of the hydrogen atoms of the NH_2 group. At this stage ($R_p=9.05$, $R_{wp}=8.63$, $R_B=5.03$, and $R_F=7.09\%$), the 17 independent hydrogen atoms

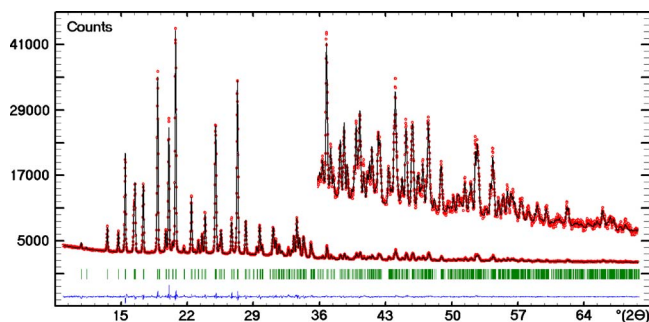


Figure 2. (Color online) Rietveld plot for $C_7H_{17}ClN_2O_2$.

were suggested by the OPEN BABEL software (Guha *et al.*, 2006) and their inclusion with 31 soft restraints on the C-H, N-H, and H-H distances in the refinement allowed to lower all the R factors by approximately 1.5% to the final values listed in Table I (see the Rietveld fit in Figure 2). Atomic coordinates, selected geometric parameters, and X-ray diffraction data are in Tables II–IV, respectively. The structure could also be solved later, during the indexing round robin,

TABLE II. Fractional atomic coordinates and isotropic displacement parameters.

	x	y	z	U_{iso}
Cl	0.7108 (3)	0.503 68 (16)	0.2406 (3)	0.087 (1)
C1	0.1624 (13)	0.0998 (4)	0.1895 (11)	0.099 (2)
H1	0.104 (5)	0.0886 (13)	0.304 (3)	0.099 (2)
H2	0.137 (5)	0.0646 (11)	0.084 (2)	0.099 (2)
H3	0.147 (5)	0.1601 (6)	0.149 (3)	0.099 (2)
C2	0.3793 (8)	0.0152 (7)	0.2538 (10)	0.099 (2)
H4	0.4984 (14)	0.015 (2)	0.263 (3)	0.099 (2)
H5	0.350 (3)	−0.024 (2)	0.151 (3)	0.099 (2)
H6	0.342 (3)	−0.005 (2)	0.3787 (19)	0.099 (2)
C3	0.3982 (9)	0.1390 (5)	0.0771 (14)	0.099 (2)
H7	0.374 (3)	0.0997 (13)	−0.030 (5)	0.099 (2)
H8	0.372 (3)	0.1946 (8)	0.046 (5)	0.099 (2)
H9	0.5236 (16)	0.1355 (14)	0.097 (6)	0.099 (2)
C4	0.3615 (10)	0.1507 (9)	0.421 (2)	0.099 (2)
H10	0.322 (3)	0.116 (3)	0.523 (7)	0.099 (2)
H11	0.475 (2)	0.141 (4)	0.415 (8)	0.099 (2)
C5	0.3103 (13)	0.2393 (9)	0.4393 (15)	0.099 (2)
H12	0.207 (4)	0.255 (5)	0.362 (8)	0.099 (2)
C6	0.3185 (8)	0.2549 (5)	0.6500 (15)	0.099 (2)
H13	0.294 (3)	0.3148 (9)	0.652 (6)	0.099 (2)
H14	0.4301 (16)	0.2453 (15)	0.660 (6)	0.099 (2)
H15	0.263 (3)	0.2237 (13)	0.741 (5)	0.099 (2)
C7	0.3330 (13)	0.3298 (9)	0.1951 (17)	0.099 (2)
N1	0.3358 (9)	0.1040 (5)	0.2419 (11)	0.076 (3)
N2	0.4209 (7)	0.3823 (5)	0.1100 (17)	0.076 (3)
H16	0.537 (2)	0.374 (2)	0.140 (10)	0.076 (3)
H17	0.399 (3)	0.4352 (18)	0.058 (8)	0.076 (3)
O1	0.3981 (8)	0.2892 (4)	0.3308 (12)	0.101 (3)
O2	0.2033 (7)	0.3187 (4)	0.1301 (10)	0.101 (3)

TABLE III. Selected geometric parameters (Å, deg).

