A K-75869 projekt támogatási időszaka alatt, a projekthez tartozó és kapcsolódó munkák ismertetése

A fölsorolás alapvetően *négy* területet érint. Ezek az - eredeti célhoz szorosan, vagy legalább koncepciójukban (és eszközeikben is) - illeszkedő kutatások:

1.) Reinecke—só és származékok előállítása: szokatlan kristályosítási technikák és nehezen kristályosítható anyagok szisztematikus vizsgálata, kémiai és szupramolekuláris szintézisek.

2.) A No-SPA® márkanéven ismert *Drotaverin·HCl só* új zárványainak, illetve új ko-kristályainak és sóinak előállítása.

3.) A tiokarbamid-alapú organokatalizátorok szerkezetvizsgálata, különös tekintettel a szolvatált és a só formákban előállíthatóakra.

4.) Olyan, “ad hoc” szerkezetvizsgálatok, amelyekben a projekt során megtanult technikák a kristályosításban vagy a méréstechnikában szerzett ismereteinkkel oldhatók meg. Ezek szerves vegyületeket, de szervetlen ionos kristályokat is érintenek. (Olyan munkákat sorolunk ide, ahol az ilyen jellegű ismeretek használata az általunk végzett munka szempontjából legalább 50% volt).

A fölsorolt munkák nagyobb része még kéziratban van. Ezek földogozása folyamatos, közlésüket a terület vezető lapjaiban (Crystal Growth and Designm CrytsEngComm) tervezzük.

¤

1.) Reinecke—só és származékok előállítása: szokatlan kristályosítási technikák és nehezen kristályosítható anyagok szisztematikus vizsgálata, kémiai és szupramolekuláris szintézisek.

Kristályosítottuk egy tucat új Reinecke-só származékát, beleértve eddig ismeretlen ferrocénium reineckátokat is.

Az alapanyag és első kation metatézis származékai szerkezetei az alábbi kéziratban.

Reinecke Complexes with Anion - Cation Layering

Veronika Kudar[a] and Mátyás Czugler*[a]

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Publication data **[DO NOT ALTER/DELETE THIS TEXT]**
DOI: 10.1039/b000000x [DO NOT ALTER/DELETE THIS TEXT]

Crystals composed from the Reinecke anion provide organic graphite-like structures, with simple N-heterocyclic cations e.g. *BMIM* · Reineckate they may also form layered non-centrosymmetric crystals.

The Reinecke salt[1] was known in the pharmaceutical analysis, in the analytics of natural compounds and of precious metals, its derivatives ("Reineckates") also appear as preferred components in anionic photoinitiation[2]. Interesting homobinuclear complexes[3], dinuclear heterometallic magnetic clusters[4] and charge-transfer complexes[5] were recently prepared by using the Reinecke anion or its derivetives. There are not many crystal structures known with the Reinecke anion[3-6], even though interest persist for this class of complexes[2-5]. Perhaps not only of historical awareness is to realize that the idiom "*crystal engineering*" was actually first coined for and used in relation with the complexes of the Reinecke anion[7]. Successful attempts were also made to place Reinecke-anion derivatives in a supramolecualr context[3]. We follow up the supramolecular chemistry of the Reinecke anion for several reasons. This anion offers a well-defined soft anion crystal environment, with its low charge dispersed over a voluminous, symmetric molecular mass with a polarizable electronic environment. The supramolecular chemistry makes versatile use of large, "soft" and structurally rigid (semi-rigid) anions such as carboranes, cyamelurates, fullerides[8], together with the so-called weakly coordinating anions (WCAs)[9]. Similarly the PF_6^--anion was used in the building of e.g.catenanes and rotaxanes[10]. These approaches lead to tailoring of new solids with new properties. Also polyoxo-metallates[11], MOF frameworks[12], molecular perovskites[13] can be devised using such tools. As materials with unusual properties and/or stuctures are also expected from crystallization experiments by the perusal of ionic liquids (ILs) for crystallization[14], we also planned to make extensive use of ILs. Apart from a variety[15] of possible tuning of the solution physical properties (viscosity, temperature and electric properties), outcome of experiments may strongly depend on the nature of the IL in such "Edisonian" experiments[14]. Some ILs which also contain large anions, were reported recently both in crystalline[16] and also in the liquid state by neutron diffraction and molecular modeling[17]. Rare earth thyocianate complexes were recently employed as anionic building blocks for low-melting metal-containing ionic liquids[18]. A Cr- derivative anionic substance may also offer some tuning by providing a variety of valency and of spin states[3-5].

Take in SCHEME.

Scrutiny of the Reinecke salt structure[19] reveals that the ammonium cation is surrounded very much like the alkylammonium cations in clathrate hydrates. The included water plays dielectric media role insulating neighbouring S atoms of thiocyanate ions. Thus this anion lends itself to crystal engineering using supramolecular chemistry tools. We first targeted crystalline Reineckates with an emphasis of simple aromatic N-heterocycles and ammines. A co-crystallization experiment using 1-butyl-3-methyl-imidazolium acetate (*BMIM* acetate) as IL solvent led to red crystals[20]. This proved to be an anion-metathesis 1:1 complex **1** of the *BMIM* cation and the Reinecke anion† (***Re***-anions, Fig.1). The cation has a normal side chain configuration[21] (C2N1CC torsion at ca. 99º). The anion, which may occupy high site - symmetry Wyckoff positions, can not adopt such here due to the *P*a space group. It may be also due to the space group, that separate cation-anion layering develops in this crystal (Fig.2.). A number of weak N-H ··· S and C-H ··· S contacts are also present. N5 ··· S2 and N6 ··· S3 interactions along the *b* axis stabilize isolated columns of ***Re***-anions extending all through in the *ab* plane. Methyl and methylene C-H contacts from each of the opposite *BMIM* cations are stabilizing the ***Re***-anion columns to thiocyanate S (2.89Å), C (2.64-2.88Å) and N (2.68Å) atoms. A BMIM C4-H to S1 contact is at 2.97Å. Noteworthy is to mention a methyl C-H contact to atom N3 of *BMIM* (2.73Å). Butyl and methyl terminal H atoms close approach (to 2.23Å) is also seen in the neighbouring *BMIM* cations. Shortest ***Re***-anion Cr ··· *BMIM*-cation ring center distance is ca. 6.99Å, while *BMIM*-cation ring centres are ca. 6.46Å from each other. Length of the *b*-axis (ca. 6.86Å) is apparently defined by the ***Re***-anions packing in this crystal. The ca. 6.58Å terminal methyl C-atom distances of the *BMIM*-cation are close to this value suggesting not only electronic but size matching as well.

From an other crystallization we obtained a quaternary complex inclusion of the pyrazinium (*pyr*H^+) ***Re***-salt with neutral pyrazine (*pyr*) molecules and water resulting in 2 : 2 : 2 : 3 *pyr*H^+ : ***Re*** : *pyr* : H_2O stoichiometry†† (and with an

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supplementary information available should be included here]. See http://dx.doi.org/10.1039/b000000x/

intriguing packing pattern (Fig.3). Main chord of this crystal seems to be distinct oval - shaped cages at around the corners and centers of the unit cells, which seem to be filled with the neutral *pyr* molecules. ***Re***-anions are arranged into separated undulating layers, that are cross-linked by H-bridges contact regions of the *pyr*H^+ cations and water. Anionic layers, separated from each other with alternating neighbours of cationic/hydrated and neutral pyrazine mulecule clefts, are also arranged into complementing layers with respect to the cationic ones. Coincidentally we note that the ca. 26.5 Å crystallographic *b*-axis of **2**, which is the repetion distance of the cationic cleft centres, too, falls close in value to both to the large cationic channel centre distance (ca. 23.7Å) as well as the hexagonal stack axis value of ca 27 Å found in the donut-shaped giant $\{Mo_{57}M_6\}$ clusters[11]. The layering topology in **1** and in **2** is deviating from the normal close packed pattern of pure ionic systems, e.g. compare for a molecular perovskite crystal structure, where cation-anion ordering follows either a *ccp* or *hcp* pattern[13]. Interaction pattern between the componenets of this crystal show series of H-bridges between charged species as well as a number of short N-H ··· X and C-H ··· X approaches (Table 2, Supplementary). It is clear that the structure model suggested herein constitutes only a first-level description as probable proton switching may easily take place between neighbouring *pyr* / *pyr*H^+ rings, also mediated by water molecules. Unusually strong diffuse scattering also point to modulating effects in this structure as well. Looking through in retrospect the available ***Re***-anion crystal structures we realize that six out of nine crystals do show some kind of cation-anion layering. Smooth or undulating layers are in CHOLRI[6a] (though choline cations were not located), in HAWZAG[6c], PYRREI[6b] and in RIBBOT[5], while corrugated layers are seen from SUXSOT[4] and XEFYUD[3] (a thiocyanato ligand also bridges to another metal in these structures). We are thus inclined to believe that the crystals made from using the ***Re***-anion might indeed called organic clays[24].

Acidified 3-Br-pyridine when used as cosolvent for a recrystallization provided cations to the crystals of **3**, with a non-centrosymmetric space group and the formation of a now closed cage-like structure around the cation (Figure 4., Supplementary).

It is interesting to note that the frequency of non-centrosymmetric space groups encountered during our feasibility experiments is high, even in cases when none of the components have chiral properties *per se*. We believe that this can be linked to the ***Re***-anion, which has several contact sites for both donating and accepting H-bridge contacts. One possibility is that an otherwise uniform torus-shaped form is once asymmetrically contacted, then asymmetric association will be generating spiral form series of contacts.

