Synthesis and Crystal Structures of Novel Glycoluril Carboxylic Acids Conglomerates

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Abstract

The two novel conglomerates were obtained by crystallization of racemic (*S*)-2-((3*aS*,6*aR*)- and (*R*)-2-((3*aR*,6*aS*)-2,5-dioxohexahydroimidazo[4,5-*d*]imidazole-1(2*H*)-yl)-3-methylbutanoic acids (racemate **I**), (*R*)-2-(3*aR*,6*aR*)- and (*S*)-2-((3*aS*,6*aS*)-4,6-dimethyl-2,5-dioxohexahydroimidazo[4,5-*d*]imidazole-1(2*H*)-yl)pentanoic acids (racemate **II**), which were synthesized by highly diastereoselective condensation of 4,5-dihydroxyimidazolidine-2-ones with racemic ureido acids for the first time. The differences in the molecular geometry of **I** and **II** are studied by X-ray diffraction that showed them to crystallize as conglomerates in non-centrosymmetric space groups $Pna2_1$ and $P2_12_12_1$, respectively.

Introduction

The course of many biological processes is based on molecular recognition, in which various classes of chemical compounds are involved. The processes of crystal formation can serve as models for studying such phenomena in biosystems [1]. In particular, crystallization is used to separate racemic drugs into enantiomers, since it is well known that enantiomers can exhibit different pharmacological activities. It is known that only (*S*)-thalidomid is a teratogen, (*R*)-enantiomer is an anti-inflammatory, immunomodulatory, and antiangiogenic properties [2–4]. (*S*)-Ketamine has an approximately 4-fold greater analgesic potency, compared with (*R*)-ketamine [5], but only *S*-isomer is responsible for agitation, hallucination, and restlessness [6]. Only (*S*)-penicillamine can be used clinically, because of (*R*)-isomer is excessive toxicity [7]. (-)-(3*aS*,6*aS*)-Albicar is stimulating effect on central nervous system (CNS), but (+)-(3*aR*,6*aR*)-Albicar is inhibitory effect on CNS [8].

It is known that tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-diones (glycolurils) are capable of forming supramolecular assemblies and supermolecules of varying complexity upon crystallization from different solvents [9–21], which can lead to spontaneous resolution of racemates into enantiomers (conglomerate formation) [22–26]. Some glycolurilcarboxylic acids [16, 17, 20, 21, 24, 25] also have such properties (Fig. 1). The ability to spontaneously resolution racemates into enantiomers is very important for obtaining enantiomerically pure glycolurils with various types of biological activity [8, 27–31]. The ability to spontaneous resolution of racemates into enantiomers is very important for obtaining enantiomerically pure glycolurils with various types of biological activity.

In this work racemates of (*S*)-2-((3*aS*,6*aR*)-, (*R*)-2-((3*aR*,6*aS*)-(2,5-dioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)-3-methylbutanoic (racemate **I**), (*S*)-2-((3*aS*,6*aS*)- (*R*)-2-((3*aR*,6*aR*)-4,6-dimethyl-2,5-dioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)pentanoic acids (racemate **II**) were synthesized and their ability to form conglomerates was studied for the first time.

Experimental

General experimental remarks

Melting points were determined in a GALLENKAMP instrument (Sanyo). The IR spectra

were recorded on a Bruker "Alpha" spectrometer in the range 400 – 4000 cm^{-1} (resolution 2 cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 and 75 MHz, respectively) in $\text{DMSO-}d_6$ with TMS as internal standard. High resolution mass spectra were recorded on a Bruker MicroTOF II instrument in positive ion mode (capillary voltage 4500 V) using electrospray ionization (ESI) and methanol as a solvent. All reagents including KOCN, urea, 1,3-dimethylurea, glyoxal (aqueous 40%), HCl (aqueous 36.5%), (*R,S*)-Val (**1a**), (*R,S*)-*nor*-Val (**1b**) were obtained from commercial sources and used without additional purification. Compound **2a** were synthesized according to the literature [32, 33] (Scheme 1).

