C. R. Chimie 18 (2015) 693–704

Contents lists available at ScienceDirect

Comptes Rendus Chimie

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Determination of the *N*-invertomer stereochemistry in *N*-substituted nortropanones and norgranatanones using computational and NMR methods

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ARTICLE INFO

Article history:
Received 5 September 2014
Accepted after revision 21 October 2014
Available online 3 April 2015

Keywords:
NMR spectroscopy
Density functional calculations
Heterocycles
Alkaloids
Amines

ABSTRACT

Several *N*-substituted nortropane and norgranatane derivatives were synthesised from tropinone and granatanone. The equilibrium distributions of the axial and equatorial *N*-invertomers of the free amine forms of the prepared products in methanol and their protonated forms (hydrochlorides) in water were studied by low-temperature and room-temperature NMR spectroscopy. Theoretical distributions in the gas phase, methanol and water solvents were calculated using DFT methods and compared with inverse gated ^{13}C NMR experiments. DFT calculations provided results in reasonable agreement with experimental data. Equatorial invertomers dominated in *N*-*tert*-butyl- and *N*-benzylnortropinone, and the equatorial/axial ratio for *N*-ethyl- and *N*-phenethylnortropinone was close to 1. The axial invertomers dominated in all of the granatanone derivatives and the *N*-isopropyl- and *N*-phenylnortropane. Our experiments indicated that nitrogen protonation shifted the invertomer equilibrium towards equatorial forms. DFT calculations reproduced this effect for tropanes.

1. Introduction

Tropane (8-methyl-8-azabicyclo-[3.2.1]octane) and granatane (9-azabicyclo[3.3.1]nonane) are bicyclic structures [1] found in numerous bioactive naturally occurring and synthetic compounds [2,3]. Tropinone (**1**, *R* = Me) and granatanone (also known as pseudopelletierine, pseudopelletrierin or *N*-methylgranatanone **2**, R = Me) [4] are simple and are among the best-known representatives of these groups of compounds (Fig. 1). Tropane, granatane and their *N*-alkyl analogues are interesting in medicinal chemistry. Tropane-derived molecules, including cocaine analogues [5], have been studied as promising ligands for biological receptors [6–8]. The granatanone skeleton is an important substructure of some compounds possessing anti-Parkinsonian [9], neuroleptic [10,11], and hypotensive [12] activity. Granatanone and its derivatives were useful for the synthesis of potential cocaine-binding site ligands [13]. The relative stability of the *N*-alkyl invertomers of tropane alkaloids and related bioactive compounds may influence interactions with receptor binding sites [14].

Some of the most synthetically useful transformations of tropane- and granatane-derived ketones are the diastereoselective and enantioselective aldol reactions [15]. Tropinone has been successfully used in this capacity for the synthesis of several bioactive derivatives, such as cocaine [16] and its analogues [6,7], as well as of several other alkaloids [17–21]. Recently, we discovered and investigated stereoselective reactions of tropinone and granatanone promoted by water. The elucidation of the configurational preference of the *N*-methyl in water helped

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http://dx.doi.org/10.1016/j.crci.2014.10.006
1631-0748/

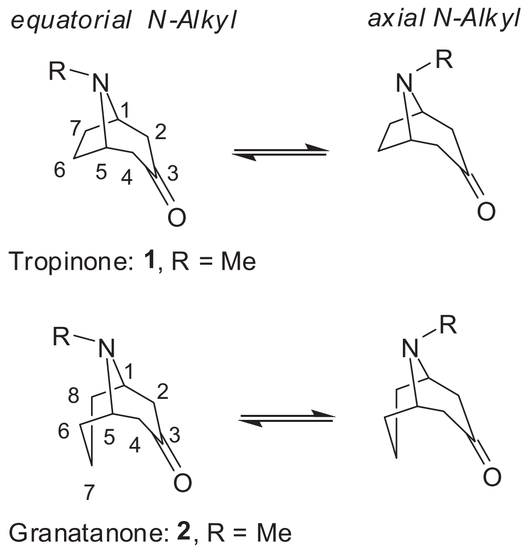

Fig. 1. Invertomers of tropan-3-one and granatan-3-one analogues showing the equatorial and axial *N*-invertomer of the piperidone ring (tropane atom numbering shown).

to rationalise reactivity and the origins of stereoselectivity in such aldol processes [22]. Similarly, the knowledge of *N*-invertomer preferences in *N*-substituted analogues in aqueous solutions may be useful for the rationalisation or the prediction of their reactivity in reactions that occur in water, including the aldol reaction.

