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Bernal, I., Lalancette, R.A. The Crystal and Molecular Structure of N-methylephedrinium 4-nitrobenzoate (I, II). Racemic Mimics Part 5. Struct Chem 36, 1419–1423 (2025). https://doi.org/10.1007/s11224-025-02528-0

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Structural Chemistry (2025) 36:1419–1423
https://doi.org/10.1007/s11224-025-02528-0

RESEARCH

The Crystal and Molecular Structure of N-methylephedrinium 4-nitrobenzoate (I, II). Racemic Mimics Part 5

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Received: 17 May 2025 / Accepted: 29 May 2025 / Published online: 10 June 2025
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Abstract

Ephedrine is an ancient Chinese medicine drug used on patients with asthma, bronchitis and hay fever. In more recent times, it is used to prevent low blood pressure during anesthesia and to treat narcolepsy and obesity. It seemed important to understand the interaction of this drug with as large a variety of substrates as possible to get hints as to its *modus operandi*. It was, therefore, of interest that it appeared to crystallize as a Racemic Mimic in the form of its 4-nitrobenzoate derivative as determined by the cell parameters of that salt when it crystallized in both racemic and Sohncke space groups. Below, we describe the procedure used to prove that ephedrine belongs in that class and to illustrate the nature of the intra- and intermolecular interactions between the constituent moieties in that monoclinic ($P2_1$ and $P2_1/c$) pair. Both crystal structures, obtained from the literature, were determined at 123 K and refined, respectively, to R-factors of 3.73 and 5.51%.

Keywords Ephedrine · Crystal structures · Racemic crystals · Racemic mimic crystals · Sohncke space groups · Hydrogen bonding · π-π bonds

Introduction

Described are the results obtained from an examination of the database CCDC [1] while searching for examples of organic molecules of biological importance that exhibit the crystallization behavior we have described earlier [2–5] as Racemic Mimics. Chirality of atoms present in such molecules was identified using MERCURY [6], which was also used to create input files for the graphics in this document, subsequently generated using the program DIAMOND [7]. An interesting example in CCDC [1] is that of the pair **(I)** and **(II)** described by Kennedy, Morrison, Briggs, Arbuckle [8] characterized by the following data:

IVULUH (I): (±)−1-Hydroxy-N,N-dimethyl-1-phenylpropan-2-ylammonium 4-nitrobenzoate, or N-methylephedrinium 4-nitrobenzoate: $C_{11}H_{18}NO^+$, $C_7H_4NO_4^-$.

Sp. Gr. = $P2_1/c$, Z = 4.0, Z' = 1.0, R = 5.51, T = 123 K

a = 5.828(< 1), b = 12.811(< 1), c = 23.207(< 1) Å, β = 91.68(< 1)°, V = 1739.406 Å.^{3} [8]

IVULOB (II): (1R,2S)-(-)−1-Hydroxy-N,N-dimethyl-1-phenylpropan-2-ylammonium 4-nitrobenzoate, or N-methylephedrinium 4-nitrobenzoate: $C_{11}H_{18}NO^+$, $C_7H_4NO_4^-$.

A pair of R,S centers on each independent ephedrinium molecule

Sp. Gr. = $P2_1$, Z = 4.0, Z' = 2.0, R = 3.73, T = 123 K.

a = 5.831(< 1), b = 12.970(< 1), c = 23.552(< 1) Å, β = 94.84(< 1)°, V = 1774.806 Å.^{3} [8]

Thus, the pair satisfies the conditions required for the crystallization within the class of Racemic Mimics [2–5].

Results and Discussion

Figure 1 *Note*: a hydrogen-bonded fragment of *a second anion* appears on the upper portion of the figure—for more details of the hydrogen bonding in the unit cell, see Fig. 2

