Journal of Molecular Structure 920 (2009) 377–382

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

# Absolute configuration and crystal packing for three chiral drugs prone to spontaneous resolution: Guaifenesin, methocarbamol and mephenesin

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ARTICLE INFO

*Article history:*
Received 29 October 2008
Received in revised form 24 November 2008
Accepted 24 November 2008
Available online 3 December 2008

*Keywords:*
Chiral drugs
Spontaneous resolution
Conglomerates
Molecular structure
Crystal packing

ABSTRACT

Popular chiral drugs, guaifenesin, methocarbamol, and mephenesin were investigated by single-crystal X-ray analysis both for enantiopure and racemic samples. The absolute configurations for all substances were established through Flack parameter method. The conglomerate-forming nature for the compounds was confirmed by equivalence of crystal characteristics of enantiopure and racemic samples. The molecular structures and crystal packing details were evaluated and compared with one another for all three investigated substances.

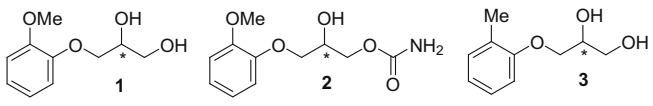


## 1. Introduction

Chiral discrimination accompanying solid phase formation plays an important role in the enantiomers separation processes [1,2]. A binary mixture of enantiomers may crystallize in some different ways [3] among which two are the most common. First, the most frequent crystallization mode of a racemate is the formation of a homogeneous crystal structure, commonly known as a racemic compound. Some theoretical arguments exist to explain this crystallization type predominance [[4] and references cited therein]. Second, each enantiomer may crystallize separately from one another, forming a mechanical mixture (in other word conglomerate) of two sets of distinct, enantiomorphic crystals. The space group of such a chiral crystal must contain only translations and rotations as symmetry operations, which limits it to one of only 65 of the 230 space groups. The phenomenon of enantiopure crystals formation from a racemate melt or solution assumes the name of spontaneous resolution. Starting with Pasteur's original demonstration of the tartrate salts spontaneous resolution during crystallization [5], this phenomenon has provoked much interest and led to a great deal of fundamental understanding. Nevertheless the authors of the last review on the subject assert that "the understanding and prediction of spontaneous resolution ... remains one of the true challenges for science in the 21st century" [6], and we share this judgment completely.

Crystal packing is the result of the competition between different factors connected with close packing requirements and intermolecular interactions. Space group symmetry results as a compromise, usually hard to predict. The modern level of theory has given no way to solve the problem "from the first principles". Under these conditions, it is desirable to have a reliable reference point, and to operate with differences, not with isolated instances. In the other words, if one knows well the intra- and inter-molecular interaction patterns stabilizing homochiral crystal packing (a conglomerate formation) for a specific substance, it would be possible to link the changes in an another substance crystal structure type with the molecular structure modifications, provided that these modifications are rather limited. It would be prudent to begin with conglomerate-forming substances because of their less abundance than racemic compounds forming ones [7].

Recently, we have disclosed [8–11] the conglomerate nature of three real chiral drugs, namely, expectorant *guaifenesin* [12a] [**1**, chemical name 3-(2-methoxyphenoxy)-propane-1,2-diol], skeletal muscle relaxants *methocarbamol* [12b] [**2**, chemical name 1-carbamoyloxy-2-hydroxy-3-(2-methoxyphenoxy)-propane], and *mephenesin* [12c] (**3**, chemical name 3-(2-methylphenoxy)-propane-1,2-diol].

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doi:10.1016/j.molstruc.2008.11.037

To the best of our knowledge, for today these compounds are the only known chiral active principles experienced to spontaneous resolution in them, not in the form of the derivatives or precursors. All three compounds belong to the very potent family of glycerol ethers to which many biologically active substances belong too. We believe that the detailed knowledge of the compounds **1**–**3** crystal structure will be the base for understanding the reasons controlling a crystallization type for different related compounds.

## 2. Experimental

### 2.1. General

Optical rotations were measured on a Perkin–Elmer model 341 polarimeter (the value of specific rotation is given in deg ml $g^{-1}$ $dm^{-1}$, and the concentration of solutions, *c*, appears in g/100 ml). Melting characteristics were measured on a Perkin–Elmer Diamond DSC differential scanning calorimeter in aluminum pans with the rate of heating of 10 °C $min^{-1}$. The mass of the samples amounted to approximately 2.5 mg. HPLC analyses were performed on a Shimadzu LC-20AD system controller, and UV monitor 275 nm was used as a detector. The column used, from Daicel, Inc., was Chiralcel OD (0.46 × 25 cm).