Cl-H2 ^a	2.81 (2)	C2-H6	1.03 (2)
Cl-H4 ^b	2.589 (13)	C6-C5	1.522 (15)
Cl-H6 ^c	2.903 (18)	C6-H13	1.007 (18)
Cl-H7 ^a	2.71 (3)	C6-H14	1.001 (16)
Cl-H10 ^c	2.73 (5)	C6-H15	0.98 (3)
Cl-H16	2.70 (3)	C7-N2	1.335 (16)
Cl-H17 ^d	2.49 (5)	C7-O1	1.281 (15)
C1-N1	1.561 (14)	C7-O2	1.226 (13)
C1-H1	1.01 (3)	N2-H16	1.05 (2)
C1-H2	0.964 (19)	N2-H17	0.96 (4)
C1-H3	1.037 (14)	O1-H12	1.81 (4)
C5-C4	1.53 (2)	O2-H12	1.96 (7)
C5-C6	1.522 (15)	H1-H2	1.66 (3)
C5-O1	1.399 (15)	H1-H3	1.67 (3)
C5-H12	1.07 (5)	H2-H3	1.64 (2)
C3-N1	1.451 (13)	H9-H8	1.68 (3)
C3-H9	1.114 (16)	H9-H7	1.66 (4)
C3-H8	0.964 (18)	H8-H7	1.65 (3)
C3-H7	1.01 (3)	H10-H11	1.66 (5)
C4-C5	1.53 (2)	H4-H5	1.63 (3)
C4-N1	1.494 (16)	H4-H6	1.69 (3)
C4-H10	1.01 (5)	H5-H6	1.66 (3)
C4-H11	1.02 (2)	H13-H14	1.66 (3)
C2-N1	1.509 (14)	H13-H15	1.65 (3)
C2-H4	1.055 (14)	H14-H15	1.67 (4)
C2-H5	1.00 (3)	H16-H17	1.66 (4)
C1-N1-C3	104.3 (11)	C4-C5-O1	109.2 (14)
C1-N1-C4	108.6 (12)	C4-C5-C6	104.4 (14)
C1-N1-C2	102.4 (11)	C6-C5-O1	117.2 (12)
C3-N1-C4	116.4 (14)	C5-O1-C7	118.9 (16)
C3-N1-C2	108.5 (11)	N2-C7-O1	115.6 (14)
C4-N1-C2	115.0 (14)	N2-C7-O2	119.1 (12)
C5-C4-N1	122.1 (14)	O1-C7-O2	125.0 (12)

^aSymmetry code: $x+1/2, -y+1/2, z+1/2$.^bSymmetry code: $-x+3/2, y+1/2, -z+1/2$.^cSymmetry code: $x+1/2, -y+1/2, z-1/2$.^dSymmetry code: $-x+1, -y+1, -z$.

by J. van de Streek using the DASH software (David *et al.* 2006) applied to the synchrotron data.

III. DISCUSSION

Bethanechol (Figure 3) is a quaternary ammonium compound, a derivative of acetylcholine. The positively charged quaternary ammonium group imparts a very high polarity to the molecule based on its permanent positive charge. The Cl⁻ ions are in a cage of hydrogen atoms belonging to four neighbouring bethanechol molecules (Figure 4). Seven of the Cl-H distances are smaller than 3 Å, the shortest being with H17 from the NH₂ groups (Table III). Indeed, the shortest distances with a non-H atom are with the N2 atom of that group from two different molecules [Cl-N2=3.277(11) and 3.337(8) Å]. But the majority of the hydrogen atoms around

the chlorine atoms belong to the ammonium group (H2, H4, H6, and H7), in accordance with the location of the positive charge of the molecule.