Notes and references

† Xray diffraction analysis of **1**: $C_8H_{15}N_2$, $C_4H_6CrN_6S_4$, R-Axis RAPID IP diffractometer, λ (MoK_α) = 0.7107Å, *T* = 295K, monoclinic *P*a (No. 7), *a* = 12.839(8)Å *b* = 6.856(3)Å *c* = 13.119(7)Å, β = 111.34(2)°, for 3107 data *R* = 0.0497, wR^2 = 0.0888, Flack *x* = 0.04(5).

†† **2**: 2[$C_4H_5N_2$, $C_4H_6CrN_6S_4$], 2[$C_4H_4N_2$], 3[H_2O], R-Axis RAPID IP diffractometer, λ (MoK_α) = 0.7107Å, *T* = 149K, orthorhombic, $Cmc2_1$ (No. 36) *a* = 21.130(4)Å *b* = 26.531(4)Å *c* = 12.563(2)Å, for 5502 data *R* = 0.0572, wR^2= 0.1412, Flack *x* = -0.02(3);
3: C_5H_5NBr, C_4H_6Cr,N_4S_4, R-Axis RAPID IP diffractometer, λ (MoK_α) = 0.7107Å, *T* = 120K, orthorhombic $Pna2_1$, (No. 33), *a* = 15.140(6)Å, *b* = 10.012(7)Å, *c* = 11.903(4)Å, for 3120 data *R* = 0.0470, wR^2 = 0.0996, Flack *x* = 0.001(15), CCDC XXXX-ZZZZZ. Bonds conforms to expected values and are equal within s.u. significance ranges for the S-C=N groups.

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20 Preparation of **1**. The IL *BMIM*-acetate was used to dissolve small amount of Reinecke salt at slightly above ambient temperatures (40°C). The resulting light red solution was covered with a fresh *BMIM*-acetate layer atop of which dilute water solution of B_1-vitamine HCl was carefully dispensed. Thin transparent red crystals appeared close to the original phase boundaries after a period of few days, while the colour of the then uniform solution faded out. After a week"s time this solution turned green and deposits redissolved again.

21 Distribution of the C2N1CC torsion angles for 1-alkyl, 3-methylimidazolium entities in the CSD prefer a torsion angle peaking between 90-120°.

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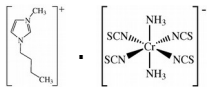
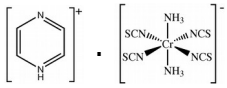
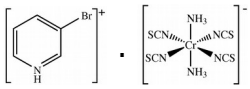
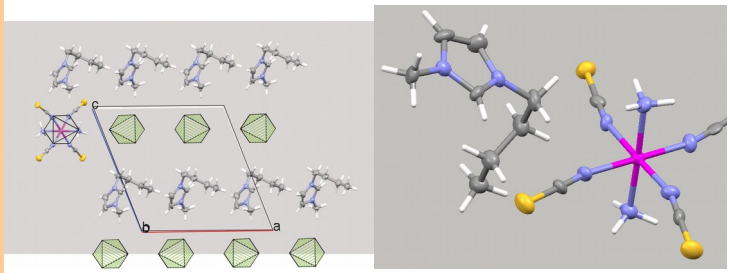
Single column figure/scheme (below)

1: 

2: 

3: 



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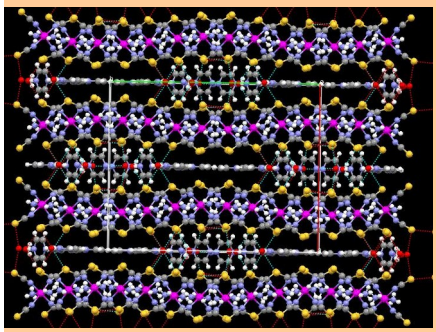

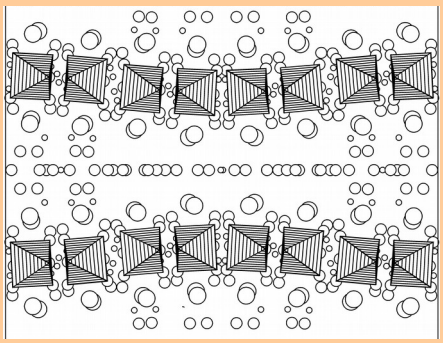

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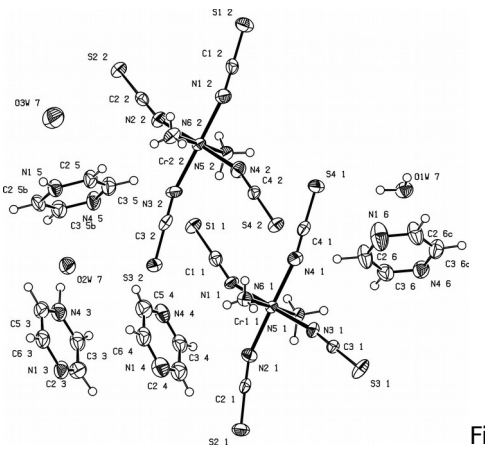

Fig. 3.
Asymmetric unit in **2** with displacement (50% probability) parameters and atomic numbering

X

Table XX Caption

Compound	a/Å	b/Å	c/Å	β/º	V/Å³	Space group	R%
R104/Pyridine-*Rk*©	6,664(2)	12,804(3)	9,839(3)	92,892(4)	838,5	$P2_1/c$	9,28
R131/Pirazine-*Rk*©	16,936(3)	12,563(2)	16,980(4)	102,931(8)	3521,3	$P2_1$	19,08
R130/BrPyr-*Rk*©	15,140(6)	10,012(7)	11,903(4)	90	1804,3	$Pna2_1$	***4,86***
R196/Bmim-*Rk*©	12.862(1)	6.861(1)	13.109(2)	111.16(1)	1078,9	*P*a	***5,8***

X

[a] Footnote text.

Table XX Caption

X

[a] Footnote text.

Engineering of Ferrocenium Reineckates: Synthesis and Crystal Structures

T. Holczbauer, Á. Gyömöre, A. Csámpai and M. Czugler

Abstract

Introduction

Early ferrocene chemistry, especially those of ferocenium and the cobaltocenium salts [1] was bound to the perusal of the Reinecke salt [2] precipitates in their analytics. By that time the Reinecke salt had a relative long history as an eminent precipitation forming analytical reagent, used mainly in the pharmaceutical analysis[3]. The analytic value of the Reinecke salt was based on its preponderance of entering into metathesis reactions with other mainly water soluble salts, especially with quaternary ammonium salts of naturally occurring aliphatic and aromatic amines[..] and their derivatives, amino acids[..] , drugs[..] and even precious metals[..] . Another interesting fact that the term „crystal engineering" was used first in conjunction with the Reinecke salt in 1954[4] . Thus this salt was also the very first instance of a compound being used conscientiously to the purpose[5]. Nevertheless growing crystals of a dominantly precipitate-froming agent

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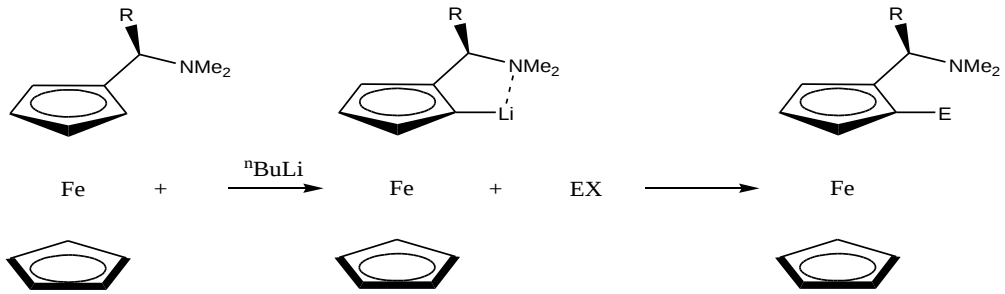
Szerves szintetikus munka: a Reinecke-sók Ferrocénium kationjainak előállítása

1.) Ferrocént tartalmazó kvaterner ammóniumsók előállítása

Kiindulási anyagként *N*,*N*-dimetilaminometilferrocént és (*S*)-(–)-*N*,*N*-dimetil-1- -ferroceniletilamint használunk. Ezeket metil-jodiddal szobahőmérsékleten kvaternerezzük (**1. ábra**). A kiindulási vegyületek azonban lítálhatóak is. A lítiálást ^{n}BuLi-al végezzük hexánban. A lítiált komplexet a megfelelő elektrofillel kvencselve jutunk a 2-szubsztituált termékhez.

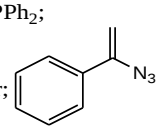


R = H; Me

E = CHO; I; PPh_2; $SiMe_3$; Br; NH_2

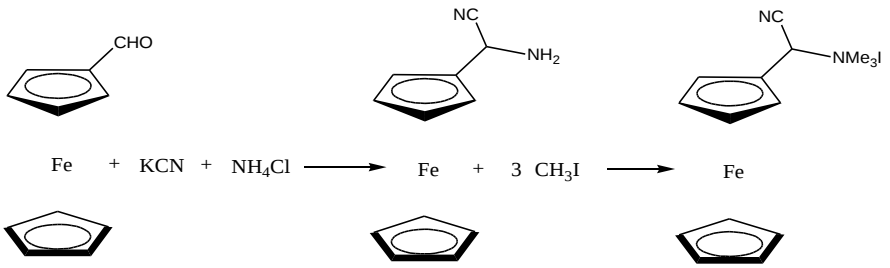
EX = $HCONMe_2$; $I(CH_2)_2I$; $ClPPh_2$;

Me_3SiCl; *p*-$BrCH_2(C_6H_4)CH_2Br$;



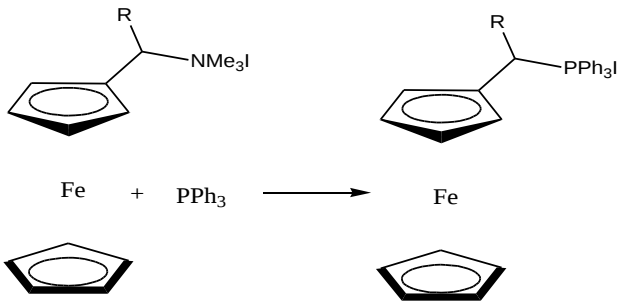
1. ábra

Ha a metilcsoportot cianocsoportra cseréljük, akkor a trimetilamin kihasadást elkerülhetjük. Ezt az anyagot Stecker-reakcióval állítjuk elő ferrocénkarboxaldehidből kiindulva (**2.ábra**).



