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FULL PAPER

Feasibility of enantiomeric separation of racemic compounds using a simple method: Theoretical investigation of anion ability to conglomerate crystal formation of ketamine salts

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In the pharmaceutical industry, there is a special interest in the resolution of chiral compounds to obtain enantiopure drugs. Conglomerate mixture is of considerable interest, since it corresponds to the possibility of spontaneous resolution of the two enantiomers. The aim of this paper was to find the achiral anions causing the conglomerate formation of Ketamine salts. For this purpose, the effect of 7 anion (X) on the heterochiral structure of Ketamine enantiomers salts was studied by Material Studio software. The crystal structures of all systems were determined by quantum calculations of CASTEP module. The investigation of the crystal structures and their respective energy showed that Ketamine salts, formed by Fumaric acid and Succinic acid, crystalized as conglomerate, favoring preferential crystallization. The AIM results confirmed the more stability of conglomerate crystal in these cases while in the presence of other salting agents as Oxalic acid, Formic acid, Carbonic acid, Acetic acid and Hydrochloric acid, racemic crystal form was calculated as the more stable crystal. Using the Forcite module, the total energy of the crystalline systems, calculated as the sum of the energies of the bonded and non-bonded interactions, are in agreement with those predicted by CASTEP module and AIM calculations.

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KEYWORDS

Ketamine; crystal structure prediction; racemic compound; conglomerate mixture; preferential crystallization.

Introduction

Kind's research attempts have been devoted to the investigation of structural and energetic features of organic crystals due to the potential applications in many industrial sectors including, foods, agrochemicals, paints, explosives and pharmaceuticals [1-5]. Generally, crystalline racemic compounds can be classified into three different categories: 1) a racemic crystal, in which both enantiomers in the unit cell is in equal stoichiometry, 2) a conglomerate crystal in which there is a mechanical mixture of the equimolar quantity of the two homochiral crystals, and 3) more rarely, a racemic solid solution, where both enantiomers are present in the unit cell with no fixed stoichiometry [6-8]. The conglomerate crystals, which is reflected by a mechanical mixture of the two pure single stereoisomers, are of considerable importance, since they correspond to the possibility of spontaneous resolution of the two enantiomers [9-11].

In a wide variety of applications, including the agrochemical, pharmaceutical and food industries, it is a necessity to obtain enantiomeric compounds in an optically pure form [12-14]. This is because only one out of a pair of enantiomers has valuable utility and desirable activity. In particular, in the pharmaceutical field, there is a special interest in optically active isomeric forms of drugs [15, 16]. Typical examples are levothyroxine and thalidomide drugs [17-21]. Crystallization and liquid chromatography (HPLC) are two widely used methods for separation of enantiomers. Because of the cost and scale of chromatographic separations, the more preferred method for separation of enantiomers is crystallization [22-25]. Results of previous studies show that the probability of finding conglomerate in the salts form of racemates is 2 or 3 times greater than that in their covalent form [24]. Thus, a particular challenge in this regard is to finding appropriate salting reagents for conglomerate crystal formation [24,25].

Doe to the importance of the subject, computer modeling and simulation techniques have recently been used [1-5, 23]. The crystalline structures of diastereomeric salts of ephedrine and chlocyphos in homo- and hetero-chiral forms are modeled and simulated [23]. To investigate agent ability in separation of enantiomers, the lattice energies obtained from computational method have been evaluated. By proposing more appropriate separating agents, such theoretical studies significantly reduce the experimental effort to finding an especial separating agent.

In the continuation of our previous research, experimentally and theoretically, concerning the possibility of crystal conglomerate formation of Medetomidine salts [26-31], we here addressed the theoretical investigation of the crystal formation between Ketamine (free base) and achiral acids.