One should not expect much accuracy from that Rietveld refinement, no more than from a single-crystal study in the 1960s to 1970s (and the refinement from the synchrotron data leads to similar atomic coordinates and estimated standard deviations). Alerts on deviating methyl C1, C2, and C6 and low precision on C-C bonds were delivered when using the PLATON software (Spek, 2003) for validation. Moreover, the refined thermal parameters are unusually high. The NC₄, CO₂N, and C₃O groups are tetrahedral, planar, and triangular pyramidal, respectively, as expected. However, stronger restraints or DFT calculations would be necessary for obtaining more acceptable bonds and angle values. In any case, the results shown here are the best obtainable from the powder data only when some parameters are allowed to be refined (at least all the non-H atoms) freely during the Rietveld refinement. The CIF was deposited at the Crystallography Open Database (www.crystallography.net) (Gražulis *et al.*, 2009).

When attempting to index the powder pattern of sample c (Figure 1) after removing the peaks clearly belonging to the stable polymorph, a probable orthorhombic cell with parameters $a=8.857(10)$ Å, $b=16.466(13)$ Å, $c=7.053(6)$ Å, $V=1028.6$ Å³, $M_{20}=15.4$, $F_{20}=24.2$ (0.0150, 55), and $McM_{20}=39.5$ was obtained (Table V). This suggests that both structures could be quite similar, which would explain the absence of a clear event on the differential scanning calorimetry before the decomposition at 227 °C for all samples. In the absence of details about the way of synthesis from the SERATEC Co., it may be suggested that the higher symmetry second polymorph would be, in fact, a slightly higher temperature form which would be the first appearing when the preparation conditions are at a temperature higher than some value, above ambient conditions. More work is needed in order to confirm that hypothesis.

IV. CONCLUSION

In the absence of a suitable single crystal, modern powder diffraction methodologies have the power sometimes to reveal crystal structures, including those of pharmaceutical compounds in use for a long time but still uncharacterized crystallographically. Even if all problems are not solved here, such a structure determination of a defined polymorph gives the chance to a pharmaceutical company to provide fine details about the exact quality of their product, a quality of purity required by the international market where national agencies such as the FDA have to be convinced before delivering import permission. Moreover, every polymorph represents a drug candidate which in turn may increase profits. Powder diffraction may therefore be of great help in such important subjects.

TABLE IV. X-ray diffraction data of bethanechol chloride (Cu $K\alpha_1$).