2. ábra

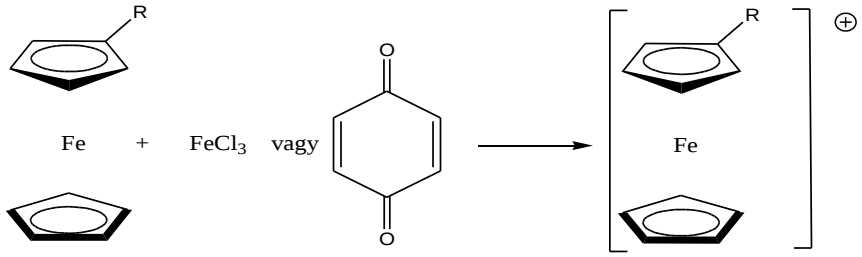
Az előállított kvaterner ammóniumsókat trifenil-foszfinnal foszfóniumsóvá alakíthatjuk (**3. ábra**).



R = Me; H; CN

3. ábra

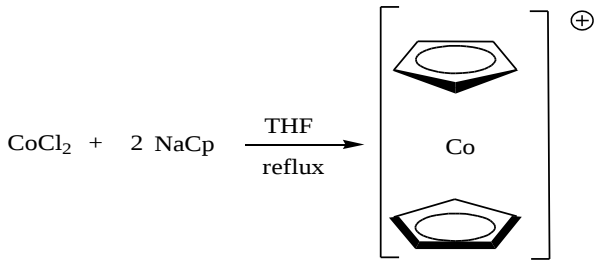
Ferrocíniumok előállítása hagyományos kémiai módszerekkel kétféleképpen lehetséges. A ferrocént vagy monoacetil ferrocént vas(III)-kloriddal, vagy kinoonal oxidálunk dietiléter oldószerben inert körülmények között[2.][3.] (**4. ábra**).



R = H; $COCH_3$

4.ábra

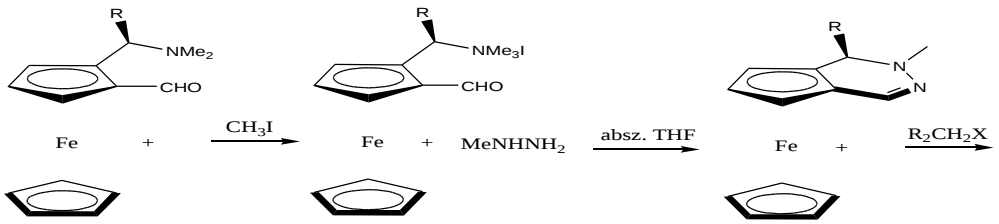
Kobaltocínium előállítása alkotóelemeiből kiindulva lehetséges. Ha reakciót nem inert körülmények között végezzük, akkor a megfelelő kobaltocínium-só képződik[1.](**5.ábra**).



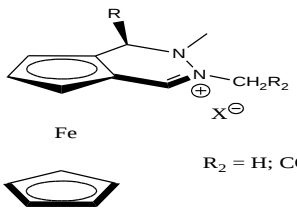
5. ábra

<u>További kvaterner ammóniumsók előállítása</u>

A kvaterner ammóniumsók esetében kihasználhatjuk azt, hogy a trimetilamin könnyen lehasad (**6. ábra**).



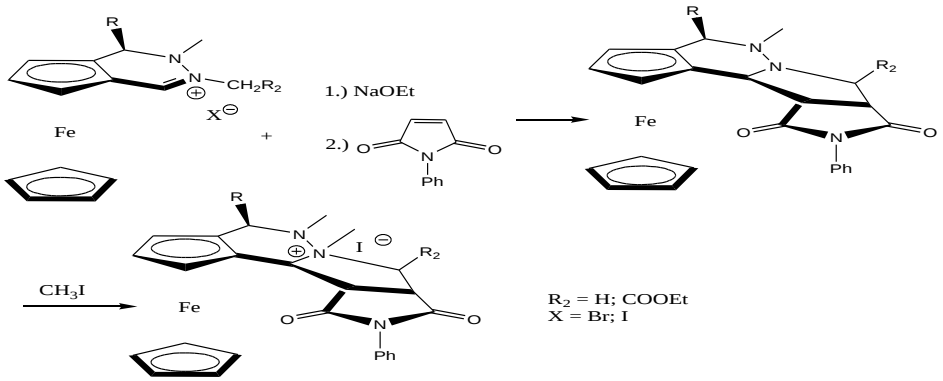
R1 = H; Me



R2 = H; COOEt

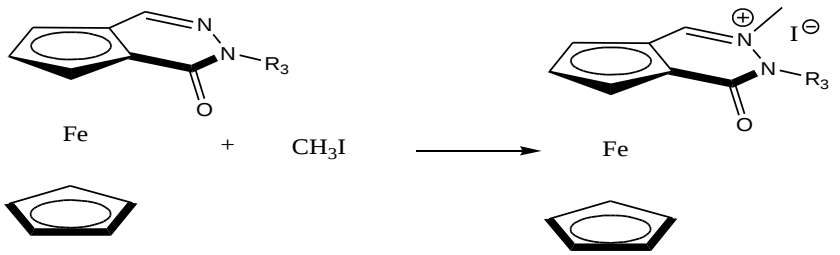
6. ábra

Az így kialakított sóból bázissal azometin ilidet állíthatunk elő, ami alkalmas 1,3-dipoláros cikloaddícióra (**7.ábra**).



7. ábra

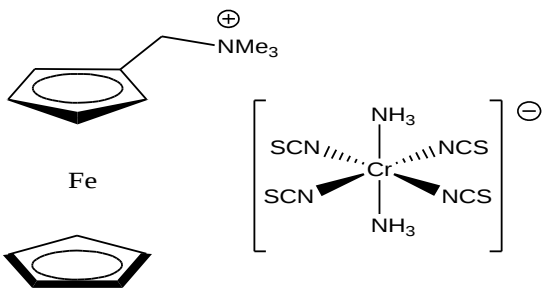
Kvaterner sókat előállíthatunk (*S*)-ferroceno[d]piridazin-1(2*H*)-on származékokból (**8. ábra**).



8. ábra

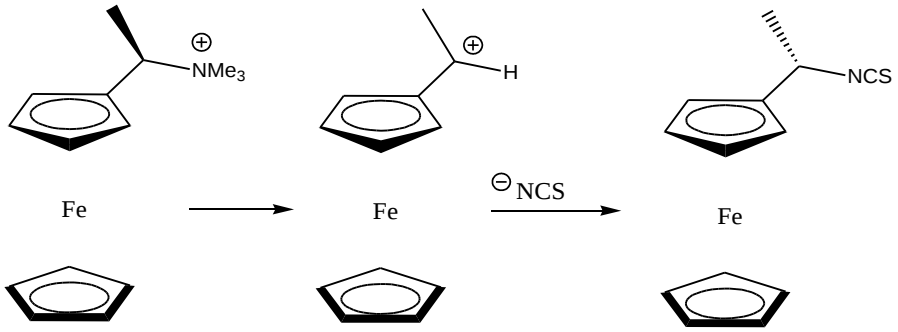
Elért eredmények

Reinecke sót eddig csak a *N,N,N*-trimetilammónium-metilferrocén jodid sójából sikerült előállítani (**9. ábra**).



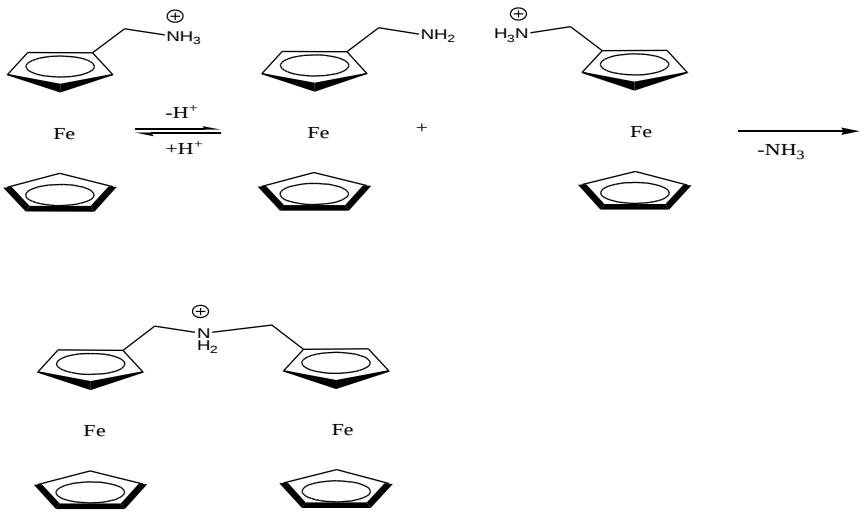
9. ábra

Az előző kation királis származékából kihasadt a trimetilamin és helyére az izocianát került. Ennek oka, hogy az elektronküldő metilcsoport és ferrocénegység stabilizálja a képződő szekunder kationt (**10. ábra**).