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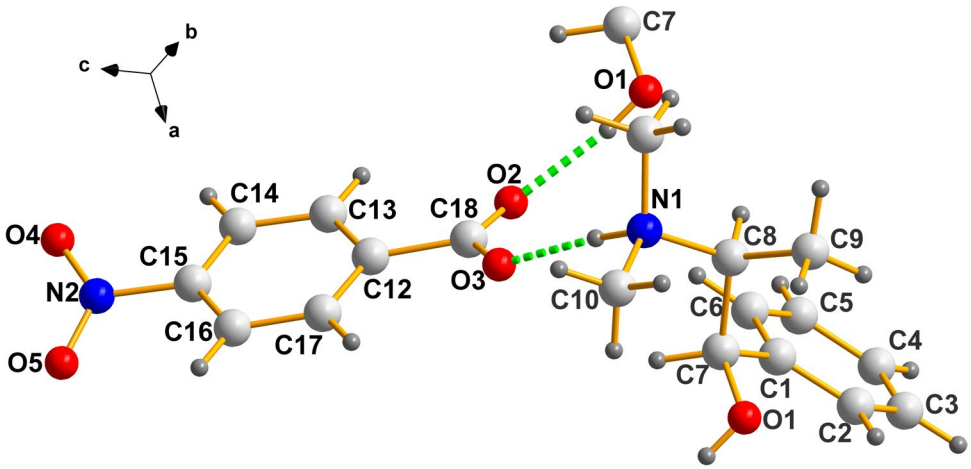


Fig. 1 describes the stereochemistry and atomic labeling of the racemate (**I**).

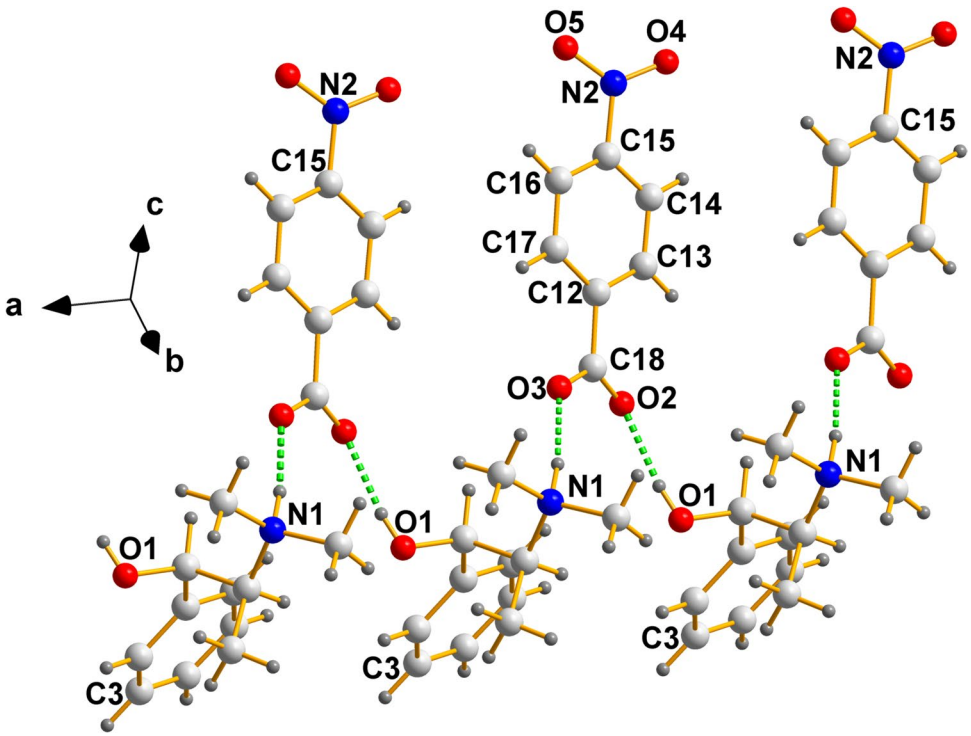


Fig. 2 Along the ***a***-axis, the strings of ephedrinium cations are stitched together by hydrogen bonds with the carboxylate fragments of the nitro benzoate anions

The arrangement of the species described above suggests π-π bonds between the phenyl (C12-17) rings; however, the spacing (5.828 Å) between them is the length of the ***a***-axis, indicating packing forces are largely responsible for such contacts – a distance considered very long by the criterion suggested by Janiak [9]. However, careful examination of the packing scheme reveals the presence of additional π-π bonds, shown in Fig. 3.