$2\theta_{\text{obs}}$	d_{obs}	I_{obs}	h	k	l	$2\theta_{\text{cal}}$	d_{cal}	I_{cal}	$\Delta 2\theta$
10.775	8.2040	1.6	0	2	0	10.772	8.2059	2.4	0.003
13.538	6.5352	10.9	0	1	1	13.542	6.5331	9.8	-0.004
14.701	6.0207	9.1	1	2	0	14.705	6.0189	8.5	-0.004
15.420	5.7415	39.4	-1	0	1	15.428	5.7385	41.3	-0.008
16.365	5.4121	19.3	-1	1	1	16.350	5.4169	15.3	0.015
16.464	5.3797	28.9	0	2	1	16.468	5.3785	3.0	-0.004
			1	0	1	16.469	5.3781	25.9	-0.005
17.338	5.1105	29.3	1	1	1	17.337	5.1107	29.6	0.001
18.852	4.7033	80.5	-1	2	1	18.854	4.7027	77.1	-0.002
19.722	4.4978	10.4	1	2	1	19.720	4.4981	9.3	-0.002
20.036	4.4280	60.5	2	0	0	20.037	4.4277	55.8	-0.001
20.458	4.3376	4.6	0	3	1	20.454	4.3383	3.9	0.004
20.762	4.2748	100.0	2	1	0	20.762	4.2748	100.0	0.000
21.641	4.1031	3.0	0	4	0	21.642	4.1030	2.3	-0.001
22.429	3.9607	26.2	-1	3	1	22.435	3.9596	25.7	-0.006
22.805	3.8962	1.4	2	2	0	22.803	3.8866	0.7	0.002
23.173	3.8352	5.8	1	3	1	23.173	3.8352	5.8	0.000
23.553	3.7741	8.9	-2	1	1	23.558	3.7733	8.9	-0.005
23.879	3.7233	19.3	1	4	0	23.883	3.7228	18.3	-0.004
24.992	3.5600	58.4	2	1	1	24.951	3.5658	11.8	0.041
			0	0	2	24.987	3.5607	30.8	0.005
25.376	3.5070	3.6	-2	2	1	25.386	3.5056	3.4	-0.010
25.575	3.4801	11.3	0	1	2	25.578	3.4798	11.3	-0.003
26.687	3.3376	17.1	-1	4	1	26.687	3.3376	15.8	0.000
26.865	3.3159	1.6	-1	1	2	26.892	3.3126	0.9	-0.027
27.308	3.2631	80.4	0	2	3	27.279	3.2666	21.7	0.029
			1	4	1	27.317	3.2620	67.8	-0.009
28.177	3.1644	15.7	-2	3	1	28.187	3.1633	17.4	-0.010
29.360	3.0395	3.8	2	3	1	29.375	3.0380	4.0	-0.015
29.649	3.0106	14.6	2	4	0	29.660	3.0095	13.7	-0.011
29.923	2.9836	4.6	0	3	2	29.916	2.9843	4.6	0.007
31.074	2.8757	13.7	-1	3	2	31.062	2.8768	11.1	0.012
			-2	0	2	31.146	2.8692	7.8	-0.072
31.366	2.8496	7.9	-1	5	1	31.370	2.8492	8.1	-0.004
31.724	2.8182	5.1	-2	4	1	31.726	2.8180	5.5	-0.002
31.944	2.7993	1.9	1	5	1	31.915	2.8018	0.7	0.029
			-3	0	1	32.017	2.7931	2.4	-0.073
32.707	2.7357	4.3	0	6	0	32.712	2.7353	3.6	-0.005
33.034	2.7094	3.1	-2	2	2	33.046	2.7084	3.4	-0.012
33.281	2.6898	10.3	0	4	2	33.289	2.6892	9.1	-0.008
33.597	2.6653	19.3	3	0	1	33.600	2.6650	20.9	-0.003
33.861	2.6451	8.5	-3	2	1	33.874	2.6441	10.1	0.013
34.293	2.6127	10.2	1	6	0	34.283	2.6135	5.2	0.010
			-1	4	2	34.333	2.6098	7.0	-0.040
34.475	2.5994	3.8	3	3	0	34.497	2.5877	3.6	-0.022
35.090	2.5552	7.8	2	2	2	35.088	2.5553	6.3	0.002
			0	6	1	35.115	2.5534	2.0	-0.025
35.281	2.5418	1.7	-2	3	2	35.293	2.5409	1.4	-0.012
			1	4	2	35.334	2.5381	0.5	-0.053
36.347	2.4697	1.2	-1	6	1	36.355	2.4691	1.1	-0.008
36.774	2.4420	6.8	2	5	1	36.780	2.4416	6.3	-0.006
37.218	2.4139	2.0	0	5	2	37.225	2.4134	1.8	-0.007
37.490	2.3970	1.2	3	3	1	37.508	2.3958	0.9	-0.018
38.203	2.3538	2.0	-1	5	2	38.176	2.3555	1.1	0.027
			-2	4	2	38.246	2.3513	1.6	-0.043
			0	1	3	38.279	2.3494	0.4	-0.076
38.643	2.3281	2.5	-1	0	3	38.577	2.3319	1.2	0.066
			2	6	0	38.660	2.3271	2.1	-0.017
			-3	1	2	38.668	2.3266	0.8	-0.025
38.963	2.3097	1.3	-3	4	1	38.977	2.3089	1.4	-0.014

TABLE IV. (Continued.)