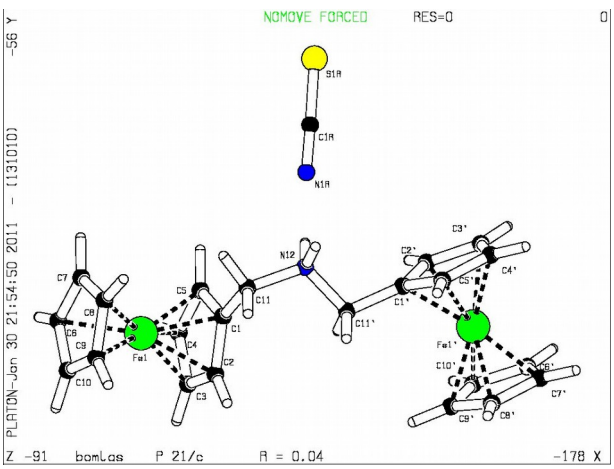
10. ábra

A ferrocenilmetilammónium kloridból áthidalt szerkezetet kaptunk. Ennek oka az, hogy az ammónium ion deprotonálódik és egy másik hidroklorid sóból kilök egy ammóniát, miközben maga összekapcsolódik a másik egységgel (**11. ábra**).

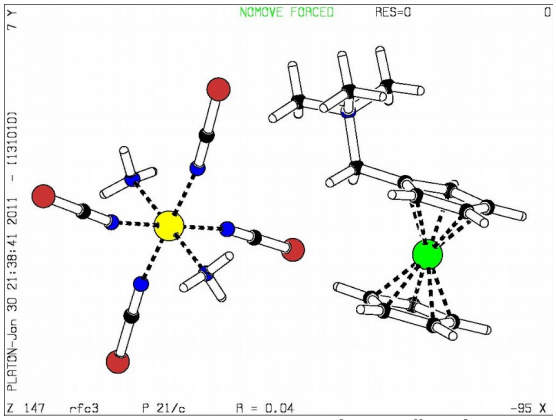


11. ábra

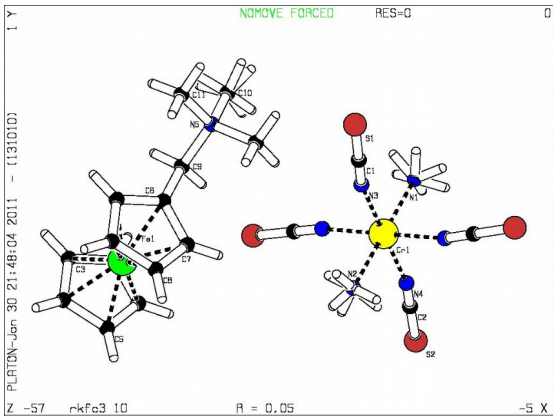
A ferrocinium reineckát sók sikeres szerkezetmeghatározásait az alábbi 6 szerkezet képviseli:



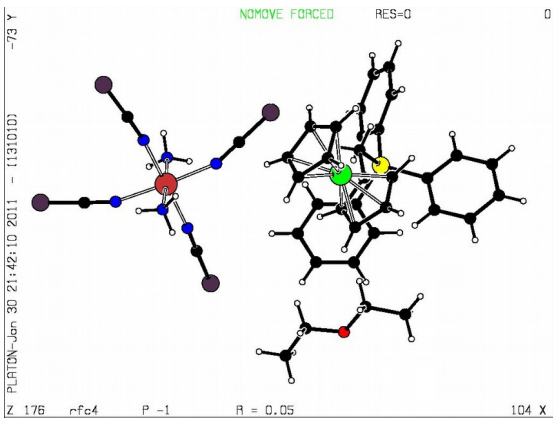
12. ábra Bomlás(-reakció)termék, lásd 11. ábra)



13. ábra RFC3 kódjelű só

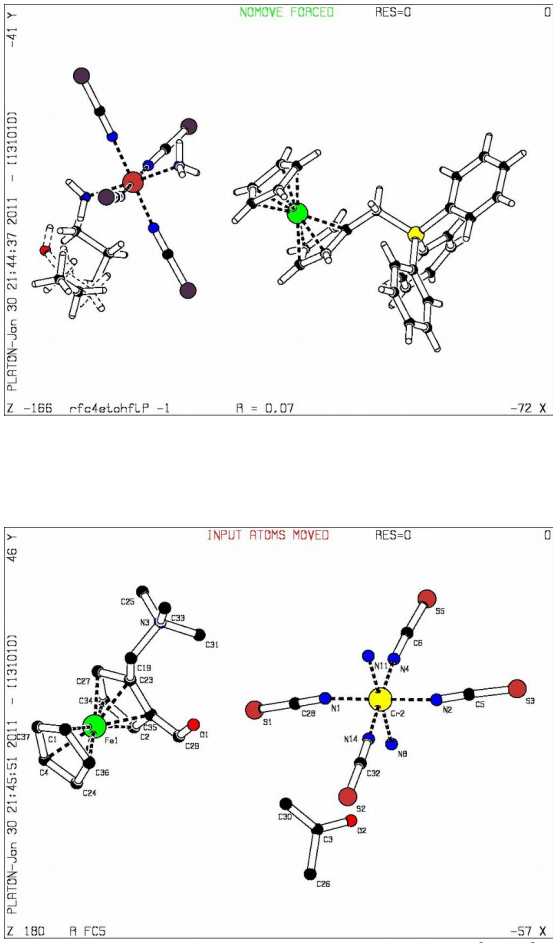


14. ábra RKFC3_10 (polimorf)



15. ábra RFC4 (dietiléter zárvány)

16. ábra RFC4_EtOH (etilakohol zárvány)



17. ábra RFC5_Aceton (Aceton zárvány)

Ahogy azt a 12-17. ábrák mutatják, ezek a sók polimorfia mellett gyakran oldószer zárványokkal képeztek kristályokat.

Kristálytani adataik és szerkezetfinomításuk jellemzői az alábbi táblázatban láthatók.

Compound Form	RKFC3_10 $C_{18}H_{14}CrFeN_7S_4$	Bomlas $C_{23}H_{24}Fe_2N_2S$	RFC3 $C_{18}H_{26}CrFeN_7S_4$	RFC4 $C_{37}H_{42}CrFeN_6OPS_4$	RFC4-EtOH $C_{37}H_{44}CrFeN_6O_2PS_4$	RFC5-Aceton CxHy
F w	564.45	472.21	576.55	853.83	871.84	
Temp.	293(2) K	131(2) K	133(2) K	93(2) K	93(2) K	93(2) K
λ Å	Mo-Kα	Mo-Kα	Mo-Kα	Cu-Kα	Cu-Kα	Cu-Kα
SYST		monoclinic	monoclinic	triclinic	triclinic	monoclinic
Spgr		*P* 21/*c*	*P* 21/*c*	*P* -1	*P* -1	*C* 2/*c*
a = Å	32.954(3)	5.9011(2)	11.6117(6)	9.9509(2)	10.0033(2)	11.999(1)
b =Å	11.088(5)	26.5474(12)	6.4305(3)	13.6579(3)	13.7543(3)	22.8658(2)
c = Å	6.989(14)	13.5202(6) Å	33.8549(18)	16.4848(3)	16.4156(3)	22.351(2)
α =	90°	90°	90°	68.751(1)°	69.778(1)°	90°
β =	90°	107.525(2)°	93.367(2)°	79.905(1)°	78.482(1)°	98.988(6)°
γ =	90°	90°	90°	77.199(1)°	78.384(1)°	90°
Vol Å³	2554(5)	2019.8(2)	2523.5(2)	2025.1(1)	2055.1(1)	6057.3
Z	4	4	4	2	2	8
Dens (calc)	1.468 Mg/m³	1.553 Mg/m³	1.518 Mg/m³	1.400 Mg/m³	1.409 Mg/m³	_
μ mm⁻¹	1.34	1.55	1.36	7.68	7.6	--
F(000)	1140	976	1188	886	906	_
Cryst colour	--	yellow	purple	red	red	_
descr	--	prism	platelet	prism	prism	
size	x x mm	0.40 x0.15 x0.15 mm	0.50 x0.30 x0.05 mm	0.50 x0.13 x0.13 mm	0.36 x0.30 x0.10 mm	
Abs corr		numerical	numerical	numerical	numerical	
transmiss	--	0.922 /0.907	0.915 / 0.573	0.335 / 0.052	0.360/ 0.073	
θ-range	3.08 ≤ θ ≤ 30.51 °	3.07 ≤ θ ≤ 29.57 °	3.07 ≤ θ ≤ 24.71 °	6.58 ≤ θ ≤ 66.58 °	6.57 ≤ θ ≤ 70.06 °	
Refls collect	60132	72623	29135	29298	29708	
Complettd	0.995	0.996	0.999	0.921	0.898	
Indep.refls [$R_{(int)}$]	4054 [0.080]	5650 [0.064]	4310 [0.098]	6591 [0.064]	7015 [0.080]	
Refls $I>2\sigma(I)$	3355	4419	3274	6290	6418	
Dat/estr /params	4054 /0 /158	5650 /0 /261	4310 /0 /285	6591 /0 /464	7015 /0 /483	
S on F^2	2.334	1.125	1.064	1.079	1.122	
R1, wR2 [$I>2\sigma(I)$]	0.045, 0.075	0.039, 0.083	0.044, 0.103	0.047, 0.119	0.069, 0.173	
*R*1, *wR*2 (all data)	0.058, 0.077	0.056, 0.092	0.066, 0.112	0.049, 0.126	0.075, 0.178	
shift/esd	0.002; 0.000	0.001; 0.000	0.002; 0.000	0.000; 0.000	0.009; 0.000	
peak-hol e.Å⁻³	0.669/-0.524	0.613/-0.502	0.568 /-0.443	0.540/-0.621	0.797/-0.853	

Az ide vonatkozó Irodalomjegyzék:

1.) Philippopoulos, A., I.; Bau, R.; Poilblanc, R.; Hadjiliadis, N. *Inorg. Chem.* **1998,** *37,* 4822-4827

2.) Gonzalez, R.; Chiozonne, R.; Kremer, C.; Guerra, F.; De Munno, G.; Lloret, F.; Julve, M.; Faus, J. *Inorg. Chem.* **2004,** *43,* 3013-3019

3.) Chavez, I.; Alvarez-Carena, A.; Molins, E.; Roig, A.; Maniukiewicz, W.; Arancibia, V.; Brand, H.; Manriquez, J., M. *J. Orgmet. Chem.* **2000,** *601,* 126-132

2.) A No-SPA® márkanéven ismert Drotaverin·HCl só új zárványainak, illetve új ko-kristályainak és sóinak előállítása.