Ketamine (Figure 1) is one of the short-acting anesthesia drugs that has been used for more than three decades. R and S Ketamine enantiomers are different in terms of their therapeutic properties, so that the enantiomer S of Ketamine is four times stronger than enantiomer R. On the other hand, enantiomer R of Ketamine causes hallucinations and delusions, accompanied by extreme happiness, damage to the senses and perception. Accordingly, the enantiomeric purification of ketamine drug is of special importance.

In this study, crystal structure prediction methods were used to study the relative stabilities of enantiopure and racemic crystals of Ketamine drug (in neutral and salt forms). Our aim was to find salting achiral agents for conglomerate formation. In so doing, seven different acids including Succinic acids (Su: $(CH_2COOH)_2$), Fumaric acid (Fu: $(CHCOOH)_2$), Oxalic acid (Ox: $(COOH)_2$), Formic acid (Fo: HCOOH), Carbonic acid (Car: H_2CO_3), Acetic acid (Ac: CH_3COOH), and Hydrochloric acid (HCl) were selected for the study. Due to the fact that this computational work will be the prelude to future industrial activities, we chose these non-chiral agents with a simple structure for economic reasons.

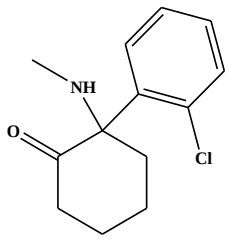


FIGURE 1 Chemical structure of Ketamine

Method

Initial conformational analyses of the molecules were performed at the B3LYP/6-311G(d) level using GAUSSIAN 09 [32]. The electrostatic potential (ESP) was determined by minimizing conformations with Dmol3. These calculations were carried out using the generalized gradient approximation (GGA)

and the Perdew, Burke and Ernzerhof (PBE) functional, applying progressively more restricted convergence criteria. A single effective core potential and a double numerical basis set were used to treat the core electrons. The Polymorph module of Materials Studio 6.1 [33] was used to find the most stable space groups for each crystal.The DREIDING force field was used in the calculations. The 8 most common space groups found in organic crystals registered in the Cambridge Structural Database (CSD) were selected (P-1, P2,P1,PC,P21,C2,PM and CM). The five potential packing structures were then subjected to the structural optimization using the DFT-D method with the generalized gradient approximation. These calculations were performed using CASTEP module and the results for the most stable structures were reported. CASTEP module of Material Studio is an ab initio quantum mechanical program employing density functional theory to simulate the properties of systems. Using Forcite module, the total energy of the systems was also calculated as the sum of the different states of the bonded and non-bonded interactions. Forcite module of Material Studio is a classical molecular mechanics tool that allows fast energies calculations and reliable geometry optimization of a molecule and periodic systems. The quantum theory of atoms in molecules (QTAIM) analysis [34] was carried out using AIMALL package [35].

Results and discussion

Molecular electrostatic potential (MEP) is an appropriate method to specify the charge distributions of molecules as three dimensional. This counter map is very useful to determine the reactive sites of molecules in both nucleophilic and electrophilic reactions for investigation of molecules. The molecular electrostatic potentials for both enantiomers of Ketamine (cationic form) and anions of acids were calculated and presented in Figure 2 and 3, to characterize the nucleophilic and electrophilic sites. The positive regions of MEP which are suitable sites for nucleophilic reactivity are specified with blue color. The negative area that is the preferred site for electrophilic reactivity is presented by red color (Figures 2 and 3). The MEP maps of acid molecules (Figure 3) showed that the red colors, proper regions for electrophilic reactivity, are around Oxygen atoms. Based on MEP results, different initial structures were considered and optimized using gaussian software. Different initial structures for R/R-enantiomers of Ketamine in presence of Fumaric acid (RR-Fu) are presented in Fig. 4 as an instance. The most stable structures were selected for crystal structure prediction.