$2\theta_{\text{obs}}$	d_{obs}	I_{obs}	h	k	l	$2\theta_{\text{cal}}$	d_{cal}	I_{cal}	$\Delta 2\theta$
			-1	1	3	38.981	2.3087	0.2	-0.018
39.750	2.2657	1.2	1	7	0	39.737	2.2665	1.3	0.013
39.935	2.2557	3.3	1	0	3	39.933	2.2558	3.4	0.002
40.145	2.2443	1.5	-1	2	3	40.169	2.2431	2.0	-0.024
40.318	2.2351	3.3	-2	6	1	40.319	2.2351	1.0	-0.001
			3	4	1	40.321	2.2349	1.6	-0.003
			1	1	3	40.325	2.2347	1.2	-0.007
40.710	2.2145	1.7	4	0	0	40.723	2.2138	1.4	-0.013
41.098	2.1945	1.1	3	5	0	41.091	2.1948	1.2	0.007
41.332	2.1826	1.2	3	1	2	41.338	2.1823	1.9	-0.006
41.588	2.1697	2.1	0	6	2	41.600	2.1692	2.6	-0.012
42.255	2.1370	2.8	-4	1	1	42.264	2.1366	2.4	-0.009
42.449	2.1277	2.2	-1	6	2	42.468	2.1268	2.6	-0.019
43.347	2.0857	1.5	1	3	3	43.353	2.0854	1.6	-0.006
43.969	2.0576	3.2	4	1	1	43.938	2.0590	3.2	0.031
44.082	2.0526	4.5	0	4	3	44.035	2.0547	1.5	0.047
			0	8	0	44.107	2.0515	3.5	-0.025
44.781	2.0222	1.0	2	1	3	44.806	2.0211	1.3	-0.025
45.172	2.0056	3.8	-2	7	1	45.156	2.0063	2.2	0.016
			-4	3	1	45.186	2.0050	0.4	-0.014
			-2	3	3	45.235	2.0029	2.3	-0.063
45.842	1.9778	3.3	-2	6	2	45.793	1.9798	2.2	0.049
			1	4	3	45.869	1.9767	2.1	-0.027
46.423	1.9544	1.1	-3	6	1	46.426	1.9543	1.6	-0.003
46.565	1.9488	1.1	4	4	0	46.577	1.9483	1.1	-0.012
46.987	1.9322	2.1	-1	8	1	47.000	1.9317	2.3	-0.013
47.376	1.9173	1.2	2	6	2	47.368	1.9176	0.4	0.008
			1	8	1	47.390	1.9168	0.5	-0.014
47.549	1.9107	3.9	-3	5	2	47.543	1.9109	3.5	0.006
48.932	1.8599	1.9	1	5	3	48.955	1.8591	1.3	-0.023
51.441	1.7749	1.4	0	8	2	51.359	1.7776	0.6	0.082
			-1	6	3	51.453	1.7745	1.4	-0.012
52.067	1.7550	1.1	4	5	1	52.095	1.7541	0.9	-0.028
52.547	1.7401	3.6	1	6	3	52.542	1.7403	1.0	0.005
			0	2	4	52.555	1.7399	2.6	-0.008
52.786	1.7328	2.4	-3	4	3	52.758	1.7337	2.2	0.028
			4	3	2	52.796	1.7325	0.5	-0.010

AKNOWLEDGMENTS

Thanks are due to P. W. Stephens for the recording of a synchrotron powder pattern at the National Synchrotron Light Source at Brookhaven National Laboratory, which is

supported by the Division of Materials Sciences and Division of Chemical Sciences, U.S. Department of Energy. The SUNY X3 beamline at NSLS is supported by the Division of