Previous conformational studies by NMR spectroscopy in $CDCl_3$ suggested axial or slight axial preferences for the *N*-substituents in tropinone [23], granatanone [24,25], and related *N*-substituted structures. However, preferences for the equatorial *N*-invertomer (by 0.62–1.2 kcal/mol) in some C-3 substituted tropanes in a $CFCl_3$ solution at –100 °C was observed by a ^{13}C NMR method [26]. Crystal structures indicated that the *N*-methyl in tropinone [27] and *N*-phenyl in the granatanone derivative [28] display the axial configuration in the solid state. The *N*-methyl configuration in the crystals depended on the derivative and was determined to be equatorial in cocaine [29] and its salts [30] as well as in phenyltropane [31], tropinone aldols [32,33], tropinone aldol tosylhydrazone [21], and granatanone aldols [34], but axial in scopolamine [35]. In some conformational studies of granatane derivatives by NMR methods [36], the *N*-methyl stereochemistry remained undetermined. The conformations of granatane and related systems have been reviewed by Zefirov and Palyulin [37]. An excellent computational and spectroscopic study of the conformational flexibility of tropinone in the gas phase reported equatorial preference 2:1 [38]. However, little is known about the *N*-invertomer preference of such compounds in polar solutions. The equatorial/axial invertomer ratio for deuterotropinone deuterochloride in D_2O was determined to be 4.2 based on NMR spectra to be 4.2 [39]. Recently, we have determined the differences in the invertomer preferences for the *N*-methyl derivatives of tropane and granatane in polar solvents [40]. X-ray diffraction revealed the *N*-benzyl group in equatorial position in *N*-benzylnortropinone aldols [41] and aldol tosylhydrazone [21]. However, as far as we know, there has been no experimental or computational study concerning the distribution of the higher *N*-alkyl or *N*-aryl invertomers in tropanes or granatanes in water (or even other polar solvents), which are essential for biological systems and green synthetic reactions. The enantioselectivity of deprotonation and diastereoselectivity of aldol reactions of higher *N*-alkyl homologues of tropinone [21,42,43] and granatanone [34] is affected by the configurational preference of the *N*-substituents in reaction medium. In an effort to extend the aqueous aldol reactions [44] to higher *N*-alkyl substrates, we decided to examine their *N*-invertomer preferences. Herein, we report our results for the preferred *N*-invertomer stereochemistry and equilibriums in representative *N*-substituted tropinone and granatanone analogues.

2. Results and discussion

We investigated the *N*-invertomer distributions in aqueous and methanol solutions using computational and NMR spectroscopic methods. The use of protic deuterated solvents (D_2O, methanol-d_4) is hampered by spontaneous protium–deuterium exchange of the acidic hydrogens at the α-position to carbonyl groups. Direct NoD-NMR methods [45] for water or methanol solutions (e.g., ROESY technique) did not provide useful information due to interferences from the non-deuterated solvent, low sample solubility and fast rate of invertomer interchange. Therefore, we used proven methods based on ^{13}C NMR combined with verified DFT calculations [40]. To probe the behaviour of these amino ketones in aqueous environments including the potential involvement of protonated amine forms in aldol and other reactions in aqueous media [44], we also included the *N*-invertomer equilibriums in the corresponding hydrochlorides.

2.1. *Synthesis of* N-*substituted tropinone and granatanone derivatives*

The higher *N*-alkyl analogues of tropinone **1** and granatanone **2** were prepared via an adapted two-step literature procedure [46], except for the *N*-benzyl derivatives (Scheme 1).

Tropinone and granatanone were *N*-methylated with methyl iodide to yield the corresponding quaternary salts. The quaternary salts were reacted with appropriate primary amines in an ethanol–water mixture. In most cases, fair or good overall yields of the desired products were obtained (30–82%). For the *tert*-butyl derivatives, incomplete reactions and low yields as well as problems with purification were encountered. Granatanone *tert*-butyl derivative **2c** was obtained in 6% yield and satisfactory purity by PTLC. The reaction medium for *N*-*tert*-butylnortropinone (**1c**) had to be changed to DMSO, to obtain the product in acceptable yield (14%). *N*-benzyl derivatives **1e** and **2e** were conveniently obtained (75 and 77% yield, respectively) via Robinson–Schopf synthesis according to a previously published procedure [47]. The amine hydrochlorides for the spectroscopic studies were