Table 1 shows energy, space group, and electron densities of the predicted more stable structure of studied systems calculated by CASTEP and Forcite modules and AIM method, where RS refers to racemic structures and SS or RR refers to homochiral crystal. The CASTEP results show that for Ketamine in the presence of Succinic acid and Fumaric acid, the homochiral crystals are more stable than the racemic crystals (ΔE=-0.5723 eV and ΔE=-1.6784 eV for Succinic acid and Fumaric acid, respectively). These results conform to a conglomerate crystal forming system in presence of Succinic acid and Fumaric acid, favoring their enantiomeric purification by preferential crystallization. The predicted crystal structures for Ketamine in presence of Succinic acid and Fumaric acid are shown in Figure 5. For Ketamine in the presence of other acids, the racemic crystals are more stable than the homochiral crystals, which means that these acids are not suitable for the separation of Ketamine enantiomers.

In order to further investigate, the nature of the interactions between Ketamine enantiomers and Fumaric acid was studied by using the quantum theory of atoms in molecules (QTAIM). The AIM analysis of the electron density shows the existence of bond critical points (BCPs) between Ketamine

enantiomers and Fumaric acid (Figure 6). The results of calculations including the electron density (ρ_b) and its Laplacian ($\nabla^2\rho_b$), kinetic electron energy density (G_b) and potential electron energy density (V_b) are given in Tables 2 and 3.

The electron densities at BCPs between Ketamine enantiomer and Fumaric acid range from 0.0007 to 0.0896 au. As can be seen from Tables 2 and 3, all value of $\nabla^2\rho_b$ are positive, which indicates depletion of electronic charge density in the interatomic surface and means a closed-shell interaction. The overall electron density for R.FU-S.Fu and R.Fu-R.Fu states are 0.3216 and 0.3548, respectively. The results demonstrate that the strength of interactions in R.Fu-R.Fu state is greater than that in R.Fu-S.Fu state. Therefore, it can be concluded that the more stability of R.Fu-R.Fu state is due to the more intermolecular interactions. The overall electron densities obtained from AIM calculations for different structures of hetero and homochiral crystals of Ketamine-anions are presented in Table 1. These results show that the structure of homochiral crystal of R.Su-R.Su is also more stable than that of R.Su-S.Su and for other anions, structures of heterochiral crystals of Ketamine-anion are more stable than those of thahomochiral crystals. The computational results of AIM are in accordance with those of energy for different structures of hetero and homochiral crystals of Ketamine-anion and confirm those results.

The total energy of the crystalline systems obtained by the Forcite module is calculated as the sum of the energies of the bonded and non-bonded interactions. Since the crystals have a salt structure, it is observed that the energy contribution of the non-bonded interaction, especially the electrostatic interaction, is greater than other interactions in the total energy of the crystal. The results obtained by Forcite module showed that the non-bonding interaction energies for Succinic and Fumaric acids in the RR-Ketamine structure were greater than that of the RS-Ketamine structure (Table 1). The results of Forcite module for the Ketamine crystals in the presence of other achiral acids showed that RS-Ketamines crystals had higher non-bonded interaction energies than that of RR-Ketamines. Thus, the results of the Forcite module for the total energy of these systems are in agreement with those of CASTEP module and AIM method.

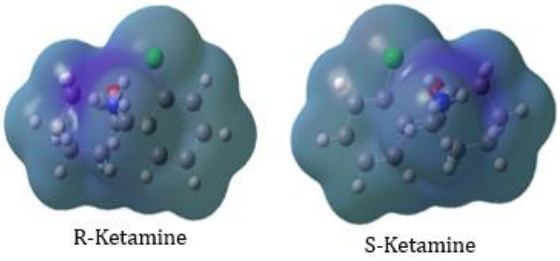


FIGURE 2 Molecular electrostatic potentials on the 0.001 (electron/Bohr3) electron density of S/R enantiomers of Ketamine in cationic form