Synthesis of 4,5-dihydroxy-1,3-dimethylimidazolidin-2-ones (**2b**+**2`b**) (Scheme 2)

The solution of KOH in H_2O (1 M) was added to the solution of 1,3-dimethylurea (13.2 g, 0.15 mol) in 40% aqueous glyoxal (17.2 mL, 0.15 mol) to pH 11. The reaction mixture was heated with stirring to 50 – 55°C, incubated for 5 h and evaporated to dryness. Resulting solid was triturated with acetone. The mixture **2b** (*trans*-isomer) + **2`b** (*cis*-isomer) (ratio 15:1) was filtered off and dry at the air.

Light beige solid, yield 95% (20.80 g), mp 141 – 143°C. ^1H NMR: (300 MHz, $\text{DMSO-}d_6$) δ 2.62 (s, 6H, Me (**2`b**)), 2.66 (s, 6H, Me (**2b**)), 4.53 (s, 2H, CH-CH (**2b**)), 4.74 (s, 2H, CH-CH (**2`b**)), 5.76 – 5.97 (br.s, 2H, OH (**2`b**)), 6.14 – 6.62 (br.s, 2H, OH (**2b**)) [34].

General procedure for the synthesis of compounds **3a,b** (Scheme 1, Scheme 2)

KCNO (8.505 g, 0.105 mol) by portionwise slowly was added to boiling solution (*R,S*)-Val **1a** (11.7 g, 0.1 mol) or (*R,S*)-*nor*-Val **1b** (11.7 g, 0.1 mol) in 200 mL of H_2O and refluxed for 20 min. The reaction mixture was cold to 10°C at the ice bath and (10.6 mL, 35%) hydrochloric acid was added dropwise to pH 1. Obtained white powder of product **3a** or **3b** was filtered off and washed with 10 mL H_2O and dried at the air.

3-Methyl-2-ureidobutanoic acid (**3a**)

White powder, yield 91% (14.56 g), mp 175-177°C (176°C [35]). IR (KBr) ν = 3455, 3353, 3297, 1689, 1633, 1575, 1469, 1401, 1309, 1175, 1164, 1136, 1102, 1011, 971, 929, 902, 777, 723, 595, 581, 516 cm^{-1} . ^1H NMR: (300 MHz, $\text{DMSO-}d_6$) δ 0.84 (d, 3H, 3J = 6.8 Hz, Me), 0.88 (d, 3H, 3J = 6.8 Hz, Me), 1.91 – 2.09 (m, 1H, CH), 4.00 (dd, 1H, 2J = 8.6 Hz, 3J = 5.0 Hz, CH), 5.62 (c, 1H, NH), 6.21 (d, 2H, 3J = 8.7 Hz, NH_2). ^{13}C NMR: (75 MHz, $\text{DMSO-}d_6$) δ 17.68, 19.19 (Me), 30.33, 57.48 (CH), 158.63 (C=O), 174.17 (COOH). HRMS (ESI): m/z calcd for $\text{C}_6\text{H}_{12}\text{N}_2\text{O}_3 + \text{H}^+$: 161.0921. Found: 161.0915; calcd for $\text{C}_6\text{H}_{12}\text{N}_2\text{O}_3 + \text{Na}^+$: 183.0740. Found: 183.0740.

2-Ureidopentanoic acid (**3b**)

