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Some observations on the crystal structure of (*R,S*)-propranolol hydrochloride

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Abstract

A recent paper addressing an apparent discrepancy in the structure of (*R,S*)-propranolol hydrochloride (Roberts and Rowe, 1994; *Int. J. Pharm.*, 109 (1994) 83–87) is shown to be redundant. Errors in comprehension of basic crystallography are highlighted.

Keywords: Powder X-ray diffraction; (*R,S*)-Propranolol hydrochloride; Polymorphism; Indexing

A crystalline solid is essentially a solid whose atoms are disposed in a regular three-dimensional periodic array. Such solids can be described at a molecular level by: (a) a unit cell specified by three linearly independent basis vectors; (b) a set of symmetry operators; (c) a set of fractional coordinates which specify the location of the symmetry independent atoms relative to the unit cell edges.

All these parameters can generally be determined by single crystal X-ray crystallography. It is often the case that several X-ray data sets and corresponding structures are reported in the literature for the same chemical entity. In such cases, the question to be asked is not, as has been suggested (Roberts and Rowe, 1994), 'which set is correct?'. Rather, the question should be, 'are the different data sets indicative of polymorphism, or do they simply represent the same structure measured with a greater degree of precision/accuracy, or the same structure viewed with a different lattice basis and/or origin?'.

(*R,S*)-Propranolol hydrochloride is an example of the latter case. Table 1 shows the unit cells and space groups previously reported for this compound. In a recent paper (Roberts and Rowe, 1994), which sets out to determine which of the two structures 'is correct', the authors have failed to recognise that the space group $P2_1/n$ is merely a different basis setting of the space group $P2_1/c$ (Hahn, 1989), a fact clearly illustrated in Fig. 1. It is a straightforward matter, using these diagrams and elementary trigonometry, to show that the $P2_1/n$ cell (Ammon et al., 1977) can be transformed into a cell in $P2_1/c$ with dimensions a =

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Table 1
Cell dimensions and space groups reported for (*R,S*)-propranolol hydrochloride

Space group	*a* (Å)	*b* (Å)	*c* (Å)	*β* (°)	Volume (Å^3)	Reference
$P2_1/n$	14.017	8.285	14.005	98.76	1607	Ammon et al. (1977)
$P2_1/c$	13.932	8.327	18.240	130.81	1602	Cotrait and Dangoumau (1971)

14.005Å, b = 8.285Å, c = 18.243Å, β = 130.59°. This is similar to the cell previously reported in $P2_1/c$ (Cotrait and Dangoumau, 1971). Neglecting the disorder of the hydroxyl oxygen highlighted by Ammon et al. (1977), the structures reported by the two groups are effectively identical (see Fig. 2) and so no confirmatory powder or single crystal experiment is needed.

Given the unit cell and space group of a compound, it is straightforward to predict where reflections will appear in a powder diffraction pattern. If the atomic co-ordinates are also available, then the full diffraction profile can be simulated. In Fig. 2 of their paper, Roberts and Rowe (1994) show only the predicted peak positions for the two single crystal structures. As the unit cells are very similar, the plots ought to be virtually superimposable, yet they are not. The peak positions they show based on the cell of Ammon et al. (1977) are certainly incorrect as there should be no peaks in the pattern around ~6.38° 2θ for a cell of these dimensions if the space group symmetry is correctly specified. It is ironic that this incorrect pattern was the one chosen as showing 'the best agreement' with the measured powder pattern. Correct simulated patterns in the ranges 5–30° 2θ and 12.3–13° 2θ for both cells at λ = 1.5406Å are shown in Fig. 3. The patterns are essentially identical, with the small differences in peak positions attributable to the differences in the exact dimensions of the measured unit cells.

It is no great surprise that (*R,S*)-propranolol hydrochloride can be indexed from a laboratory X-ray measurement — many hundreds of compounds of this cell size and beyond have been indexed on laboratory sources. However, to state

