

Diesters on the basis of 16-hydroxyisosteviol and dicarboxylic acids as carriers of Fe(III) picrates

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Abstract Diesters on the basis of 16-hydroxyisosteviol and dicarboxylic acids, exhibiting anti-tubercular activity, transport Fe(III) through liquid chloroform membrane which models a cell membrane. It is revealed that fluxes and anti-tubercular activity increase, as the length of the chain (spacer) between two *ent*-beyeran skeletons of diesters increases. Computations on the level DFT/PBE explain the dependence of complexes stability on a structure of diterpenoid ligands. The structures of three diesters were established by single crystal X-ray analysis.

Keywords Diterpenoids · Isosteviol · Beyerans · Transport of Fe(III) · Anti-tubercular activity · Siderophores

Introduction

Our group reported recently [1] that diesters **1–4** on the basis of some dicarboxylic acids and 16-hydroxyisosteviol synthesized from diterpenoid isosteviol (*ent*-16-oxobeyeran-19-oic acid) **5** [2] exhibit medium-level anti-tubercular activity against *M. tuberculosis* H₃₇R_V in vitro. It is significant that diester **4** has the same activity (12.5 µg/ml) as pyrazineamide [3] and some podands containing heterocyclic fragments [4]. Anti-tubercular activity of those

podands was clarified by its ability for transport of metal cations, including Fe(III), through lipophilic mycobacterium membranes and its competition in a transport of metal with natural siderophores [5, 6] which are produced by aerobic bacteriums (including *Mycobacterium tuberculosis*) for transport of Fe(III) cations into a cell which are necessary for their vital functions [7]. We suppose that anti-tubercular activity of diesters **1–4** [1], as well as the activity of podands with heterocyclic fragments described in [4–6] depends on their ability to bind metal cations.

In this paper we present the result of the investigation of transport of Fe(III) picrates by biologically active diesters **1–4** and isosteviol **5** through liquid chloroform membrane, as well as the dependence of anti-tubercular activity of diesters **1–4** on their structure and ability for binding Fe(III) cations.

Experimental

Materials

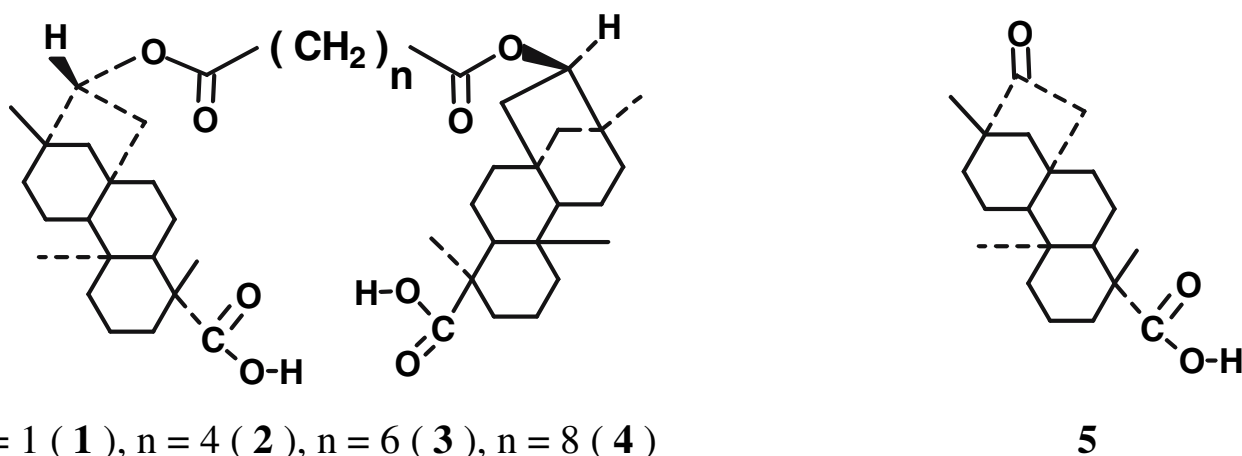
Compounds **1–4** were synthesized analogously to [1]. Isosteviol **5** was obtained by acid hydrolysis of glycosides containing in the plant *Stevia rebaudiana* Bertoni in a similar manner as in [8].