Másféltucat kristályszerkezetet építettünk föl egy régóta ismert *No-SPA®* gyógyszer zárványaiból, illetve azok teljesen új asszociátumaival és újtípusú sóiból is.

Ezeknek csak egy áttekintő táblázatát adjuk itt meg, valamint a készülőben levő, sajnos korántsem végleges kéziratát:

Number	***Guest***	***1 : Guest ratio***	***Space Gr.***	***a (Å)***	***b (Å)***	***c (Å)***	***α (°)***	***β (°)***	***γ (°)***	***V (Å³)***	***T(K)***
1	**1**	***1: 0***	***P2₁/c***	***5.07***	***11.15***	***43.07***		***97***		***2419***	***294(2)***
1a	**1-propanol**	**2: 1**	***P*-1**	**12.1**	**14.1**	**15.7**	**81**	**90**	**71**	**2513**	**117(2)**
1b	**2-propanol**	**2: 1**	***P*-1**	**12.2**	**14.4**	**15.7**	**82**	**90**	**71**	**2554**	**136(2)**
1c	**1-butanol**	**2: 1**	***P*-1**	**12**	**14.4**	**15.6**	**98**	**91**	**109**	**2528**	**120(2)**
1d	***tert*-butanol**	**2: 1**	***P*-1**	**12.3**	**14.1**	**16**	**80**	**89**	**69**	**2565**	**113(2)**
1e	**1-pentanol (1-butanol)**	**2: 1**	***P*-1**	**12.4**	**14.3**	**15.7**	**80**	**89**	**79**	**2571**	**125(2)**
1f	**2-pentanol**	**2: 1**	***P*-1**	**12.5**	**14.6**	**15.6**	**81**	**89**	**67**	**2583**	**116(2)**
1g	**ethylene glycol**	**2: 1**	***P*-1**	**12.1**	**14.2**	**15.6**	**98**	**90**	**110**	**2482**	**105(2)**
1h	**urea**	**2: 1**	***P*-1**	**12.2**	**14.2**	**15.8**	**81**	**90**	**70**	**2530**	**294(2)**
1i	**fluoroacetic acid**	**2:1**	***P*-1**	**12.3**	**14.4**	**16.0**	**81**	**89**	**71**	**2639**	**295(2)**
1j	**bromoacetic acid**	**1:1**	***P2₁/c***	**15.1**	**12.6**	**16.3**		**115.2**		**2798**	**93(2)**
1k	**propanoic acid**	**1: 1**	***P2₁/c***	**15.1**	**12.3**	**16.4**		**115**		**2763**	**121(2)**
1l	**lactic acid**	**1: 1**	***P2₁/c***	**15.2**	**12.6**	**16.2**		**114**		**2855**	**294(2)**
1m	**p-methylbenzyl-hydroperoxide**	**1: 1**	***P2₁/c***	**16**	**12.7**	**15.2**		**98**		**3053**	**93(2)**
1n	**ethanoic acid - water**	**1: 1: 1**	***Pbca***	**12.2**	**15.9**	**28.6**				**5548**	**295(2)**
2	**trifluoroacetic acid**	**1 : 3**	***P*-1**	**8.51**	**14.09**	**15.95**	**115**	**101**	**96**	**1658**	**103(2)**
3	**maleic acid**	**2: 4**	***P*-1**	**9.14**	**11.09**	**34.04**	**85**	**86**	**66**	**3131**	**93(2)**
4	**oxalic acid**	**1: 2**	***P*-1**	**5.5**	**12.1**	**20.6**	**94**	**95**	**96**	**1348**	**93(2)**

Table 1. summary of the basic crystallographic data of the associates of **1**.

A kézirat jelenlegi váza:

Crystal Engineering of the Drotaverin Salt Associates

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1. Abstract

Drotaverin hydrochloride salt is a long known anti-spasmolitic drug with pronounced tendency of forming solvent inclusions. 18 New crystal structures were produced from this salt to further exploring and to understanding this property. The studies reveal a robust host molecule and a fairly consistent way of inclusion formation from the anionic salt bridges to proton-donor guests. However, these experiments led to unexpected results in several cases. Recrystallization from an aged p-xylene solvent a decomposition product of p-xylene - peroxide crystallized forming a 1:1 salt: guest inclusion. In an other instance perusal of salicylic acid as cocrystallization partner formation of solvent - free drotaverin salt was observed via epitaxial crystal growth. An oxalic acid recrystallization revealed an anion-metathesis reaction. 1 more RELEVANT sentence

2. Introduction

The cocrystal and in general association formation of active pharmaceutical ingredients (API) (and polymorphs) of medicinal drugs appears to be an important area of pharmaceutical research[1-13] giving rise for various crystal engineering studies[14-20]. Many of the supramolecular interactions observable in the crystalline state may determine some of the macroscopic, of physico - chemical properties such as of stability, of solubility, among others, under physiological conditions. Thus design of cocrystals became an important and developing area for desirable properties[21-24] using the crystal engineering approach for modulating the physical-chemical properties of the API. *(17) Guidance for Industry: Regulatory Classification of Pharmaceutical Co-crystals; Food and Drug Administration: Silver Spring, MD, December 2011.*

The hydrochloride salt of drotaverin (1-(3,4-Diethoxybenzyl)-6,7-diethoxy-3,4-dihydroisoquinolinium chloride) is a well - known anti - spasmolitic compound and is marketed under the trade name No-Spa® in Hungary (Fig. 1.). Formation of crystalline drotaverin salt associates were reported earlier for several solvents and in one case for a cocrystal [25-26]. Chemists were aware that it readily forms inclusions with a number of solvents, some many of them being undesirable in a pharmacological preparation.
To understand the reasons of this phenomena as well as the good opportunity of a crystal engineering exercise a more systematic search for new crystal forms was initiated. Exploring the solvent space makes also sense in that obtaining cocrystal forms from solution may be hampered efficiently by solvent competition. Thus selection of solvents which either do not form clathrates or only rather labile ones may be an advantage at

cocrystal formation. Thus solvents that do not crystallize with the targeted drug were also sought.

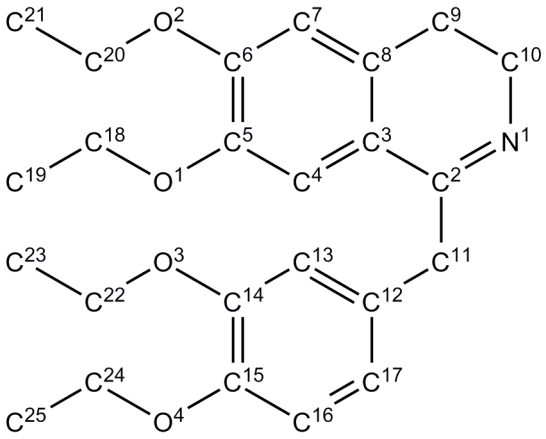

Fig. 1. Drotaverin base scheme

3. Experimental Section

All solvents were commercially available (by Sigma Aldrich, Alfa Aesar, etc.). Simple crystallisation techniques were resorted by reason of easy repeat and it open the way for a larger size repeat for the industry as well. 250 g No-Spa was a gift from the late Dr Hermecz (Sanofi Aventis-Chinoin).

Table 1

Table 2[27,28]

*(Crystallizations of the associate forms of **1**)*

1 (1.6 g; 3.69 mmol) and salicylic acid (0.53 g, 3.8 mmol, 1.03 eq.) were mixed and dissolved in water (20 ml) in room temperature (at 21°C). The solubility was improved by heating (85 °C). The solution was cooled down slowly (about 2-3 hours). After an hour small colourless crystals appeared.

1a (**1**: *n*-propanol 2:1), **1** (20 mg, 0.0461 mmol) was dissolved partially in *n*-propanol solvent (0.5 mL), complete solubilisation took place at 50°C. Solution was cooled to room temperatures and diethyl ether (5-10 ml) was added to the closed system with vapour diffusion method. One or two days later yellow crystals appeared in the ampoule.

1b (**1**: *i*-propanol 2:1), **1** (20 mg, 0.0461 mmol) was dissolved partially in *i*-propanol (1.0 mL), complete solubilisation took place at 50°C. Solution was cooled to room temperatures and a few hours later yellow crystals appeared in the ampoule.