Notable features of these dimeric entities are as follows: (a) the C–C distances, listed below, are less than 4.0 Å and, thus, fit well with the suggested criterion of Janiak [9] for strong π-π bonds; (b) by arranging the contacts to be head-to-tail, electrostatic repulsions between the negatively charged species are minimized while forming some very significant π-π bonds; (c) interestingly, it seems that some very substantial π-π bonds (shown in Table 1). between N2 and

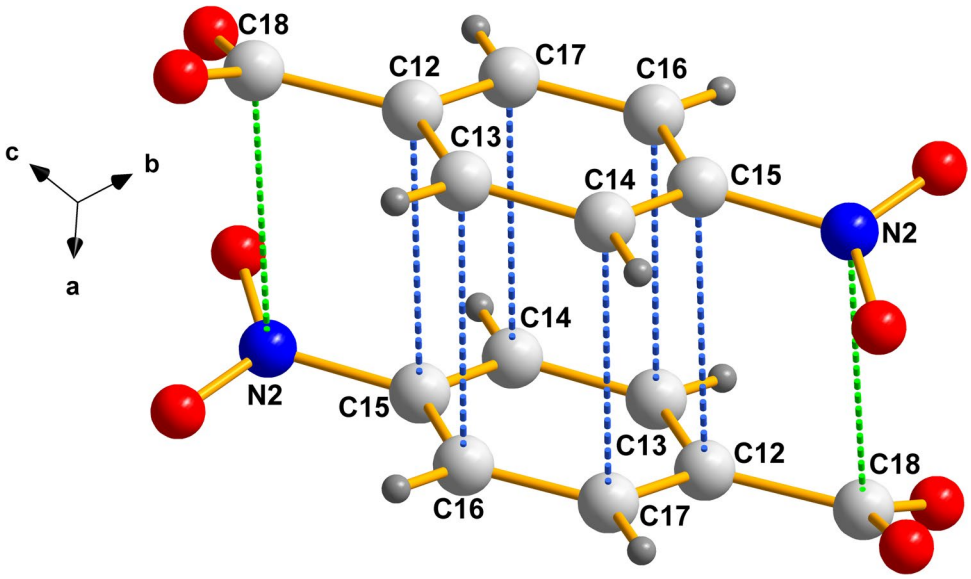


Fig. 3 Regarding π-π bonding, note the interesting head-to-tail arrangement of pairs of the carboxylate anions in (**I**)

Table 1 π-π bond distances in **IVULUH (I)**, in Å

C12 – C15*	3.892	C15 – C12*	3.892
C13 – C16*	3.900	C16 – C13*	3.900
C14 – C17*	3.863	C17 – C14*	3.863
N2 – C18*	3.884	C18 – N2*	3.884

* Symmetry [1 + x, 3/2—y, ½ + z].

C18 are formed in a pairwise manner. C-N π-π bonds were described by Janiak [9].

As in the case of (**I**), the ephedrine cations in (**II**) have two chiral centers labeled C7 and C8, already shown in Fig. 1. Fortunately, the authors [8] preserved the labels of both studies, making comparisons considerably easier.

The cation–anion pair present in the chiral crystals (**II**) is depicted in a labeled view, Fig. 4.

In this ionic complex, there is π-π stacking between the two independent carboxylate anions. Table 2 points these out.

A good gauge of the diastereoisomeric difference(s) in the cation pair in (**II**) is shown in Fig. 5.

Table 2 π-π bond distances in the two independent anions in **IVULOB (II)**, in Å

C23 – C33	3.733	C29 – N4	3.649
C24 – C34	3.717	O3 – O9	3.209
C25 – C35	3.795	O4 – O10	4.041
C26 – C30	3.904	N3 – C36	4.004
C27 – C31	3.909	O6 – O8	3.686
C28 – C32	3.823	O5 – O7	4.547*

*This distance is very long relative to the others in this anion because of the free rotation of the NO_2 group *vs*. the ring.