Metal picrate transport

Transport experiments were performed analogously to [9]. The apparatus consisted of a cylindrical glass vessel (an internal diameter 42 mm), and a glass tube (an internal diameter 30 mm) which located in the vessel so that the distance between the bottom of the glass tube and the vessel bottom equals 0.2–0.5 mm. About 20 mL of 10⁻⁴ M

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solution of the carrier in chloroform (liquid chloroform membrane) was placed into the cylindrical glass vessel, then 20 mL of 10^{-4} M solution of Fe(III) picrates in doubly distilled water (source aqueous phase) was carefully added into the space between the internal wall of the vessel and the external wall of the glass tube. The glass tube itself was filled with 20 mL of doubly distilled water (receiving aqueous phase). Thus, this glass tube separates the two aqueous phases (source and receiving), and organic layer (liquid chloroform membrane) lies below them and bridges them across the separation by the central glass tube. The chloroform phase was stirred with a magnetic stirrer at 100 rpm for 6 h at $293 \pm 1^\circ\text{K}$. Each experiment was repeated three times and the results were averaged. Metal cations transport was checked by monitoring changes in picrate anion concentration in the source and the receiving phases and in the chloroform by UV measurements ($\lambda = 357$ nm).

X-ray structure analysis of compounds 1–3

Intensity data measurements of the compounds **1** and **2** were carried out on an Enraf-Nonius four circle diffractometer using graphite monochromated Cu K_α (1.54178 \AA) radiation. Compound **3** was studied on a Nonius Kappa CCD diffractometer using Mo K_α (0.71073 \AA) radiation. All structures were solved by direct method using program SIR [10] and refined using the SHELXL [11] and WinGX [12] software packages. All the non-hydrogen atoms were refined with anisotropic atomic displacement parameters, and hydrogen atoms bonded to carbon were inserted at calculated positions using a riding model. Hydrogen atoms bonded to oxygens were located from difference maps. Absolute structure of the compounds were determined from reference molecules [8] and Flack [13] parameters. Data collection and data reduction were performed on Alpha Station 200 computer using MoLEN [14] program. All

figures were made using the program PLATON [15]. Crystal data and parameters for data collection and refinements are summarized in Table 1.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 609479 (**1**), 609480 (**2**), 609478 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

Results and discussion

Transport of Fe(III) picrates

The data on transportation of Fe(III) by diesters **1–4** are presented in Table 2. In order to compare them with some literature data, we listed here several receptors and carriers possessing two carboxylic groups analogously to diesters **1–4** [16–25]. The Rebek receptor obtained by interaction of Kemp acid with aromatic diamines was probably the first unique receptor in which two CO_2H groups are rigidly fixed one opposite another [16]. This receptor binds heterocyclic diamines, diacids [17], selectively carries amino acids with aromatic moieties through liquid chloroform membrane [18], forms strong complexes with Fe(III) cations isolated in individual form [19]. There is no rigid fixation of two CO_2H groups in convergent form in other receptors, having these two functions, which we could find in literature, anyway they also reveal selectivity in binding. Thus, receptor derived from the condensation of 2-hydroxy-5-methyl benzene-1,3-dicarbaldehyde with *o*-amino benzoic acid appeared to be a better carrier for the transport of Cu(II) ions across liquid membrane (91%) in comparison with the result for Pb(II) ions (only 12%) [20]. The extension of the spacer