White powder, yield 89% (14.24 g), mp 170-172°C (164°C [36]). IR (KBr) ν = 3450, 3293, 1694, 1636, 1560, 1468, 1450, 1405, 1382, 1366, 1309, 1293, 1256, 1218, 1165, 1128, 1096, 1056, 996, 921, 838, 779, 747, 726, 677, 619, 572 cm^{-1} . ^1H NMR: (300 MHz, $\text{DMSO-}d_6$) δ 0.85 (t, 3H, 3J = 7.2 Hz, Me), 1.20 – 1.36 (m, 2H, CH_2), 1.43 – 1.65 (m, 2H, CH_2), 3.97 – 4.07 (m, 1H, CH), 5.60 (s, 2H, NH_2), 6.35 (d, 1H, 3J = 8.0 Hz, NH). ^{13}C NMR: (75 MHz, $\text{DMSO-}d_6$) δ 14.05 (Me), 18.90, 34.42 (CH_2), 52.63 (CH), 159.38 (C=O), 175.52 (COOH). HRMS (EI): m/z calcd for $\text{C}_6\text{H}_{12}\text{N}_2\text{O}_3 + \text{H}^+$: 161.0921. Found: 161.0927; calcd for $\text{C}_6\text{H}_{12}\text{N}_2\text{O}_3 + \text{Na}^+$: 183.0740. Found: 183.0752.

Synthesis of racemate I and compound 4a (Scheme 1)

The hydrochloric acid (0.3 mL, 36% aqueous solution) was added to the suspension of racemic 3-methyl-2-ureidobutanoic acid **3a** (1.60 g, 0.01 mol) and DHI **2a** (1.18 g, 0.01 mol) in the mixture of H_2O (10 mL) and *i*PrOH (10 mL). The reaction mixture was refluxed for 2 h, cooled at r.t., left for 48 h, filtered the solid **I**. The hydantoin crystals **4a** were isolated from the filtrate and crystallized from H_2O .

The crystals **I** were obtained by crystallization from MeOH.

(S)-2-((3a S,6aR)- and (R)-2-((3aR,6aS)-(2,5-dioxohexahydroimidazo[4,5-d]imidazol-1(2H)-yl)-3-methylbutanoic acid (I)

Colorless crystals, yield 16% (0.39 g), mp 261-263°C (MeOH). IR (KBr) ν = 3396, 3276, 3081, 1746, 1722, 1662, 1490, 1456, 1388, 1349, 1295, 1266, 1247, 1206, 1174, 1133, 1116, 999, 977, 924, 908, 885, 861, 817, 777, 761, 713, 626, 531 cm^{-1} . ^1H NMR: (300 MHz, $\text{DMSO-}d_6$) δ 0.91 (d, 3H, 3J = 6.8 Hz, Me), 0.93 (d, 3H, 3J = 6.9 Hz, Me), 2.11 – 2.20 (m, 1H, CH), 3.92 (d, 1H, 3J = 9.6 Hz, CH), 5.28 (d, 1H, 3J = 8.3 Hz, CH), 5.52 (d, 1H, 3J = 8.4 Hz, CH), 7.31 (s, 1H, NH), 7.39 (s, 1H, NH), 7.54 (s, 1H, NH), 12.20 – 13.30 (br.s, 1H, COOH). ^{13}C NMR: (75 MHz, $\text{DMSO-}d_6$) δ 19.64, 19.84 (Me), 27.75, 61.01, 62.68, 67.19 (CH), 159.43, 161.28 (C=O), 172.14 (COOH). HRMS (EI): m/z calcd for $\text{C}_9\text{H}_{14}\text{N}_4\text{O}_4 + \text{H}^+$: 243.1088; found: 243.1088; calcd for $\text{C}_9\text{H}_{14}\text{N}_4\text{O}_4 + \text{Na}^+$: 265.0907; found: 265.0906.

5-Isopropylimidazolidine-2,4-dione (4a)

Colorless needle crystals, yield 78% (1.11 g), mp 145 – 146°C ($\text{H}_2\text{O}:\textit{i}$ PrOH (1:1)) (145 – 146 °C (H_2O))[37], ^1H NMR: (300 MHz, $\text{DMSO-}d_6$) δ 0.80 (d, 3H, 3J = 6.8 Hz, Me), 0.94 (d, 3H, 3J = 7.0 Hz, Me), 1.91 – 2.09 (m, 1H, CH(*i*Pr)), 3.91 (dd, 1H, 3J = 3.5 Hz, 3J = 1.4 Hz, CH), 7.90 (s, 1H, NH), 10.52 – 10.68 (br.s, 1H, NH). [38]