1c (**1**: *n*-butanol 2:1), **1** (20 mg, 0.0461 mmol) was dissolved partially in *n*-butanol (0.5 mL), Otherwise procedures at **1a** was followed.

1d (**1**: *tert*-butanol 2:1), **1** (32 mg, 0.0737 mmol) was dissolved partially in *tert*-butanol (2 mL). The temperature oscillated between 40 and 50°C. In the oscillation method gives better crystals in the neck of the ampoule than the slow cooling method. The colours of crystals were yellow.

1e (**1**: 1-pentanol 2:1), **1** (30 mg, 0.0691 mmol) was dissolved partially in n-pentanol (1.5 mL). Otherwise procedures at **1a** was followed.

1f (**1**: 2-pentanol 2:1), **1** (20.5 mg, 0.0472 mmol) was dissolved partially in 2-pentanol (2 mL). Otherwise procedures outlined at **1b** was followed.
1g (**1**: ethylene glycol 2:1), **1** (32.3 mg, 0.0744 mmol) was dissolved partially in ethylene-glycol (0.2 mL). Otherwise procedures outlined at **1b** was followed.
1h (**1**: urea 2:1), **1** (39.2 mg, 0,0903 mmol) and urea (5.6 mg, 0.0933 mmol, 1.03 eqv.) were dissolved partially in 1,3-propanediol (0.5 mL). Otherwise procedures outlined at 1**b** was followed.
1i (**1**: fluoroacetic acid 2:1), **1** (20 mg, 0,0461 mmol) was dissolved in two drops trifluoroacetic acid (~10 μL) and in acetone (40 μL). After a few days crystals appeared in the ampoulle.
1j (**1**: bromoacetic acid 1:1), **1** (20 mg, 0,0461 mmol) was dissolved in one spatula bromoacetic acid (~10 mg) and in acetone (200 μL). After a few days crystals appeared in the ampoulle.
1k (**1**: propanoic acid 1:1), **1** (10.6 mg, 0.0244 mmol) was dissolved partially in propanoic acid (2.0 mL). Otherwise procedures outlined at **1b** was followed.
1l (**1**: lactic acid 1:1), **1** (544.4 mg, 1.254 mmol) was dissolved partially in lactic acid (0.5 mL). Otherwise procedures outlined at **1b** was followed.
1m (**1**: 1-(hydroperoxymethyl)-4-methylbenzene 1:1), **1** (21.4 mg, 0.0493 mmol) was dissolved in p-xylene (1.0 mL). Otherwise procedures outlined at **1b** was followed.
2 (**1**: acetylic acid: water 1:1:1), **1** (244 mg, 0.562 mmol) was dissolved in acetylic-acid (1.0 mL). Otherwise procedures outlined at **1b** was followed.
3 (**1**: maleic acid 2:4), **1** (203.9 mg, 0.470 mmol) and maleic acid (475.9 mg, 4.099 mmol, 8.72 eqv.) were dissolved partially in water (1.0 mL). Otherwise procedures outlined at **1b** was followed.
4 (**1**: oxalic acid 1:2), **1** (20.8 mg, 0.0479 mmol) and oxalic acid (5.8 mg, 0.0644 mmol, 1.34 eqv.) were mixed and dissolved in room temperature in butanone (0.5 mL). The solvent evaporated for a few weeks and crystals appeared in the ampoule.
5 (1: trifluoroacetic acid 1:3), **1** (20 mg, 0.0461 mmol) was dissolved in trifluoroacetic acid (~200 μL). After a few days crystals appeared in the brown resin/dense oil.

An alternate way was found to crystallize **1**. **1** (9 mg, 0.0207 mmol) was dissolved in acetone (3.0 mL) Otherwise procedures at **1a** was followed.
Through **1j** crystallisation the chloride anion was exchanged with bromide anion. Bromide anion was not use for crystallisation, the logic explanation is the decomposition of the bromoacetic acid.

Single crystal XRD, general procedures
Intensity data were collected on a Rigaku RAXIS-RAPID diffractometer[29-30] (graphite monochromator, Mo-Kα and Cu-Kα radiaton). Data reductions were made by program using programs CrystalClear[29] and program SORTAV[30].
Numerical[31] or empirical[32] absorption correction was applied to the data. Structures were solved by direct methods[33] (and subsequent difference syntheses) by using programs PLATON[34], WinGX[35] and SIR2008[36-37]. International Table[38] was used to define the order of scattering factors, space groups. Anisotropic full-matrix least-squares refinement[33] on F^2 for all non-hydrogen

atoms. The weighting scheme applied was w = 1/[$\sigma^2(Fo^2)+(aP)^2+bP$] where P = $(Fo^2+2Fc^2)/3$; and a,b were variable parameters through the refining. The electron residual density were observed through the refinement by using programs pxx and weed.
Most of the hydrogen atomic positions were calculated from assumed geometries. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the U(eq) value of the atom they were bonded to.
Programs Xseed[39], WinGX[35] and ISOS[40-41] were used for cell transformation and for isostructurality and cell similarity calculations.
Molecular graphics and cavity calculations were made by using program Platon[34]. Program Mercury[42] was used to check Inter-molecular potentials[43-44]. Hirshfeld surface calculations[45] and fingerprint plots[46] were made by using program CrystalExplorer.
Cambridge Structural Database[47] was used to checking other similar structures by using program CCDC Conquest[48]. Distances, angles and torsion angles of known structures were analysed by using the program Vista part of the program CCDC Conquest.
Further crystallographic measurement details are in the Table 3 or in the supplementary information.
Crystallographic data (excluding structure factors) for the crystal structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC xxyyyz.

Table 3.

4. Result and Discussion

4.1 *The unsolvated pure **1** crystal*

The drotaverin HCl salt **1** crystallized without any guest molecules in only one instance providing the first solvent free crystal structure at all. We found a solvent (water), which did not give solvent crystals with drotaverin and salicylic acid, which do not give cocrystals[49]. In the measured crystal the donor and acceptor sites of the salicylic acid directed outward organise the arrangement of drotaverin molecules at the connecting surfaces[50]. All crystals seems like twins with polarizer (Fig. 2.) This structure has the second largest cell axis from the analysed crystals. The chloride anion has a hydrogen bond toward the protonated nitrogen and chloride anion has six C – H … Cl^- interaction more.

Fig. 2.

4.2. ***The triclinic** crystal forms(**1a - 1i**, **6a**, **6b**)*

7 New alcohol solvated crystals were crystallised with the drotaverinium salt. Additionally the urea co-crystal as well as a monofluoroacetic acid inclusion belongs to this group. General description of such triclinic forms is as follows. In the asymmetric unit, there are always two drotaverin salts and one solvent / guest molecule as well. Thus the general host : guest ratio is 2 : 1, for this line, as first described by Simon *et al.* for the ethanol

and benzene inclusions[25]. The hydrogen bridge motifs are alike in these structures (Fig. 3.). The principal ionic link is between the drotaverinium cations and chloride anions for each formula units. Next one of the two anions binds the protic guest solvent as a strong hydrogen bridge acceptor. The unequal involvement in guest binding might give a clue for the 2:1 stoichiometry and *vice versa*.

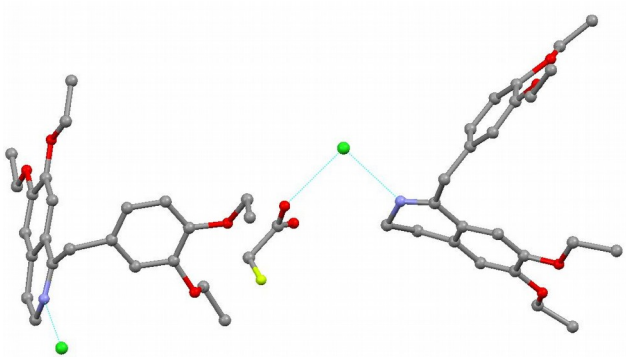

Fig. 3.

These crystals are isostructural, have the same space group *P*-1, and approximately similar cell parameters ranging from/to: a : 12.0 – 12.5 Å, b : 14.1 – 14.6 Å, c : 15.6 – 16.0 Å, angles α : 80 - 82 °, β : 89 - 91 °, γ : 67 - 79 °, and volumes 2480 - 2630 Å^3. Cell similarity and isostructurality calculations quantify these results[40-41] (Fig. 4., Table 4.). The numerical model used involves the position of the host drotaverin and chloride position in the same part of the unit cell without the hydrogen atoms. It is also instructive to examine larger deviations from similarity as indicated for **1c**, **1d**, **1e** and especially for **1f**. These structures have a (3 carbon - 5 carbon) long alcohol guest molecule. The longest racemes 2-pentanol guest molecule (**1f**) needs the largest cavity and stretched out the structure the most. The other cause is the two configurations of the 2-pentanol in the same place that needs more space once more.

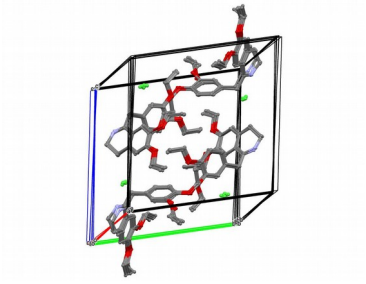

Fig. 4.

Table 4.

4.2. ***The monoclinic*** *crystal forms* **1j**, **1k**, **1l** *and* **1m**

In this branch of inclusions the host : guest ratio changes for 1:1, the unit cell symmetry is monoclinic $P2_1/c$, being three crystal structures **1j - 1l** ~~are~~ isostructural (Tabl. 5.). It is notable, however, that the unit cell volumes accounting for Z=4 formula units with 1:1 ratio are only larger approximately corresponding to two more guests in their respective unit cells, as compared for the basic *P*-1 unit with also four drotaverinium salts

and with only two solvent / guest molecules. Thus packing and density will only moderately vary under these circumstances.