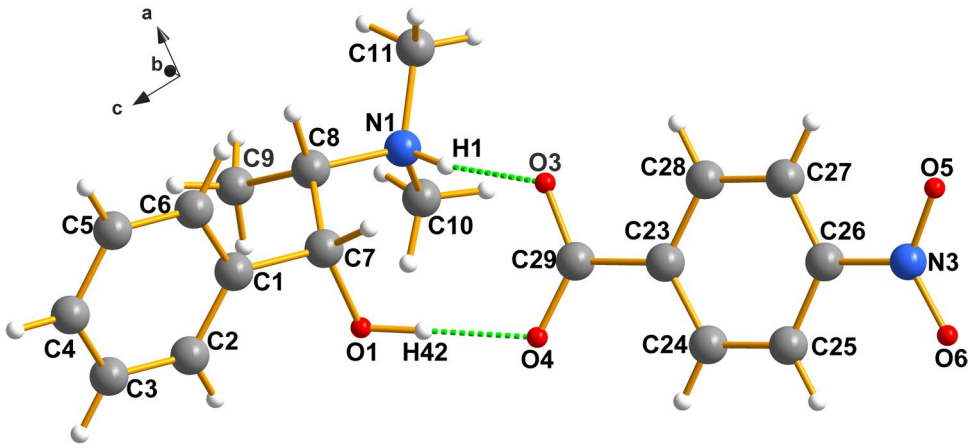


Fig. 4 C7(R) and C8(S) are the chiral carbons on the ephedrine cation. Note the hydrogen-bonded cation–anion pair in (**II**) is essentially identical with that in (**I**) (see Fig. 1)

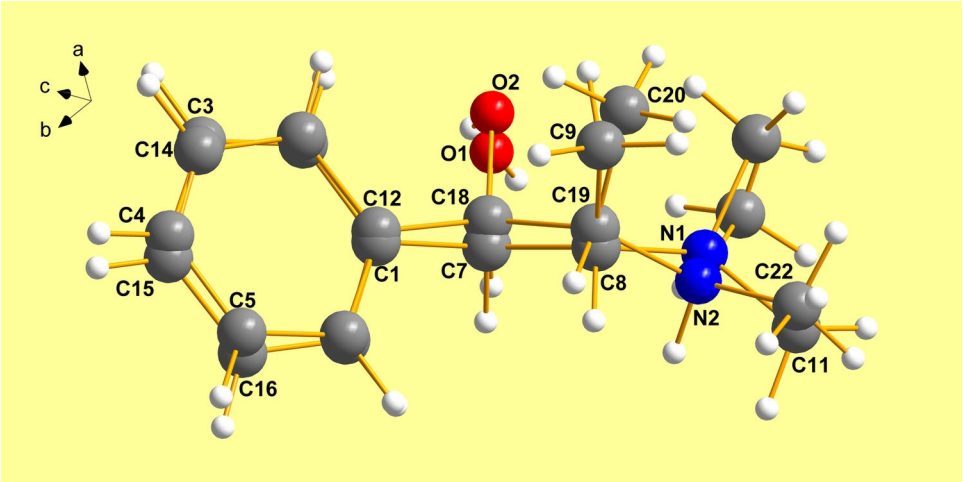


Fig. 5 The overlay of the two independent molecules in (**II**) was carried out with the cation coordinates directly from the final CIF. Note the chirality at C7-C18 (R and R) and C8-C19 (S and S) pairs are preserved

For cations with large, flexible, aliphatic chains such as present in this pair, we find it remarkable that they possess diastereoisomeric conformations so similar. As shown below in Fig. 6, the same is true of the anionic pair.

Those deviations are fairly minor, as demonstrated by the distances between pairs shown in Table 3.

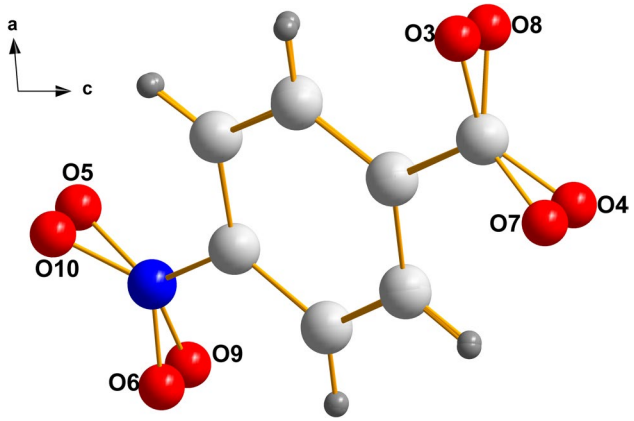


Fig. 6 The only significant deviation from near-perfect overlay is in the external oxygens associated with the nitro and carboxylic fragments, which are quite free to rotate about the single bonds to the phenyl rings

Table 3 Distance between the pairs of oxygen atoms in the nitro groups from the overlay of the nitrobenzoate anions in (**II**), in Å

O3-O8 = 0.461	O5-O10 = 0.509
O4-O7 = 0.485	O6-O9 = 0.486

Figure 7 illustrates the packing in the unit cell while also depicting the location of the Center of Mass of that fragment of (**II**).