Table 1 Crystal data collection and refinement parameters for compounds **1–3**

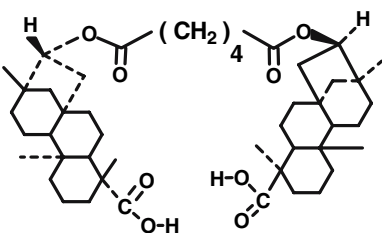
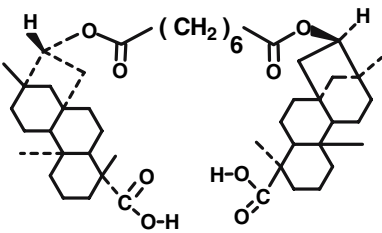
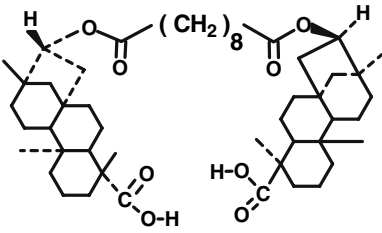
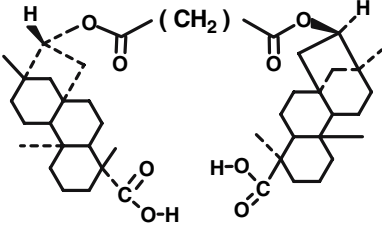
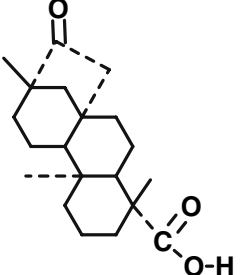
	1	2	3
Empirical formula	C ₄₃ H ₆₄ O ₈	2(C ₄₆ H ₇₀ O ₈)	C ₄₈ H ₇₄ O ₈
Formula weight	708.94	751.02	779.07
Temperature (K)	293(2)	293(2)	223(2)
Wavelength (Å)	1.54184	1.54178	0.71073
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	C2	P2 ₁	P2 ₁ 2 ₁ 2 ₁
Unit cell dimensions			
<i>a</i> (Å)	23.93(2)	12.087(2)	7.4490(15)
<i>b</i> (Å)	7.526(8)	29.027(7)	21.571(4)
<i>c</i> (Å)	23.68(1)	12.902(2)	28.096(6)
α (°)	90.00(2)	90.00(2)	90.000(5)
β (°)	108.79(6)	108.81(1)	90.000(5)
γ (°)	90.00(2)	90.00(2)	90.000(5)
Volume (Å ³)	4,037(6)	4,285(1)	4,515(1)
<i>Z</i>	4	2	4
Density (calculated) (Mg/m ³)	1.116	1.164	1.146
Absorption coefficient (mm ⁻¹)	0.628	0.617	0.076
		Absorption correction is not applied	
<i>F</i> (000)	1,544	1,640	1,704
Crystal size (mm ³)	0.2 × 0.2 × 0.2	0.24 × 0.2 × 0.1	0.3 × 0.2 × 0.2
θ Range for data collection (°)	3.90 to 64.95	3.04 to 57.21	2.83 to 22.98
Index ranges	-24 ≤ <i>h</i> ≤ 28, -8 ≤ <i>k</i> ≤ 7, -27 ≤ <i>l</i> ≤ 24	-12 ≤ <i>h</i> ≤ 13, -28 ≤ <i>k</i> ≤ 31, -14 ≤ <i>l</i> ≤ 13	-8 ≤ <i>h</i> ≤ 8, -22 ≤ <i>k</i> ≤ 23, -28 ≤ <i>l</i> ≤ 27
Reflections collected	7,568	10,226	3,959
Independent reflections	5,444 [<i>R</i> (int) = 0.224]	9,352 [<i>R</i> (int) = 0.1000]	3,631 [<i>R</i> (int) = 0.0300]
Refinement method		Full-matrix least-squares on <i>F</i> ²	
Data/restraints/parameters	5,444/1/437	9,352/1/967	3,631/0/507
Goodness-of-fit on <i>F</i> ²	0.918	0.951	1.054
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> 1 = 0.0836 <i>wR</i> 2 = 0.1729	<i>R</i> 1 = 0.0638 <i>wR</i> 2 = 0.1058	<i>R</i> 1 = 0.0766 <i>wR</i> 2 = 0.1662
<i>R</i> indices (all data)	<i>R</i> 1 = 0.2485 <i>WR</i> 2 = 0.2449	<i>R</i> 1 = 0.2920 <i>wR</i> 2 = 0.1523	<i>R</i> 1 = 0.1152 <i>wR</i> 2 = 0.1915
Largest diff. peak and hole (e Å ⁻³)	0.227 and -0.265	0.201 and -0.222	0.195 and -0.148