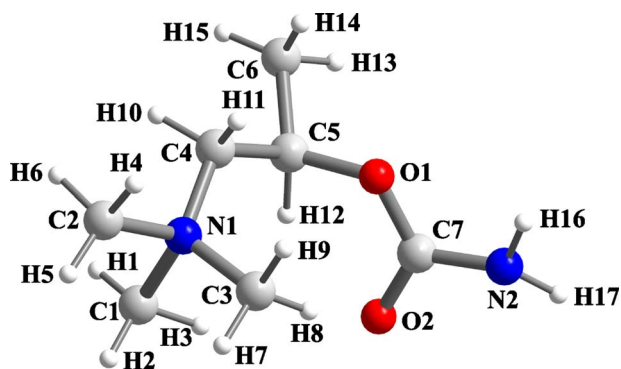


Figure 3. (Color online) Bethanechol molecule with atom numbering.

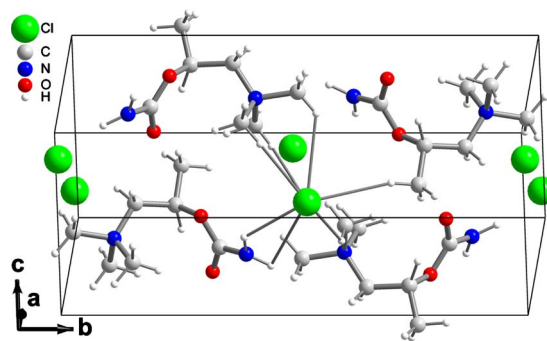


Figure 4. (Color online) Projection of the structure in a direction close to the a axis, showing the bethanechol molecules stacking. The seven shorter Cl-H bonds interlinking four molecules are marked for one Cl atom only for the sake of clarity.

TABLE V. The 20 peaks used for indexing the sample c routine powder pattern shown on Figure 1, excluding peaks obviously corresponding to the sample a ($\text{Cu K}\alpha_1$).

$2\theta_{\text{obs}}$	d_{obs}	I_{obs}	h	k	l	$2\theta_{\text{cal}}$	d_{cal}	$\Delta 2\theta$
10.757	8.2177	1.4	0	2	0	10.737	8.2332	0.020
13.557	6.5261	1.7	0	1	1	13.647	6.4834	-0.090
16.041	5.5206	31.7	1	0	1	16.051	5.5174	-0.009
16.927	5.2336	22.9	1	1	1	16.934	5.2315	-0.007
18.974	4.6734	19.1	1	3	0	19.007	5.2315	-0.033
19.372	4.5782	39.6	1	2	1	19.351	4.5834	0.021
20.020	4.4315	59.0	2	0	0	20.035	4.4284	-0.015
20.736	4.2801	100.0	2	1	0	20.754	4.2764	-0.018
22.810	3.8954	12.4	1	3	1	22.835	3.8912	-0.025
23.852	3.7275	20.2	1	4	0	23.817	3.7331	0.035
24.338	3.6542	16.4	2	1	1	24.321	3.6568	0.017
25.024	3.5555	35.2	0	4	1	25.026	3.5553	-0.002
28.816	3.0957	12.6	2	3	1	28.808	3.0966	0.008
29.661	3.0094	16.3	2	4	0	29.604	3.0151	0.057
31.637	2.8258	5.8	1	5	1	31.614	2.8278	0.023
32.578	2.7463	13.3	0	6	0	32.602	2.7444	-0.024
32.908	2.7195	11.7	2	1	2	32.893	2.7208	0.015
33.412	2.6796	16.1	0	4	2	33.431	2.6782	-0.019
34.178	2.6213	10.3	1	6	0	34.177	2.6214	0.001
34.965	2.5641	8.0	1	4	2	34.973	2.5635	-0.008

Basic Energy Sciences of the U.S. Department of Energy under Grant No. DE-FG02-86ER45231.