Table 5.

The guests of **1j**-**1l** crystals have lower pK_a value as related to the applied alcohols so the acidity can be also one of the factors causing the t~~he key to understand the~~ change from the *P* -1 space group for the $P2_1/c$ one. The weaker organic acids in this group can not replace ~~compete with~~ HCl ~~molecule~~ as the anionic component yet, ~~for drotaverin molecule~~ but ~~searching~~ they can be in the second best hydrogen acceptor position and break the 2:1 host: guest motifs. However, the organization of the crystal structures in *P* $2_1/c$ space group are ~~very~~ similar ~~with~~ to the *P* -1 structures. The voids are very similar as well (Fig. 5a. and Fig. 5b.).

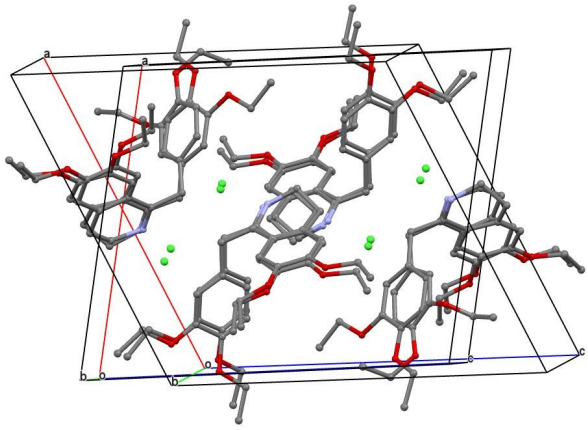

Fig. 5.

1m: Analogous to the benzene inclusion[25] xylene was applied as solvent for the crystal growth. After finding the initial structure model large residual electron density was found close to one of the methyl termini of the supposed *p*-xylene molecule. Based on their geometry these additional peaks were assigned as O atoms. Thus a hydroperoxide auto-oxidation product was assumed, in line with the literature evidences[51-54]. Subsequently new sample was crystallised using the same xylene batch and fresh crystals were used to re-measure pertinent data with the same outcome. Thus one may conclude that **1** selectively includes the hydroperoxy derivative preferring the impurity with a more productive hydrogen bond system over the abundant xylene solvent (Fig. 6.). *p*-Xylene is part of the fraction of benzyl, toluene and the xylene isomers (BTX) in the petrol industry. The separation is a lengthy ~~separation~~ method ~~with/by~~ using distillation, adsorption or crystallization as these molecules are important for chemical industry. *p*-Xylene is the precursor to terephtalic acid and the intermediary of the oxidation between *p*-xylene and therephatlic acid is this peroxide compound. more references at least: [51-54].

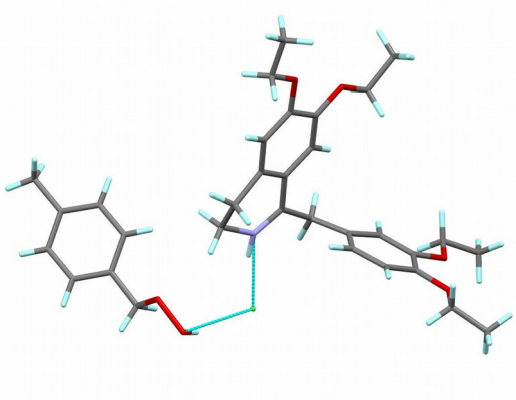

Fig. 6.

Other hydroperoxide containing molecules were searched in the Cambridge Crystallographic Data Centre (CCDC)[47]. More than 140 crystal structures were found containing a hydroperoxide fragment. The O-O distance (1.478(6) Å) of solved structure is within the limit of acceptability (where the mean is 1.462 with 0.001 error Å), and the measured C-O-O angle (108.1(5) °) within margin of error is indistinguishable from the earlier measured crystal data (where the mean is 108.05(12) °). (The distance and angle analysis is in Fig. 7a. and Fig. 7b.). It seems the crystal phase is stopped between the oxidation from *p*-xylene to p-methylbenzoic acid.

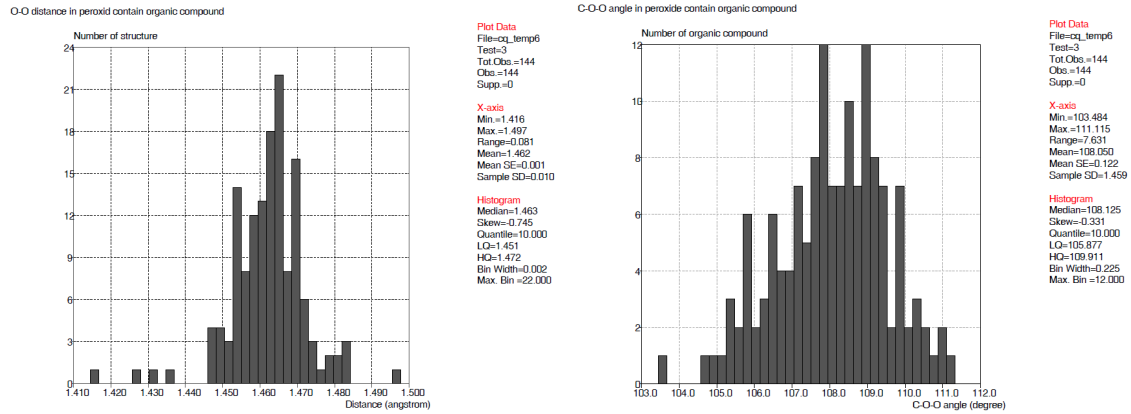

Fig. 7a. and Fig. 7b.

*4.4. **Ternary** and other unusual forms **2**, **3**, **4** and **5***

2: This is the highest symmetry of all the studied forms and has a half occupancy water molecule in the asymmetric unit. **2** is the first obtained crystal structure with water molecule inside and the first three component system. The water is hydrogen bonded to two ether oxygen of ethoxy group. The distances between them and water are 2.978(5) Å (O1_1 … O3_2) and 3.056(6) Å (O4_1 … O3_2). Water molecule has two other weaker ether type interactions to O2_1 (3.37(1) Å) and to O3_1 (3.32(1) Å).

3,**4**,**5***:*After successful crystallisation of drotaverin with maleic acid (pK_a: ~1.9 and 6.1) (**3**) and oxalic acid (pK_a: ~1.3 and 4.3) (**4**) further low pK_a value acids were sought. Trifluoroacetic acid (pK_a: ~0.2) (**5**) seemed and proved to be a strong mono-carboxylic acid, and for monitoring the spread in this pK_a area mono-fluoroacetic acid (pK_a: ~2.6) (**1i**) and bromoacetic acid (pK_a: ~2.86) (**1j**) (Table 5.) were also tested.

Table 6.

3,**4** Cocrystals: These compounds are also related to salt solvates, an extremely well-known class of crystalline solids which also contain ions and neutral molecules (usually water or the solvent from which the crystal was grown), and some researchers now define co-crystals as being composed of two or more normally solid compounds in order to distinguish co-crystals from solvates.

When inorganic ions are present in the co-crystal, the compound can be clearly described as having both ions and neutral species, and Braga et al. have advocated reserving the term ionic co-crystal for these structures. Defining the ions in an ionic co-crystal becomes more complicated if there are multiple possible ionization states for the components, and the stoichiometry implies that some must be neutral and others must be ionized.

Kelley, reference be cited! In this particular case, we succeed replacing the chloride anion by/through salt metathesis into a maleate and oxalate anion[49,55]. In these cocrystal structures are the oxalate, maleate anion and neutral maleic acid oxalic acid form as guest as well. These two structures have the same *P*-1 space group, but they have different ratio in the asymmetric unit (**3**: drotaverin: maleic acid: maleate = 2: 2: 2; **4**: drotaverin: oxalic acid:oxalate = 1: 1: 1). Between the anions, there is a neutral form of guest and these guests make a layer as the anions as well. Compared to the two drotaverin molecules in the asymmetric unit of structure **3** little differences can be found (Fig. 8.). The differences are the place of ethoxy group of the drotaverin molecules. It causes a non-realised inversion centre in the asymmetric unit between them. The median of the atomic position of the two drotaverin give a nearly perfect position for an inversion centre (a axis: 0.491; b axis: 0.499; c axis: 0.250) (Fig. 9a. and Table 7.). Without the differences of the drotaverin molecules, the consequent can be a half-long c axis (Fig. 9b.). Maybe the perfect alternating two different ethoxy groups cause this long c axis and not a half long c axis with a disorder in the ethoxy population.

Fig. 8.
Fig. 9a.
Fig. 9b.
Table 7.

5: We were able to produce a new structure that contains trifluoroacetic acid molecules in the crystal lattice. There is counter trifluoroacetate anion and two trifluoroacetic acid molecules as guest in the asymmetric unit as well. It has drotaverin guest ratio (1: 3) in the *P* -1 space group. This crystal structure has another hydrogen bonds motive as well. In this case, the chloride anion was replaced with trifluoroacetate anion. It has not a general hydrogen bond. Anion and cation layers are separated in the unit cell. The anion has two trifluoroacetic acid neighboroughs. The cation H-N part of the isoquinoline is shielded with hydrogen bonds of the two ether oxygen of the ethoxy group of another drotaverin molecule organised by the symmetry centre (N1 ... O3 distance is 2.835(2) and N1 ... O4 distance is 3.105(2) Å). This O3 oxygen has a π interaction to the phenyl ring of the neighboroughing molecule. The distance between the O3 and the centre of phenyl ring is 3.24(1) Å. The ethyl of O3 ethoxy group turn out from the benzene plane for the isoquinoline N-H --- O bond (Fig 10. and Fig. 11.).