(the substitution of benzene spacer for phenanthroline one) in receptor molecule leads to the opposite situation - the percentage of Pb(II) ions in receiving phase increases up to 83%, whereas the percentage of Cu(II) ions in receiving phase decreases down to 9% [20]. Exceptionally high selectivity in extraction of Pb(III) ions (96%) in comparison with Cu(II), Ni(II), Zn(II) ions (the extraction degree is less than 1%) was demonstrated by receptors on the basis of two molecules of *o*-benzoic acid connected by spacers of various nature [21]. By introducing 4th, 12th and 16th carboxylic groups in calix[4]arene system, a new type of receptors,

namely, *O*-(carboxymethyl) calix[4]pyrogallols [22] were synthesized, which appeared to be more selective towards alkaline metals and lanthanides than well known complexes on the basis of polycarbonic acids [23]. Receptors on the basis of rigid steroid skeleton, namely some derivatives of bile acids which also bind an alkaline metals are described [24, 25].

The maximum extraction degree observed in the case of our diesters (Table 2) equals 34%, that is, in comparison with literature data for known receptors with two carboxylic groups, diesters **1–4** are rather moderate

Table 2 The transport of Fe(III) picrates by compounds 1–5 through liquid chloroform membrane^a

Carrier	Fluxes J , 10^{10} M/cm ² s	Extraction degree, %	The quantity of metal held in chloroform phase, %	The quantity of metal cations transported from source aqueous phase into receiving aqueous phase, %
 <p>1</p>	1.6	8.9	0.79	8.11
 <p>2</p>	3.2	18.35	2.84	15.51
 <p>3</p>	2.8	22.5	7.56	14.94
 <p>4</p>	6.9	34.02	0.52	33.50
 <p>5</p>	4.4	21.86	0	21.86

^a Experiments accomplished 6 h; estimated errors of measurements are $\pm 2\%$; blank experiments (without carrier) exhibited no observable transport (and extraction) for Fe(III) picrates

extragents. However, it should be noted that they reveal the flux of Fe(III) (Table 2) comparable with the flux of Fe(III), observed for some tetradentate siderophore and siderophore mimic ligands ($0.5\text{--}3.0 \times 10^{-10} \text{ mol s}^{-1} \text{ cm}^{-2}$ [26]).

When analyzing our results outlined in Table 2, one should note that the quantity of Fe(III) ions in receiving phase (reextraction degree) increases four times when going from diester **1** (8.11%) to diester **4** (33.5%) and fluxes increase from 1.6 to $6.9 \times 10^{-10} \text{ mol s}^{-1} \text{ cm}^{-2}$. It is evident from Table 2, that this increase correlates with the increase of the length of the spacer connecting two *ent*-beyeran skeletons, in other words, with the increase of the distance between two carboxylic groups.

X-ray analysis of diesters 1–3

According to X-ray single crystal analysis, the distance between two carboxylic groups indeed increases as the spacer length increases. Diester **1** in crystal has tweezer-like structure in which carboxylic groups are oriented definitely one opposite another and they come close together forming intramolecular H-bond (Fig. 1). Molecules of diester **2** have also tweezer-like structure in crystal, however carboxyl groups in this structure are rather separated and there is no H-bonding between them. Very interesting dimer of pseudocatenane-like structure is realized for