Synthesis of racemate II and compound 4b (Scheme 2)

The hydrochloric acid (0.3 mL, 35% aqueous solution) was added to the suspension of racemic 2-ureidopentanoic acid **3b** (1.60 g, 0.01 mol) and DHI **2b** (1.46 g, 0.01 mol) in the mixture of H_2O (10 mL) and *i*PrOH (10 mL). The reaction mixture was refluxed for 2 h, cooled at r.t., left for 48 h, filtered the

crystals of hydantoin **4b**. The filtrate was left for 48 h at r.t.. The formed precipitate **II** was filtered. The crystals **II** were obtained by crystallization from H₂O:*i*PrOH (1:1).

(S)-2-((3aS,6aS)-, (R)-2-((3aR,6aR)-4,6-dimethyl-2,5-dioxohexahydroimidazo[4,5-d]imidazol-1(2H)-yl)pentanoic acids (II)

Colorless crystals, yield 7% (0.19 g), mp 240-242°C. IR (KBr) ν = 3369, 1710, 1649, 1502, 1467, 1413, 1397, 1371, 1314, 1259, 1228, 1190, 1171, 1100, 1083, 1038, 986, 940, 890, 865, 810, 787, 762, 733, 697, 671, 637, 620, 579, 553 cm⁻¹. ¹H NMR: (300 MHz, DMSO-*d*₆) δ 0.90 (t, 3H, ³*J* = 7.3 Hz, Me), 1.22 – 1.42 (m, 2H, CH₂), 1.83 – 2.03 (m, 2H, CH₂), 2.67 (s, 3H, Me), 2.77 (s, 3H, Me), 4.03 (dd, 1H, ²*J* = 10.0 Hz, ³*J* = 5.2 Hz, CH), 5.14 (s, 2H, CH-CH), 7.77 (s, 1H, NH), 12.55 – 13.80 (br.s, 1H, COOH). ¹³C NMR: (75 MHz, DMSO-*d*₆) δ 13.63, 27.86, 29.82 (Me), 19.34, 30.22 (CH₂), 55.99, 66.17, 72.14 (CH), 158.36, 160.03 (C=O), 173.02 (COOH). HRMS (EI): *m/z* calcd for C₁₁H₁₈N₄O₄+H⁺: 271.1401; found: 271.1398; calcd for C₁₁H₁₈N₄O₄+Na⁺: 293.1220; found: 293.1216.

5-Propylimidazolidine-2,4-dione (4b)

Colorless needle crystals, yield 71% (1.01 g), mp 137 – 138°C (H₂O:*i*PrOH (1:1)) (136 – 137 °C (EtOH)) [39], ¹H NMR: (300 MHz, DMSO-*d*₆) δ 0.89 (t, 3H, ³*J* = 7.3 Hz, Me), 1.28 – 1.40 (m, 2H, CH₂), 1.42 – 1.57 (m, 1H, CH₂), 1.59 – 1.70 (m, 1H, CH₂), 3.96 – 4.03 (m, 1H, CH), 7.97 (s, 1H, NH), 10.60 (s, 1H, NH).[40]

X-ray data collection and refinement

X-ray diffraction data for **I** and **II** were collected at 120 K with a Bruker APEXII DUO CCD diffractometer, using the graphite monochromated Mo-K α radiation (λ = 0.71073 Å). Using Olex2 [41], the structures were solved with the ShelXT structure solution program [42] using Intrinsic Phasing and refined with XL refinement package [43] using Least Squares minimisation. Hydrogen atoms of OH and NH groups were located in difference Fourier synthesis. Positions of other hydrogen atoms were calculated, and they all were refined in the isotropic approximation in the riding model. Crystal data and structure refinement parameters for the three crystallosolvates are given in Table 1. CCDC 2089267 and 2089265 contain the supplementary crystallographic data for **I** and **II**, respectively.