The origin is located between atoms sharing the same label which is in the center of the quartet labeled O2-O2-O7-O7 appearing at the center of the figure. Recall that in space group $P2_1$, the origin at ***y*** is arbitrary and must be defined and fixed. Thus, we can set it at 0.5000 and the origin of the entire array would be at 0.5049, 0.5000, 0.5110 which is quite close to a true inversion center of 0.5000, 0.5000, 0.5000, as occurs in the case of (**I**) crystallizing in $P2_1/c$. Note that the value of the pseudo-center in $P2_1$ is very close to the "true" center in $P2_1/c$ in the other one-half of the racemic mimic.

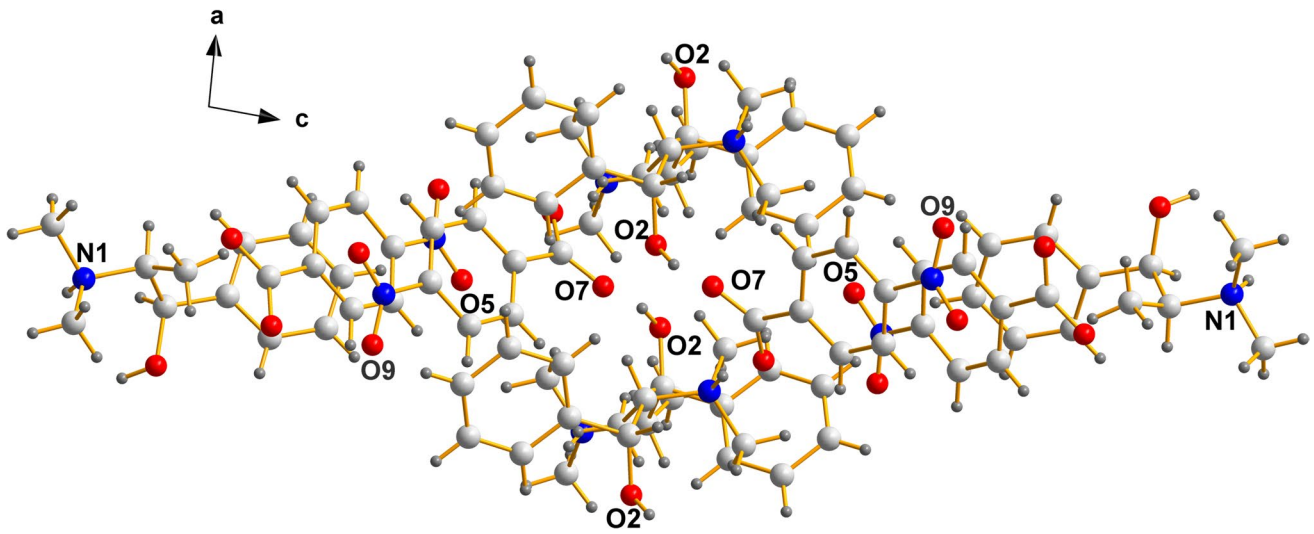


Fig. 7 The Center of Mass is located at 0.5049, 0. 4360, 0.5110

Conclusions

The pair of ephedrine crystals described belongs in the Racemic Mimic class, as defined above. That is an important conclusion since this mode of crystallization has only recently come to our attention and our understanding; its role in nature and its importance in chemistry is to be determined only if enough examples are revealed that provide the needed information.

Acknowledgements There are no sources to acknowledge.

Author contributions The manuscript was written by Ivan Bernal and Roger Lalancette.

Funding There are no funding sources used to support this research.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics All ethical guidelines have been adhered.

Conflict of interest statement The authors declare no competing interests.

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