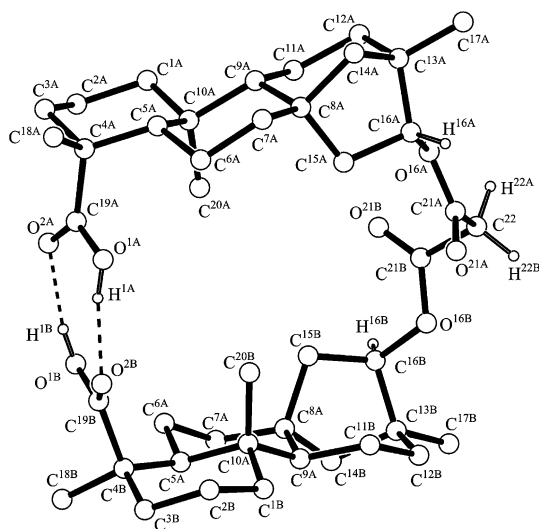


Fig. 1 Intramolecular hydrogen bonds (dashed lines) in a crystal of compound **1**. The parameters of O–H...O interactions are: $d(\text{H}^{1\text{A}}\dots\text{O}^{2\text{B}})$ 1.83 Å, $d(\text{O}^{1\text{A}}\dots\text{O}^{2\text{B}})$ 2.64(1) Å, $\angle(\text{O}^{1\text{A}}\text{--H}^{1\text{A}}\dots\text{O}^{2\text{B}})$ 169° and $d(\text{H}^{1\text{B}}\dots\text{O}^{2\text{A}})$ 1.87 Å, $d(\text{O}^{1\text{B}}\dots\text{O}^{2\text{A}})$ 2.68(1) Å, $\angle(\text{O}^{1\text{B}}\text{--H}^{1\text{B}}\dots\text{O}^{2\text{A}})$ 169°

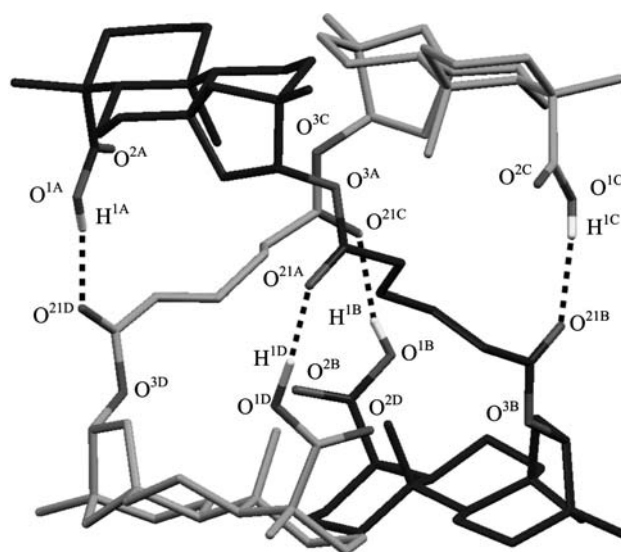


Fig. 2 H-dimer formation in the crystal of compound **2** due to intermolecular hydrogen bonds (dashed lines) between two independent molecules. Only hydrogen atoms participated in H-bonding are shown