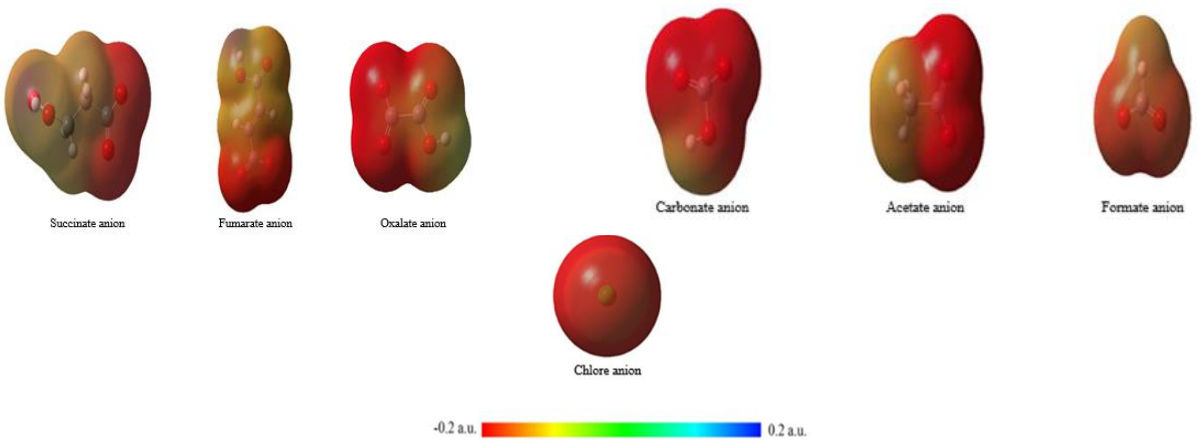


FIGURE 3 Molecular electrostatic potentials on the 0.001 (electron/Bohr3) electron density of anions