Table 1 Crystal data and structure refinement parameters for **I** and **II**.

	I	II
Formula unit	C ₉ H ₁₄ N ₄ O ₄	C ₁₁ H ₁₈ N ₄ O ₄
Formula weight	242.24	270.29
T, K	120	120
Crystal system	Orthorhombic	Orthorhombic
Space group	Pna2 ₁	P2 ₁ 2 ₁ 2 ₁
Z	8	4
a, Å	14.5941(14)	9.7011(6)
b, Å	7.1221(7)	11.1901(7)
c, Å	22.150(2)	12.0069(8)
V, Å ³	2302.3(4)	1303.42(14)
D _{calc} (g cm ⁻³)	1.398	1.377
Linear absorption, <i>m</i> (cm ⁻¹)	1.11	1.06
F(000)	1024	576
2Q _{max} , °	54	56
Reflections measured	20691	13038
Independent reflections	5010	3133
Observed reflections [<i>I</i> > 2s(<i>I</i>)]	3915	2826
Parameters	312	176
R1	0.0616	0.0409
wR2	0.1607	0.1159
GOOF	0.996	1.072
Δ <i>r</i> _{max} /Δ <i>r</i> _{min} (e Å ⁻³)	0.844/-0.211	0.575/-0.197

Results And Discussion

Synthesis

It is known that 4,5-dihydroxyimidazilidine-2-ones (DHI) exist in the form of two isomers, which differ in the *cis*- and *trans*-arrangement of hydroxy groups at the C (4) and C (5) atoms relative to the plane of the imidazolidine ring [32]. They are obtained by diastereoselective reactions of ureas with α-dicarbonyl compounds. The ratio of diastereomers is determined from the integral intensity of signals from the protons of CH-CH groups in the ¹H NMR spectra [44].

Starting compound **2a** (*trans*-isomer) were synthesized highly diastereoselective from urea 40% aqueous glyoxal according to the literature [32, 33] (Scheme 1). The mixture (**2b**+**2'b**) (ratio 15:1 correspondingly)

was prepared from 1,3-dimethylurea and 40% aqueous glyoxal (Scheme 2). The synthesis of racemic 2-ureidoalkyl acids **3a,b** were carried out from (*R,S*)-Val (**1a**), (*R,S*)-*nor*-Val (**1b**) and KCNO (Schemes 1,2). Racemate **I** was synthesized by highly diastereoselective cyclocondensation of DHI **2a** with racemic 3-methyl-2-ureidobutanoic acid **3a** (Scheme 1). Racemate **II** was prepared by interection of compounds (**2b+2`b**) and racemic 2-ureidopentanoic acid **3b**. Earlier a similar approach to obtain enantiomerically pure (*S*)-2-((3*aS*,6*aR*)-glycoluril-3-methylbutanoic acid and 4,5-dimethyl-2-glycolurilpentanoic acid was used [45, 46]. Moreover the relative configuration of chiral centers has not been established in last acid [46]. Hydantoins **4a,b** were obtained of intramolecular cyclization of *N*- α -carbamoylamino acids **3a,b** (Schemes 1,2).

Single-crystal X-ray diffraction

The study of crystallization processes for the production of conglomerates is an important task in crystal chemistry. This nature-like process is widely used to obtain enantiomerically pure compounds [47]. Therefore, we investigated the crystallization of racemates **I** and **II** from H₂O, MeOH, *i*PrOH and a mixture of H₂O:*i*PrOH. Single crystals **I** and **II** were obtained from a mixture of H₂O:*i*PrOH (in a 1:1 ratio) and from MeOH, respectively. Their X-ray diffraction analysis (Fig. 2) showed them to crystallize as conglomerates in non-centrosymmetric space groups Pna2₁ and P2₁2₁2₁ with two and one symmetry-independent molecules, respectively. Owing to the different substituents at the carbon atom C(5), the isopropyl or the propyl group, these compounds features an important difference in their molecular geometry, which is the rotation of the COOH group relative to the bond C(2)-C(5). The corresponding torsion angle N(1)C(5)C(6)O(3) being much higher in **I** (76.0(4) and 77.3(4)° in its two symmetrically-independent molecules) than in **II** (23.6(3)°) may be attributed to the steric effect of the bulky isopropyl group in the former compound.