diester **2** in crystal (Fig. 2). Two tweezer-like molecules of diester **2** are combined in this dimer owing to four intermolecular H-bonds $\text{--C}(\text{O})\text{--OH}\dots\text{O}=\text{C}<$ between atoms of both carboxylic groups of one diester molecule and carbonyl oxygen atoms of ester groups of another diester molecule (Fig. 2). The parameters of O–H...O interactions are: $d(\text{H}^{1\text{A}}\dots\text{O}^{21\text{D}})$ 1.75 Å, $d(\text{O}^{1\text{B}}\dots\text{O}^{21\text{D}})$ 2.70(1) Å, $\angle(\text{O}^{1\text{B}}\text{--H}^{1\text{A}}\dots\text{O}^{21\text{D}})$ 141°, $d(\text{H}^{1\text{A}}\dots\text{O}^{21\text{C}})$ 1.98 Å, $d(\text{O}^{1\text{A}}\dots\text{O}^{21\text{C}})$ 2.77(1) Å, $\angle(\text{O}^{1\text{A}}\text{--H}^{1\text{A}}\dots\text{O}^{21\text{C}})$ 162°, $d(\text{H}^{1\text{C}}\dots\text{O}^{21\text{A}})$ 1.97 Å, $d(\text{O}^{1\text{C}}\dots\text{O}^{21\text{A}})$ 2.76(1) Å, $\angle(\text{O}^{1\text{C}}\text{--H}^{1\text{C}}\dots\text{O}^{21\text{A}})$ 163°, $d(\text{H}^{1\text{D}}\dots\text{O}^{21\text{B}})$ 1.84 Å, $d(\text{O}^{1\text{D}}\dots\text{O}^{21\text{B}})$ 2.63(1) Å, $\angle(\text{O}^{1\text{D}}\text{--H}^{1\text{D}}\dots\text{O}^{21\text{B}})$ 163°. When the spacer length increases up to six methylene units, tweezer-like structure becomes unfavorable and diester **3** has an extended structure in crystal (Fig. 3) with a maximum distance between carboxyl groups of one molecule in comparison with diesters **1** and **2**. Each molecule of compound **3** participates in four hydrogen bonds (as a donor in two of them and as an acceptor in two other ones). The parameters of intermolecular O–H...O interactions are: $d(\text{H}^{1\text{A}}\dots\text{O}^{21\text{B}})$ 1.90 Å, $d(\text{O}^{1\text{A}}\dots\text{O}^{21\text{B}})$ 2.65(1) Å, $\angle(\text{O}^{1\text{A}}\text{--H}^{1\text{A}}\dots\text{O}^{21\text{B}})$ 152° (symmetry operation $\frac{1}{2} - x, 1 - y, -1/2 + z$) and $d(\text{H}^{1\text{B}}\dots\text{O}^{21\text{A}})$ 1.97 Å, $d(\text{O}^{1\text{B}}\dots\text{O}^{21\text{A}})$ 2.73(1) Å, $\angle(\text{O}^{1\text{B}}\text{--H}^{1\text{B}}\dots\text{O}^{21\text{A}})$ 153° (symmetry operation $3/2 - x, 1 - y, 1/2 + z$). Due to these interactions, the molecules form infinite two-dimensional network - planes of zigzag (spiral) chains parallel to crystallographic plane (010).

Probably, extended structure with sizeable distance between carboxyl groups of one molecule is also distinctive for diester **4** having a spacer consisted of already eight methylene units.

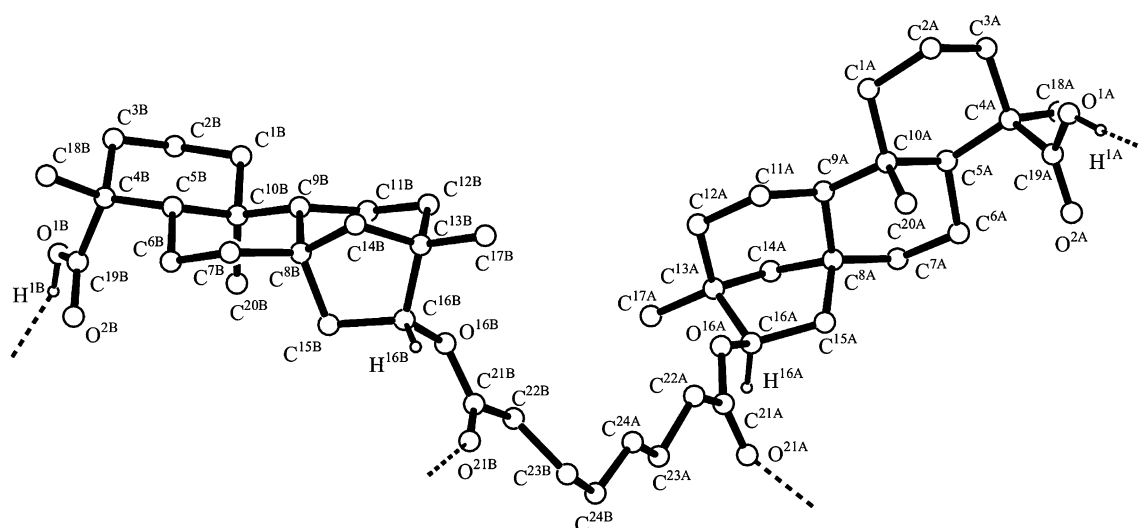


Fig. 3 Molecular structure of diester **3** in crystal. Only hydrogen atoms of carboxylic and ester groups are shown