### 2.2. Materials

The syntheses of the compounds **1–3** in racemic and enantiopure form are described in our preceding papers [9–11]. For all compounds single-crystal X-ray diffraction experiments have been performed at first with enantiopure samples in attempt to establish the absolute configuration for these valuable drugs. The sample of (*R*)-**1**, 99.5% ee, was crystallized from water and was characterized by mp 97.2 °C, $[\alpha]_D^{20} = -9.4$ (*c* 1.0, MeOH). The sample of (*S*)-**2**, 99.9% ee, was crystallized from ethyl acetate and was characterized by mp 112.3 °C, $[\alpha]_D^{20} = +0.8$ (*c* 1.1, MeOH). The sample of (*R*)-**3**, 99.8% ee, was crystallized from hexane and was characterized by mp 91.0 °C, $[\alpha]_D^{20} = +12.8$ (*c* 1.1, $MeOBu^t$). Crystal information listed in Table 1 belongs to these samples. Other set of X-ray diffraction experiments have been performed with individual crystals piked up from the bulk racemate samples of the compounds **1–3**, mp 79.9, 93.8, and 70.6 °C, respectively. For all three substances the space groups and the unit cell parameters for accidentally hand-piked single crystals were identical with those for enantiopure samples.

### 2.3. X-ray crystal structure analysis

The X-ray diffraction data for the crystals of **1–3** (see Section 2.2) were collected on a Bruker Kappa Apex2 CCD automatic diffractometer using graphite monochromated CuKα (1.54184 Å) radiation. The crystal data, data collection, and the refinement are given in Table 1. Data were corrected for absorption using SADABS [13] program. The structures were solved by direct method and refined by the full-matrix least-squares using SHELXTL [14] and WinGX [15] programs. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms for compound **2** were located on a difference map and refined isotropically. The hydrogen atoms for compounds **1** and **3** were calculated and refined as riding atoms except the hydrogen atoms on hydroxyl groups which were located on difference map and refined isotropically. The absolute structure of the single crystals was determined on the basis of the Flack [16] parameter. Data collections: images were indexed, integrates, and scaled using the APEX2 [17] data reduction package. All figures were made using the program PLATON [18].

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 693625 for **1**, 693624 for **2**, and 693626 for **3**. Copies of the data can be obtained free of charge upon application to the CCDC (12 Union Road, Cambridge CB2 1EZ UK. Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

## 3. Discussion

### 3.1. Guaifenesin

Here, we represent the results of single-crystal X-ray investigation for enantiopure sample with predetermined chiroptical characteristics. Being successful, this experiment would allow

**Table 1**
Crystallographic data for guaifenesin (**1**), methocarbamol (**2**), and mephenesin (**3**).

| Compound | (**1**) | (**2**) | (**3**) |
|---|---|---|---|
| Formula | $C_{10}H_{14}O_4$ | $C_{11}H_{15}NO_5$ | $C_{10}H_{14}O_3$ |
| *M* (g/mol) | 198.21 | 241.24 | 182.21 |
| Temperature (K) | 293 | | |
| Crystal class | Orthorhombic | Monoclinic | Monoclinic |
| Space group | $P\,2_1\,2_1\,2_1$ | $P\,2_1$ | $P\,2_1$ |
| *Z* | 4 | 2 | 4 |
| Radiation type | CuKα | | |
| Cell parameters | | | |
| *a* | 4.9729(2) | 7.5500(3) | 13.0132(8) |
| *b* | 7.6537(3) | 4.9283(2) | 4.8558(3) |
| *c* | 25.6486(9) Å | 15.3906(5) Å | 16.371(1) Å |
| *β* | | 94.798(2)° | 109.235(3)° |
| *V* (Å$^3$) | 976.21(6) | 570.66(4) | 976.7(1) |
| *F*(000) | 424 | 256 | 392 |
| $\rho_{calc}$ (g/cm$^3$) | 1.349 | 1.404 | 1.239 |
| $\mu$ ($cm^{-1}$) | 8.7 | 9.43 | 7.45 |
| $\theta$ (deg) | $3.45 \leqslant \theta \leqslant 63.66$ | $2.88 \leqslant \theta \leqslant 70.00$ | $3.60 \leqslant \theta \leqslant 68.17$ |
| Reflections measured | 11,964 | 6729 | 11,577 |
| Independent reflections | 1526 [*R*(int) = 0.0509] | 1928 [*R*(int) = 0.0639] | 3045 [*R*(int) = 0.0250] |
| Reflections [$I > 2\sigma(I)$] | 1518 | 1906 | 2893 |
| Flack parameter | 0.0(1) | 0.0(1) | 0.0(2) |
| $R_1$ | *R* = 0.0250 | *R* = 0.0367 | *R* = 0.0263 |
| $wR_2$ | *Rw* = 0.0699 | *Rw* = 0.1010 | *Rw* = 0.0683 |
| GOF | 1.077 | 1.024 | 1.108 |
| $\rho_{max}/\rho_{min}$ (e Å$^{-3}$) | 0.139/−0.120 | 0.189/−0.159 | 0.110/−0.116 |