Two extra methyl groups at the nitrogen atoms in **II** results in its supramolecular organization being different from one in **I**. In both cases, the main structural motif is an infinite chain (Fig. 3) formed by a hydrogen bond between the hydroxyl group and one of the carboxy groups of the heterocyclic core (O...O 2.596(5) and 2.557(2) Å, OHO 173.8(2) and 171.64(11)° в **I** и **II**, respectively). In **I**, they hold together different symmetry-independent molecules that alternate to produce a 3D-framework through hydrogen bonds of three NH groups (N...O 2.779(6) – 3.013(5) Å, NHO 149.1(3) – 176.6(3)°) and oxygen atoms of the carboxy groups. In **II**, however, the only NH group is hydrogen-bonded to the oxygen atom of the COOH functionality (N...O 3.089(3) Å, NHO 149.52(12)°), thereby additionally stabilizing the above infinite chains.

Conclusions

Thus racemates (*S*)-2-((3*aS*,6*aR*)- and (*R*)-2-((3*aR*,6*aS*)-2,5-dioxohexahydroimidazo[4,5-*d*]imidazole-1(2*H*)-yl)-3-methylbutanoic acids (**I**), (*R*)-2-(3*aR*,6*aR*)- and (*S*)-2-((3*aS*,6*aS*)-4,6-dimethyl-2,5-dioxohexahydroimidazo[4,5-*d*]imidazole-1(2*H*)-yl)pentanoic acids (**II**) were synthesized by highly diastereoselective condensation of 4,5-dihydroxyimidazolidine-2-ones with ureido acids for the first time.

Two new conglomerates (as gauged by space groups $Pna2_1$ and $P2_12_12_1$) were identified by X-ray diffraction among the crystallization products of the racemates **I** and **II**. The key difference between these two compounds, which is the different rotation of the COOH group relative to the bond C(2)-C(5), may be attributed to the steric effect of the bulky isopropyl group in **I**.

Declarations

Supplementary Information The online version contains supplementary material available at

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Author contribution The authors of the current manuscript Vladimir V. Baranov, Tatyana N. Vol'khina and Angelina N. Kravchenko contributed equally to this work. All authors read and approved the final manuscript.

Data Availability The structures have been deposited at the Cambridge Crystallographic Data Center with the reference CCDC numbers 2089267, 2089265; they also contain the supplementary crystallographic data. These data can be obtained free of charge from the CCDC via <http://www.ccdc.cam.ac.uk/>

The online version of this article contains electronic supplementary material (ESM) on IR, NMR, and HRMS data for all new compounds.

Code availability Not applicable.

Conflict of interest The authors declare no competing interests.

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Figures

Figure 1

Known examples of conglomerate-forming glycolurilcarboxylic acids. In this work racemates of (S)-2-((3aS,6aR)-, (R)-2-((3aR,6aS)-(2,5-dioxohexahydroimidazo[4,5-d]imidazol-1(2H)-yl)-3-methylbutanoic (racemate I), (S)-2-((3aS,6aS)- (R)-2-((3aR,6aR)-4,6-dimethyl-2,5-dioxohexahydroimidazo[4,5-d]imidazol-1(2H)-yl)pentanoic acids (racemate II) were synthesized and their ability to form conglomerates was studied for the first time.

Figure 2

General view of I (left) and II (right). Hereinafter, hydrogen atoms except those of OH and NH groups are omitted, and non-hydrogen atoms are shown as thermal ellipsoids at 50% probability level.

Figure 3

Fragments of the crystal packing in I (top) and II (bottom) illustrating the formation of hydrogen-bonded chains along the crystallographic axes *b* and *a*, respectively.

Supplementary Files

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