Quantum-chemical calculations

We carried out several computations on the level of gradient-correlated density functional theory with Perdew-Burke-Ernzerhof exchange-correlation functional (DFT/PBE) and three exponential basis (TZ2P) [27, 28] with the aim to explain the observed increase of ability of diesters **1–4** to bind Fe(III) cations in the sequence from **1** to **4**. Since these compounds contain isosteviol moieties, therefore, at first, we studied the ability of isosteviol **5** itself to bind Fe(III) cations. Our computations reveal that isosteviol **5**, as any carbonic acid, easily forms intermolecular

H-bonding dimers. The energy of its dimerization equals 18 kcal/mol that is close to experimentally (IR) observed H-bonding energy of carbonic acids [29]. Interestingly that PM3 computations underestimate this value about by half [30]. It was revealed earlier that isosteviol **5** in fact forms H-bonding dimers both in crystal [8] and in dilute solution of CCl₄ [31] where the energy of its dimerization was estimated by IR measurements as 17 kcal/M [31]. Thus isosteviol **5**, existing in dilute solution as H-bonded dimers, is preorganized for binding Fe(III) cations. We supposed that complex [Fe³⁺(*isost*)₂¹⁻(H₂O)₂]⁺Pic⁻ **6**, where *isost* is a deprotonated molecule of isosteviol **5**, is formed under

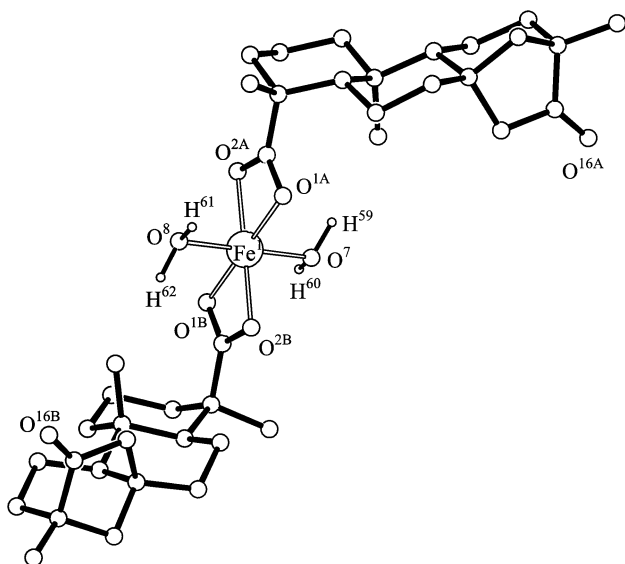


Fig. 4 Molecular structure of a complex [Fe³⁺(*isost*)₂¹⁻(H₂O)₂]⁺Pic⁻ **6**, where *isost* is a deprotonated molecule of isosteviol **5**, optimized by DFT/PBE