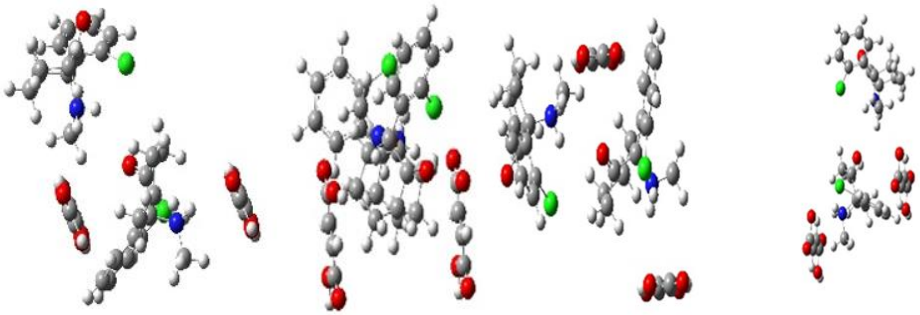


FIGURE 4 Different initial structures for R.Fu-R.Fu system

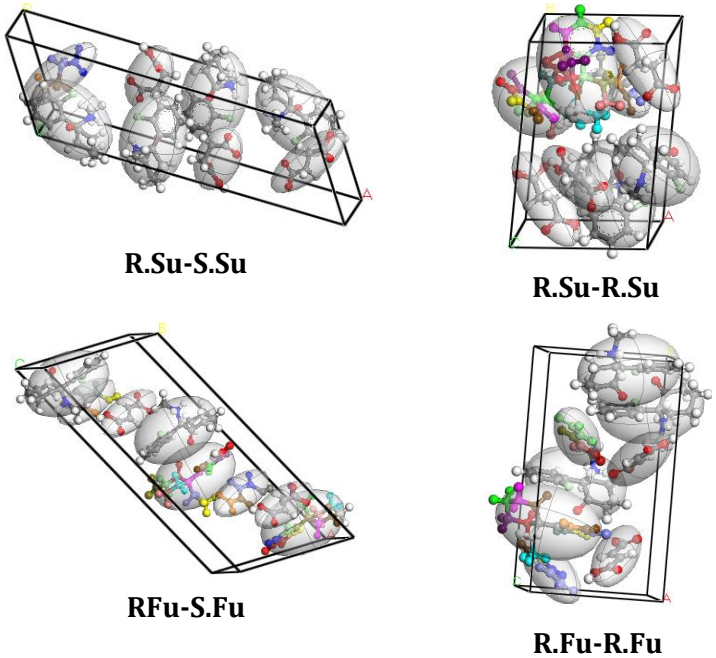
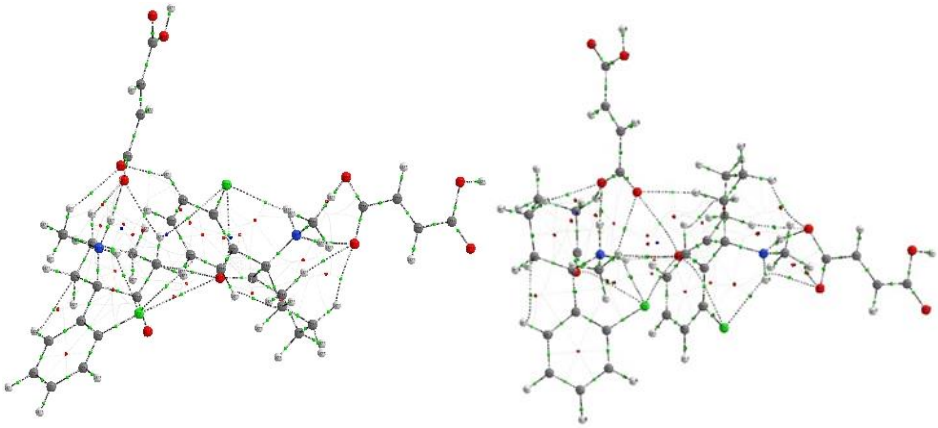


FIGURE 5 Predicted crystal structures of Ketamine salts formed by Ketamine enantiomers and Succinic acid and Fumaric acid (R.Su-S.Su, R.Su-R.Su, R.Fu-S.Fu and R.Fu-R.Fu)



R.Fu-S.Fu R.Fu-R.Fu

FIGURE 6 AIM graph for Ketamine salts formed by Fumaric acid (R.Fu-S.Fu & R.Fu-R.Fu)

TABLE 1 The energy (CASTEP and Forcite modules results), space group and electron densities (AIM results) of predicted structures for homochiral and heterochiral crystallization of Ketamine salts formed by Succinic acid (Su), Fumaric acid (Fu), Oxalic acid (Ox), Formic acid (Fo), Carbonic acid (Car), Acetic acid (Ac), Hydrochloric acid (HCl).

System	Energy						Space group	Electron Densities	
	CASTEP module (eV)		Forcite module (kcal/mol)						
	Total Energy	ΔE	Valence energy[a]	Non-bond energy[b]	Total Energy	ΔE		ρ	$\Delta\rho$
R.Su-S.Su	-23722.0665	-0.5723	83.535	-581.840	-498.30	-7.47	P-1	0.2356	0.076
R.Su-R.Su	-23722.6388		78.392	-584.157	-505.76		P-1	0.3114	
R.Fu-S.Fu	-23587.0406	-1.6784	79.138	-569.525	-490.38	-10.73	P-1	0.2367	0.004
R.Fu-R.Fu	-23588.7190		68.752	-569.862	-501.11		P21	0.2407	
R.Ox-S.Ox	-22198.9609	0.6166	82.822	-226.398	-143.58	9.48	P2	0.3371	-0.007
R.Ox-R.Ox	-22198.3443		83.217	-217.278	-134.10		P2	0.3298	
R.Car-S.Car	-19816.4197	1.308	63.96	-583.360	-519.40	11.29	P21	0.3040	-0.006
R.Car-R.Car	-19815.1117		64.946	-573.057	-508.11		P-1	0.2980	
R.Ac-S.Ac	-18817.2210	0.9467	67.496	-520.273	-452.78	5.06	PC	0.2381	-0.007
R.Ac-R.Ac	-18816.2743		77.173	-524.896	-447.72		PC	0.2315	
R.Fo-S.Fo	-18055.4338	0.4998	70.235	-478.832	-408.60	6.59	PC	0.2728	-0.008
R.Fo-R.Fo	-18054.9340		70.219	-472.231	-402.01		P-1	0.2646	
R.HCl-S.HCl	-15541.3166	0.6897	75.913	-475.162	-398.25	8.21	P2	0.2616	-0.010
R.HCl-R.HCl	-15540.6269		71.508	-462.545	-391.04		PC	0.2513	

