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Crystal Structure of Guaifenesin, 3-(2-methoxyphenoxy)-1,2-propanediol.

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The crystal structure of the common expectorant guaifenesin, 3-(2-methoxyphenoxy)-1,2-propanediol ($C_{10}H_{14}O_4$) was solved by applying Monte Carlo simulated annealing techniques to synchrotron powder data, and refined using the Rietveld method. Initial structure solutions yielded an unreasonable conformation, and an unacceptable refinement. Quantum chemical geometry optimizations were used to identify the correct conformation. Guaifenesin crystallizes in the orthorhombic space group $P2_12_12_1$ (#19), with $a = 7.65705(7)$, $b = 25.67020(24)$, $c = 4.97966(4)$ Å, $V = 978.79(2)$ Å³, and $Z = 4$. Both hydroxyl groups act as hydrogen bond donors and acceptors, resulting in the formation of a 2-dimensional network of strong hydrogen bonds in the ac plane. The solid state conformation is ~4 kcal/mole higher in energy than the minimum-energy conformation of an isolated molecule, but the formation of the hydrogen bonds results in an energy gain of ~100 kcal/mole. Knowledge of the crystal structure permits quantitative phase analysis of guaifenesin-containing pharmaceuticals (such as Duratuss GP 120-1200) by the Rietveld method.