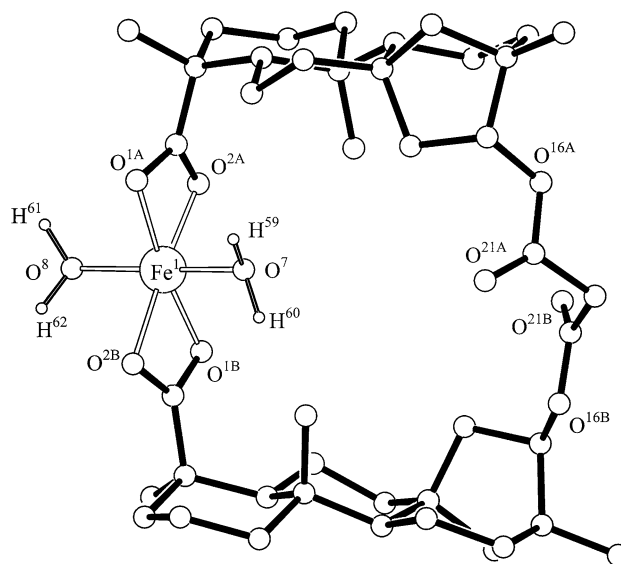


Fig. 5 Molecular structure of a complex [Fe³⁺(*diester*)₂²⁻(H₂O)₂]⁺Pic⁻ **7**, where *diester* is a deprotonated molecule of diester **1**, optimized by DFT/PBE

experimental conditions we used. The structure of complex **6** optimised by DFT/PBE is shown in Fig. 4. Our computations for diester **1** are in a good agreement with X-ray data (Fig. 1) and testify to the fact that tweezer-like structure with intramolecular H-bonding is preferable and the energy of this H-bonding equals 16 kcal/mol that is in a good agreement with a data for isosteviol **5** [31] and carbonic acids [29]. Geometrical parameters of this bonding calculated by DFT/PBE theory are close to values obtained by X-ray analysis for diester **1**. Molecular structure of complex $[\text{Fe}^{3+}(\text{diester})^{2-}(\text{H}_2\text{O})_2]^+\text{Pic}^-$ **7**, optimized by DFT/PBE, where *diester* is a deprotonated molecule of diester **1**, is shown in Fig. 5. According to our computations, the formation of complex **6** is by 6 kcal/mol preferable than that of complex **7**. Possible reason of this phenomenon is as follows. In order that Fe(III) cation can penetrate between carboxyl groups of diester **1** molecule, they should be slightly separated, so conformational reorganization of spacer connecting isosteviol moieties is needed and about 6 kcal/mol is spent. One can suppose that there is no need for such structural changes in the case diester **3** and **4**, because these compounds possess extended structure in which two carboxylic groups of one molecule are separated by substantial distance (Fig. 3). Besides, according to the data of dipole moment method and IR spectroscopy [32], these diesters in dilute solutions as well as isosteviol **5** itself combine in dimers owing to intermolecular H-bonding between carboxylic groups of different molecules. Thus, one can suppose that the energy of formation complexes of diesters **3** and **4** with Fe(III) is similar to that of isosteviol **5**, so they should have equal ability to bind Fe(III) cations and transport them through liquid chloroform membrane. Indeed, fluxes, degrees of extraction and reextraction of diester **4** and isosteviol **5** are the same and diester **3** has rather similar values (Table 2).

Conclusion

The comparison of the data observed for transport of Fe(III) cations by diesters **1–4** and isosteviol **5** with their anti-tubercular activity show that diester **4** being the best carrier of Fe(III) cations, has the best anti-tubercular activity among compounds studied (its minimal inhibition concentration equals 12.5 $\mu\text{g}/\text{ml}$ [1]). Isosteviol **5** reveals the transport properties which are the average of the properties of diesters **3–4**, while its anti-tubercular activity is worse (minimal inhibition concentration is about 50–100 $\mu\text{g}/\text{ml}$ [1]). Hence anti-tubercular activity of diester **1–4** depends both on their ability to transport Fe(III) through liquid chloroform membrane and their lipophilicity which is twice as much of isosteviol **5**.

Therefore there is a direct dependence between anti-tubercular activity of diesters **1–4** on the basis of isosteviol **5** and their ability to bind Fe(III) cations and transport them through a liquid chloroform membrane which models a cell membrane. That is why, in our opinion, diesters on the basis of isosteviol **1–4** could be named as a novel type of synthetic analogues of siderophores which are inhibitors of *Mycobacterium tuberculosis* vital functions. We would like to note that compounds studied can actually compete with natural siderophores in transport of Fe(III) cations since their flux of these cations (Table 2) is similar to the literature data for some siderophores ($2.8 \times 10^{-10} \text{ mol s}^{-1} \text{ cm}^{-2}$ [20]).

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