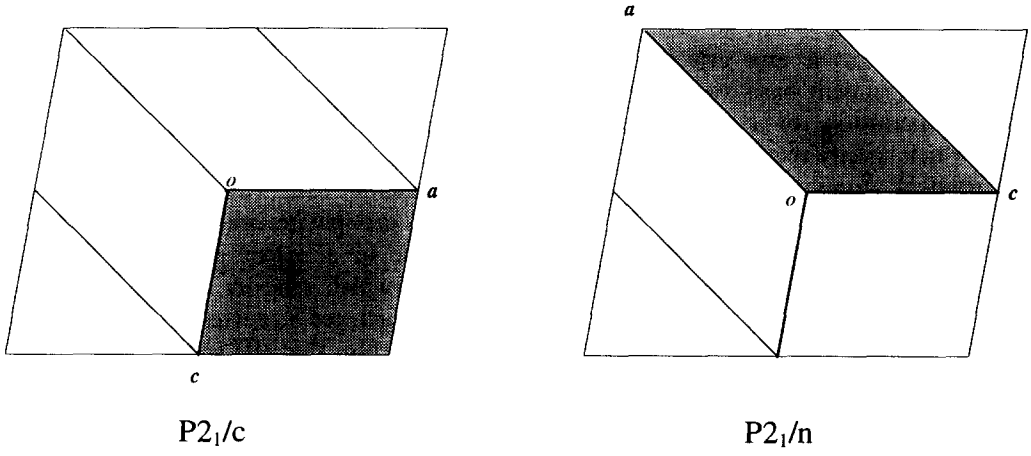

Fig. 1. Two cell choices for space group number 14, $P2_1/c$ and $P2_1/n$. Each diagram shows four adjacent unit cells viewed down the unique axis *b* (*b* pointing out of the paper) with the chosen unit cells highlighted.

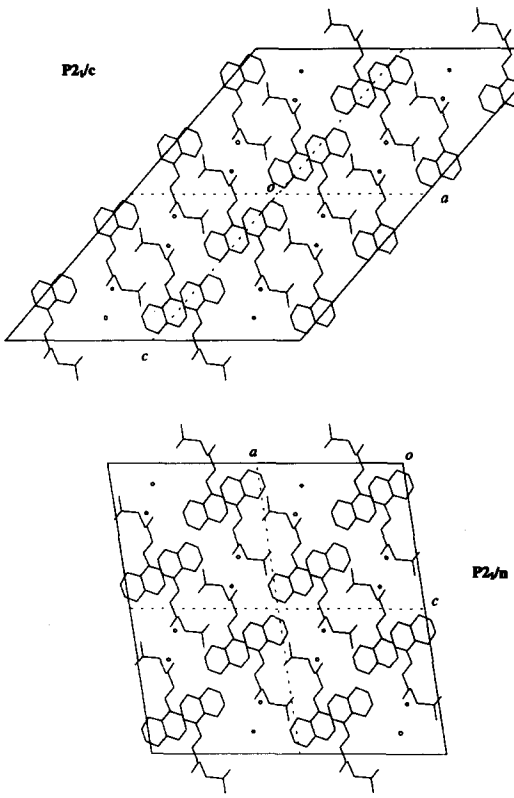

Fig. 2. The single crystal structures reported for (*R*,*S*)-propranolol hydrochloride. Four adjacent unit cells are shown in projection down the *b* axis for each structure. Note that the structures have been reported in different handed coordinate systems and so the $P2_1/n$ cell is shown here with the *b* axis pointing into the paper.

that the accuracy attainable with laboratory based powder X-ray diffractometers "obviates the need to use synchrotron X-rays to generate accurate powder patterns to enable definition of lattice parameters (as recently determined for cimetidine)" (Roberts and Rowe, 1994) is overstating the case. In the specific case of cimetidine, data were collected at a synchrotron source with a view to attempting to solve the crystal structure ab initio, not only index the cell (Cernik et al., 1991). This is not a trivial task and requires data of the highest quality. In the general case, it is the high instrumental resolution as well as the positional accuracy attainable at synchrotron sources that is of benefit when indexing patterns. For example, without an a priori knowledge of the cell, it would be difficult to deduce that the peaks at $\sim 12.4°$ 2θ and $\sim 12.8°$ 2θ shown in close-up in Fig. 3 both contain intensity contributions from more than one reflection. Thus two or more reflections can easily be mistaken for one. Table 2 shows how such peak overlap affected the accuracy of the reflection positions used by Roberts and Rowe as input to the TREOR indexing program. Each of the nine measured peaks were treated as individual reflections for the purposes of indexing, yet peaks 3, 4, 8 and 9 actually consist of pairs of reflections, whilst peak 7 is a triplet of reflections. The two weak singlets ignored in the indexing process do correspond to real reflections. All in all, the first 7 lines input into TREOR constitute less than half the true number of lines in this region. The fact that a correct solution was obtained is testament to the power of the semi-exhaustive trial and error powder indexing method implemented in TREOR rather than the quality of the input data. In cases such as this, there is a considerable advantage in using a high resolution powder diffractometer such as the one sited in station 9.1 of the Daresbury Synchrotron Radiation Source, provided that instrumental resolution (and not intrinsic peak width) is the limiting factor. Many overlapping peaks will be split and the additional information gleaned may make the difference between success and failure when indexing a pattern, particularly one associated with a large unit cell and a low symmetry space group.

It is important to remember that even with a high resolution diffractometer, it may still be difficult to assess how many reflections actually contribute to any given measured peak. A probabilistic basis for making such a judgement has been outlined (Sivia et al., 1993) and successfully used to determine the unit cell of sotalol hydrochloride using laboratory X-ray diffraction data (Shankland and Sivia, 1996). The method helps bridge some of the gaps in the complexity of indexing problems that can currently be tackled using laboratory and synchrotron X-rays.

