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Enantiomer systems of carnitinamide inorganic salts: introductory studies to a successful entrainment resolution

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Abstract—The ready availability of (*R*)-carnitinamide, an immediate synthetic precursor of (*R*)-carnitine, is an ambitious goal and resolutions, due to the very low cost of racemic carnitinamide, can be the most convenient technology to achieve it. Before developing a new advantageous resolution of carnitinamide chloride by entrainment, we characterized the enantiomer systems formed by the chloride, nitrate and sulfate of carnitinamide, mainly by DSC and IR analyses, proving that a different type of racemate is produced by each of these salts: a conglomerate by the chloride, a racemic compound by the nitrate and a solid solution, a very rare type of enantiomer system, by the sulfate.
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1. Introduction

Due to its important role in the biochemical pathways for β-oxidation of fatty acids and in other metabolic functions, (*R*)-carnitine (*R*)-**1** has found many significant applications in therapy and in nutrition. In recent years, the increasing demand for this enantiopure compound has led to the development of a number of procedures for its preparation, based on different approaches, such as asymmetric chemical synthesis, biotransformation of achiral precursors, resolution through diastereomeric derivatives, enzymatic resolution or the use of non-racemic chiral starting materials. However, to the best of our knowledge, only two of these methods have been scaled up and are currently being applied to industrial production: the biotransformation of 4-butyrobetaine[1] and the resolution of carnitinamide **2**, a very inexpensive carnitine precursor, with D-camphoric acid, followed by the hydrolysis of the amide functional group.[2] In 2006, we patented a simple and efficient entrainment resolution of chloride **2** after studying the nature of the racemates of three readily available salts, such as nitrate, chloride and sulfate.[3] Herein, we report the results of those investigations, which interestingly allowed us to

recognize the three known different forms of the racemate, namely that of the racemic compound and the less frequent ones of a conglomerate and pseudoracemate, in the nitrate, chloride and sulfate of **2**, respectively.

2. Results and discussion

Nitrate **2** was prepared from the readily available chloride, the most common salt of **2**, resulting from HCl treatment of cyanocarnitine,[4] in turn obtained as a chloride, from epichlorohydrin, trimethylamine and hydrogen cyanide.[5] Conversion of the chloride into the nitrate was accomplished by treatment of an aqueous solution of chloride **2** with stoichiometric silver nitrate. After the removal of silver chloride precipitate, nitrate **2** was isolated by concentration of the filtrate and, after prolonged drying under high vacuum, characterized by ^{1}H NMR and elemental analyses. The same procedure was applied to chloride (*R*)-**2** obtaining nitrate (*R*)-**2**. The melting point of this latter compound (133.7 °C) proved to be about 10 ° higher

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Figure 1. IR spectra of (*R*)-carnitinamide nitrate (upper) and of racemic carnitinamide nitrate (lower) in the crystalline phase.
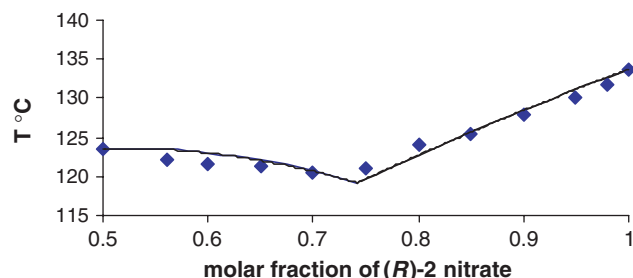

Figure 2. Binary melting-point phase diagram for carnitinamide nitrate. The solid curve represents the values calculated on the basis of the Prigogine–Defay and the Schröder–van Laar equations.

The two curves intersect at the 0.742 molar fraction of nitrate (*R*)-**2**. Such a theoretical value of eutectic composition is consistent with the experimental observation that, unique among the DSC curves recorded for the 10 differently proportioned nitrate **2**/nitrate (*R*)-**2** mixtures, that of a sample with 0.75 mole fraction of (*R*)-**2** nitrate [1/1 mixture of **2** and nitrates (*R*)-**2**] shows only one sharp melting peak at 120.3 °C.

In the case of chloride **2**, the nature of a 1/1 mechanical mixture of enantiomers or conglomerate was suggested by the melting points reported by Kato and Hosein in 1968,[6] notably higher for the enantiomers (238 °C) than for the racemate (206 °C), and successively demonstrated by the identical infrared spectra of the chlorides of (*R*)-**2**, (*S*)-**2** and **2** described by Lorenz in 1980.[7] On the basis of these indications, we performed thermal analyses of chloride **2**, chloride (*R*)-**2** and their four different mixtures. By DSC analysis, the melting points of chloride (*R*)-**2** and of the racemate were estimated to be 241.6 and 210.1 °C, respectively. However, the heat of fusion of the pure enantiomer could not be evaluated, because of thermal decomposition that started before the fusion was complete. This hampered the calculation of the theoretical binary phase diagram by the Schröder–van Laar equation. The DSC curves of the four mixtures showed two clearly detectable fusions, the former of the eutectic, consisting in the racemic mixture, at temperatures ranging between 210 and 211 °C, the latter of the exceeding (*R*)-enantiomer at higher temperatures, increasing with the enantiomeric excess. As shown in Figure 3, plotting the approximate extrapolated offset temperatures of the higher melting peak of the four mixtures and the melting temperatures of the racemic mixture and of the pure (*R*)-enantiomer against mole fraction of this latter resulted in an experimental binary phase diagram, which is consistent with the claimed nature of the conglomerate for chloride **2** on the basis of IR analyses.[7] Furthermore, determining of relative solubilities of the racemic mixture and the pure enantiomer, which indicated a ratio little lower than 2, conforms to the solubility rules formulated for conglomerate systems, produced by ionic compounds, which state that the solubility of a racemate is $\sqrt{2}$ times the solubility of the corresponding enantiomer.[8]

Finally, we examined the neutral sulfate of **2** and (*R*)-**2**, prepared by treatment of the corresponding chlorides with

than that of the corresponding racemate (123.6 °C). Moreover, the respective IR spectra turned out to be different (see Fig. 1).

Such data suggested that nitrate **2** forms a racemic compound melting at a lower temperature than the enantiomers. This was confirmed by DSC analyses of nitrate **2**, nitrate (*R*)-**2** and a number of their mixtures, which allowed us to construct the binary phase diagram, depicted in Figure 2 for mole fractions of (*R*)-**2** nitrate ranging from 0.5 to 1. The melting profiles of the differently proportioned **2** nitrate/(*R*)-**2** nitrate mixtures were characterized by the presence of two peaks, the first, between 120 and 122 °C, representing the fusion of the eutectic, a nearly 1/1 mixture of the racemic compound and (*R*)-enantiomer, the second, representing the fusion of the excess of racemic compound or (*R*)-enantiomer over the eutectic composition at temperatures increasing with such an excess. As can be seen in the same figure, the experimental values fit well with the theoretical ones (solid curves), calculated on the basis of the melting point of nitrate (*R*)-**2** and of its heat of fusion (122.2 J/g) by the Schröder–van Laar equation and of the melting point of nitrate **2** and of its heat of fusion (175.8 J/g) by the Prigogine–Defay equation.