[a]valence energy (sum of bond, angle, torsion and inversion energy)

[b]nan-bond energy (sum of hydrogen bond, van der waals, long range correction and electrostatic energy)

TABLE 2 AIM results for Ketamine salts formed by Ketamine enantiomers (R&S) and Fumaric acid (R.Fu-S.Fu). All units are a.u.

V_b	G_b	$\nabla^2\rho_b$	ρ_b
-0.0929	0.0656	0.1538	0.0896
-0.0099	0.0113	0.0513	0.0148
-0.0071	0.0083	0.0384	0.0106
-0.0072	0.0085	0.0392	0.0114
-0.0909	0.0646	0.1536	0.0882
-0.0079	0.0092	0.0419	0.0120
-0.0093	0.0111	0.0515	0.0136
-0.0079	0.0095	0.0444	0.0122
-0.0089	0.0103	0.0473	0.0140
-0.0020	0.0027	0.0137	0.0035
-0.0061	0.0077	0.0372	0.0094
-0.0023	0.0032	0.0167	0.0042
-0.0002	0.0004	0.0026	0.0007
-0.0113	0.0137	0.0642	0.0177
-0.0112	0.0135	0.0637	0.0175
-0.0009	0.0013	0.0068	0.0022

Table 3. AIM results for Ketamine formed by Ketamine enantiomers (R&R) and Fumaric acid (R.Fu-R.Fu). All units are a.u.

V_b	G_b	$\nabla^2\rho_b$	ρ_b
- 0.0872	0.0631	0.1561	0.0849
- 0.0058	0.0068	0.0309	0.0087
-0.0103	0.0117	0.0529	0.0153
-0.0118	0.0136	0.0618	0.0164
-0.0065	0.0076	0.0348	0.0096
-0.0684	0.0541	0.1590	0.0681
-0.0110	0.0128	0.0585	0.0159
- 0.0085	0.0100	0.0464	0.0126
-0.0108	0.0126	0.0576	0.0161
-0.0080	0.0093	0.0422	0.0130
-0.0025	0.0032	0.0154	0.0040
-0.0125	0.0153	0.0722	0.0168
-0.0043	0.0054	0.0266	0.0071
-0.0051	0.0065	0.0317	0.0080
-0.0121	0.0145	0.0680	0.0184
-0.0077	0.0100	0.0491	0.0130
-0.0065	0.0083	0.0401	0.0102
-0.0012	0.0016	0.0082	0.0026
-0.0100	0.0124	0.0598	0.0141

Conclusion

In order to find salting reagents for separation of Ketamine enantiomers, seven different acids including Succinic acid, Fumaric acid, Oxalic acid, Formic acid, Carbonic acid, Acetic acid and Hydrochloric acid were investigated. The results of calculations by CASTEP module indicated that for Ketamine in presence of Succinic acid and Fumaric acid, the homochiral crystals are more stable than the racemic crystals. Further, The AIM calculations demonstrate that the strength of

interactions in R.Su-R.Su and R.Fu-R.Fu state is greater than that in R.Su-S.Su and R.Fu-S.Fu system. The results obtained by the Forcite module are also in agreement with those of CASTEP module and AIM calculations and predict the conglomerate crystal formation in presence of Succinic acid and Fumaric acid.

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