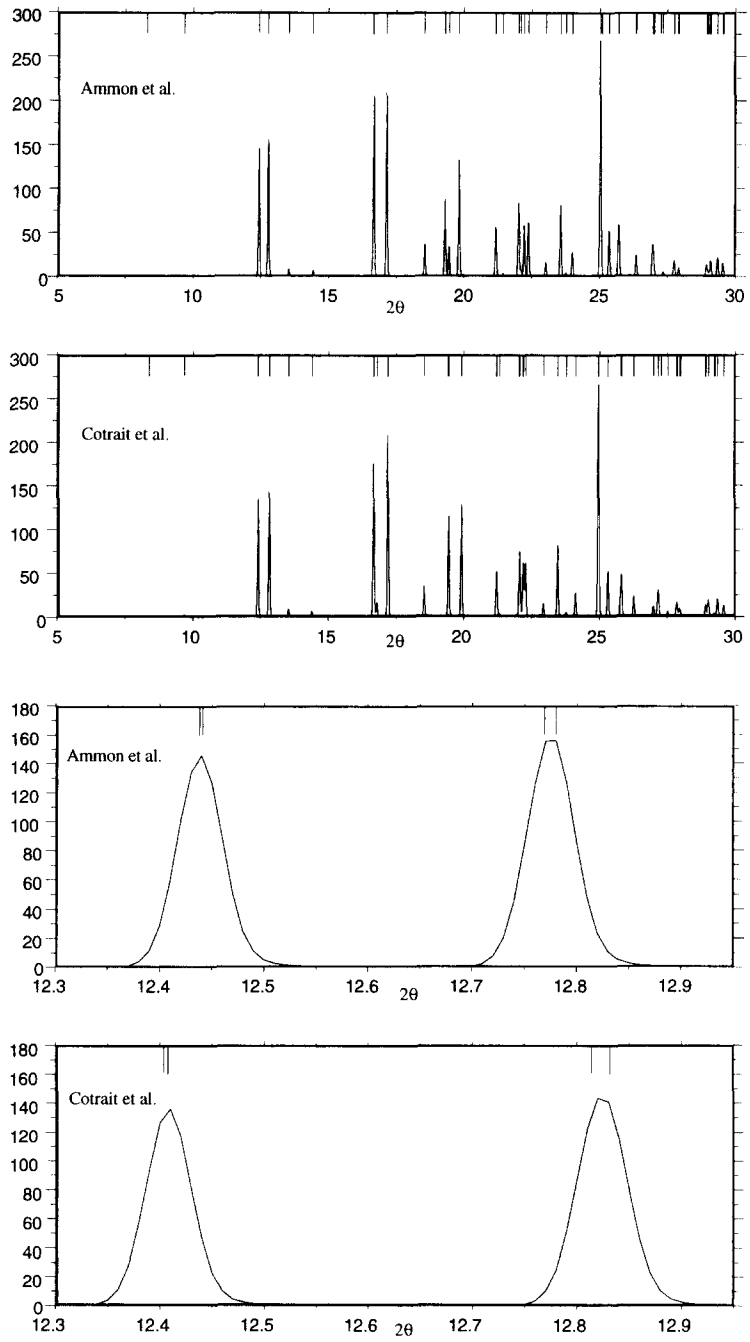

Fig. 3. Simulated powder CuKα_1 X-ray diffraction patterns for the reported (*R*,*S*)-propranolol hydrochloride structures. In each case the ordinate units are degrees and the abscissa have arbitrary units of intensity. The tick marks indicate the calculated reflection positions based on the known unit cells. To simplify comparison of the structures, hydrogen atoms were not included in the calculations. Without their scattering contribution, there is so little intensity in the peaks at $\sim 8.3°2\theta$ and $\sim 9.7°2\theta$ that they do not appear on scale in the plots shown here.

Table 2
A comparison of the positions of the first nine peaks given in Table 1 of the paper of Roberts and Rowe (1994) with the correct reflection positions calculated using the cell determined by Ammon et al. (1977). Note that the (−1 1 2) reflection is very weak and is unlikely to be visible adjacent to the strong (−2 1 1) reflection.

Measured line positions		Calculated reflection positions	
Line number	Position (°2θ)	Reflection	Position (°2θ)
1	8.317	−1 0 1	8.307
2	9.736	1 0 1	9.688
3	12.471	−1 1 0	12.438
		0 1 1	12.441
4	12.777	2 0 0	12.769
		0 0 2	12.780
5 (not used in TREOR)	13.555	−1 1 1	13.537
6 (not used in TREOR)	14.466	1 1 1	14.431
7	16.664	−2 0 2	16.658
		−2 1 0	16.669
		0 1 2	16.677
8	17.150	−2 1 1	17.146
		−1 1 2	17.152
9	18.576	2 1 1	18.555
		1 1 2	18.561

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