- Bergmann, J., Le Bail, A., Shirley, R., and Zlokazov, V. (2004). "Renewed interest in powder diffraction data indexing," *Z. Kristallogr.* **219**, 783–790.
- Carter, W. J. (2008). "Unexpected benefits of bethanechol in adults with cerebral palsy," *Med. J. Aust.* **189**, 293.
- Cummings, J. L., and Kaufer, D. (1996). "Neuropsychiatric aspects of Alzheimer's disease: The cholinergic hypothesis revisited," *Neurology* **47**, 876–883.
- David, W. I. F., Shankland, K., van de Streek, J., Pidcock, E., Motherwell, W. D. S., and Cole, J. C. (2006). "DASH: A program for crystal structure determination from powder diffraction data," *J. Appl. Crystallogr.* **39**, 910–915.
- de Wolff, P. M. (1968). "A simplified criterion for the reliability of a powder pattern indexing," *J. Appl. Crystallogr.* **1**, 108–113.
- Gražulis, S., Chateigner, D., Downs, R. T., Yokochi, A. F. T., Quirós, M., Lutterotti, L., Manakova, E., Butkus, J., Moeck, P., and Le Bail, A. (2009). "Crystallography open database—An open-access collection of crystal structures," *J. Appl. Crystallogr.* **42**, 726–729.
- Guha, R., Howard, M. T., Hutchison, G. R., Murray-Rust, P., Rzepa, H., Steinbeck, C., Wegner, J., and Willighagen, E. L. (2006). "The blue obelisk—Interoperability in chemical informatics," *J. Chem. Inf. Model.* **46**, 991–998.
- Le Bail, A. (2001). "ESPOIR: A program for solving structures by Monte Carlo from powder diffraction data," *Mater. Sci. Forum* **378–381**, 65–70.
- Le Bail, A. (2004). "Monte Carlo indexing with MCMAILLÉ," *Powder Diffr.* **19**, 249–254.
- Le Bail, A. (2005). "Whole powder pattern decomposition methods and applications—A retrospection," *Powder Diffr.* **20**, 316–326.
- Le Bail, A. (2008). *Principles and Applications of Powder Diffraction*, edited by A. Clearfield, J. Reibenspies, and N. Bhuvanesh (Wiley, New York), pp. 261–309.
- Le Bail, A., Cranswick, L. M. D., Adil, K., Altomare, A., Avdeev, M., Cerny, R., Cuocci, C., Giacovazzo, C., Halasz, I., Lapidus, S. H., Louwen, J. N., Moliterni, A., Palatinus, L., Rizzi, R., Schilder, E. C., Stephens, P. W., Stone, K. H., and van Mechelen, J. (2009). "Third structure determination by powder diffractometry round robin (SDPDRR-3)," *Powder Diffr.* **24**, 254–262.
- Le Bail, A., Marcos, M. D., and Amorós, P. (1994). "Ab initio crystal structure determination of $\text{VO}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$ from X-ray and neutron powder diffraction data. A monodimensional vanadium(IV) hypophosphate," *Inorg. Chem.* **33**, 2607–2613.
- Major, R. T. and Bonnett, H. T. (1943). US Patent No. 2,322,375 (22 June).
- Rietveld, H. M. (1969). "A profile refinement method for nuclear and magnetic structures," *J. Appl. Crystallogr.* **2**, 65–71.
- Rodríguez-Carvajal, J. (1993). "Recent advances in magnetic-structure determination by neutron powder diffraction," *Physica B* **192**, 55–69.
- Smith, G. S., and Snyder, R. L. (1979). " F_N : A criterion for rating powder diffraction patterns and evaluating the reliability of powder-pattern indexing," *J. Appl. Crystallogr.* **12**, 60–65.
- Spek, A. L. (2003). "Single-crystal structure validation with the program PLATON," *J. Appl. Crystallogr.* **36**, 7–13.