Fig. 10.
Fig. 11.

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4.6. Conformation of drotaverin molecules: Only one fragment has larger conformational changes in the molecule. This point was defined with a torsion angle between the part of isoquinoline and part of benzyl. The

asymmetricity of 3,4-Diethoxybenzyl gives four extreme opportunity for conformation changes to explain the two drotaverin in the asymmetric unit (Scheme 2a. and Scheme 2b.) in two dimension. If the free rotating bond goes around it describe a conic. Nevertheless, all the point of the circle of conic the phenyl group can rotate around.

Fig. 12.

Fig. 13.

All the case the space group of the crystal structures are centrosymmetric. It means the positive or negative signs of torsion angle are irrelevant.

If the asymmetric unit has one drotaverin, it has very similar conformation except the case of **2**, **6***. If the asymmetric unit has two drotaverin, the first has the same conformation as the case of the one drotaverin per asymmetric unit. The second drotaverin in the asymmetric unit has other conformation from 11 cases 10 times, except the case of **3**. It was clear for us: the conformational energy is similar.

The sum of the torsion angle of the two drotaverin in the asymmetric unit has a nearly 202(4) degree in all the 10 case, except **3**. It means the plane of two phenyl group have a nearly reverse placement (Diagram 1.).

Fig. 14.

The ethoxy part of the drotaverin has a higher flexibility. In most of the cases, the terminal ethoxy groups can be found in the plane of the phenyl or of the isoquinoline rings. We could observe a rule of the place of the ethoxy group. In 5 structures the terminal ethoxy group of isoquinoline turns out of the plane of the aromatic ring. The guest is stabilized by the hydrogen bond to the neighborough Cl1 atom, and if the guest shape is good and long enough, the ethoxy groups of isoquinoline turn out of plane for more cavities to the guest (Fig. 10.).

Fig. 15.

4.7. Conformation of drotaverin molecules: There are four diethoxy groups in the benzyl groups as a flexible part in the molecule as well. They have a cavity around them; they have diffuse electron density, larger disorder and ellipsoid in the final x-ray diffraction picture.

4.8. Conformation of drotaverin molecules: On other quiet rigid part on the drotaverin structure is the two CH2 part of the isoquinoline. These parts have a stabilize-like C-H … O interaction with the neighbour drotaverin.

4.9. Intermolecular (drotaverin – drotaverin) interactions: There is a π – π and bifurcal CH-O interactions between the hydroisoquinoline moieties of neighboroughing drotaverins (fig. 11.). It is a frequenty occurring interaction, 30 of 34 drotaverin structures has this kind of intermolecular interactions. Between these two neighbours molecules have an inversion centre. / The connection between these two neighbours molecules is an inversion centre. (The only two different structures are **2**, **3**, **4** and hydrochloride forms (**1**). The hydrochloride structure has only a drift (elcsúszás). / in the case of hydrochloride crystal 1, the interaction is weaker because the two isoquinoline are drift in the crystal.)

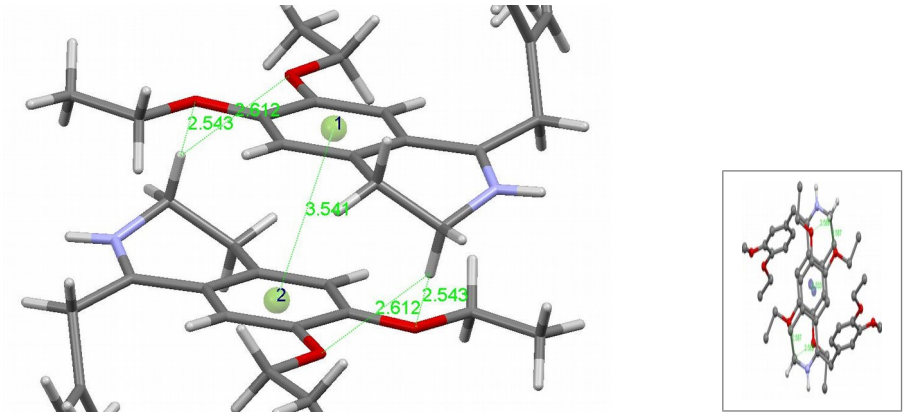
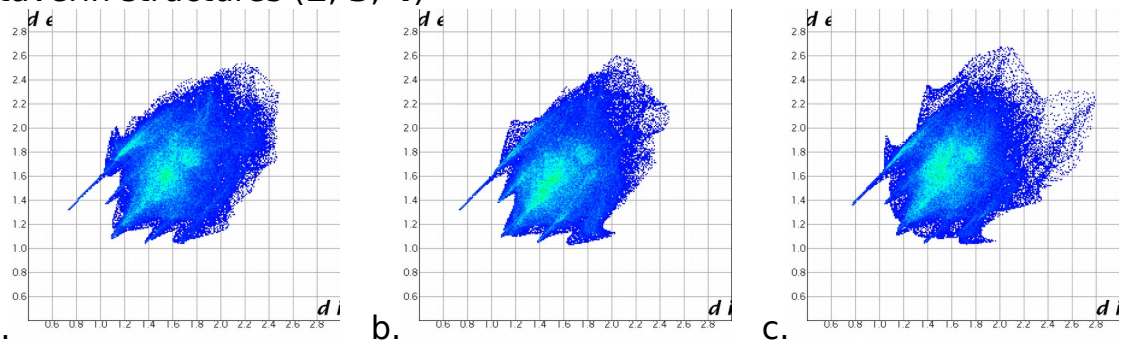


Fig. 16. Bent lementeni

All structures have a similar cohesive interaction between two neighbour drotaverin molecules.

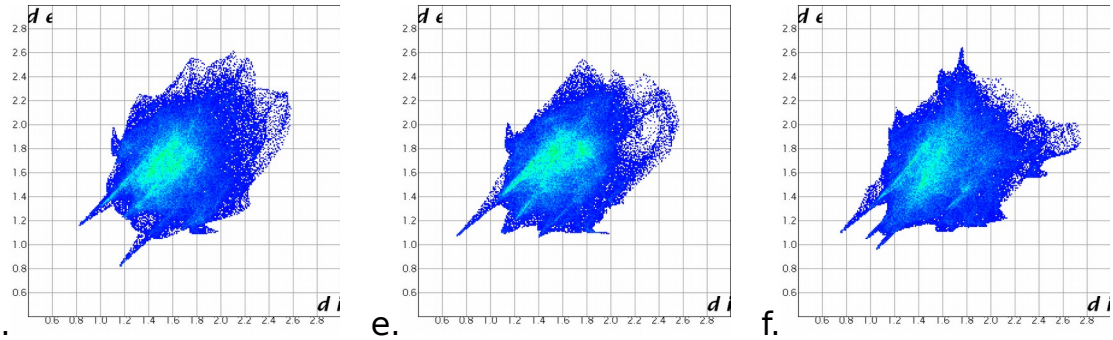
There are some interaction between two 1,2,3,4-tetrahydroisoquinoline part of drotaverin molecules in the part of / around an inversion centre. The π-π interaction between the unsaturated part of isoquinoline and the ether-HC interaction are strong stabilizer / establishment interactions. CH_2 part of molecules was stabilized by ether-HC interaction. We could not find any disorder of the two CH_2 part. In the acetic acid structure is a non-series-egyedi structure in the present case, because the second CH_2 from N had ether-HCH interaction. That reason gave the other conformation for the two CH_2 as the other structures.

By using Hirshfeld surface, we can visualise the full weak interaction network. It seems there are a few differences between the drotaverin molecules. We compared the drotaverins in the *P* -1 (**1d**) structure and a *P* 21/c structure (**1k**) (Fig. 12a.). In other case, the chloride anion free drotaverin structures (**2**, **3**, **4**)



a. b. c.

Fig. 17. Bent lementeni



d. e. f.

Fig. 18. Bent lementeni

5. Conclusion

The investigation of the structural conformational possibility is an important researching area in the case of the drotaverin API molecules. The other important area is the creating of new polymorphs and cocrystals with APIs.

*In the article, we have studied the formation of 18 new crystal forms of drotaverin. In 12 cases, we have made a solvates containing crystal of dr*otaverin. In three cases, we have made cocrystals, and only in one case, we have made the simplest crystal structure only with chloride ion without partners. The guest of cocrystals was easily available for all laboratory and many of the solid partners was harmless for the human body.

The solvates of the alcohols (**1a-1g**), the thiourea (**1h**) and monofluoroacetic acid (**1i**) containing crystal structures are isostructural. The molecules with harder carboxylic acid part give diverse crystal structure. We "successfully" crystallized peroxide as well.

*More than 800,000 organic crystal structures well known in the CCDC. One of every three structures has the spa*ce group *P* 21/*c* and one of every five has *P*-1. The sixth most frequent space group is *Pbca*. Although drotaverin is only one organic molecule the characteristic space groups are observable here: 12 of 18 crystal structures have the same *P*-1 space group (**1a-1i, 2, 3, 4**), 5 have *P*21/*c* space group (**1, 1j- 1m**) and one structure has *Pbca* (**1n**).

Almost all the case has a same contact between the molecules in the crystals. Same C-H … O π-π and CH-π interaction. Only a few harder acidity partners could replace the chloride anion and break these motifs.

The flexible -CH_2- part between the isoquinoline ring and phenyl ring gave two differential conformations that appeared in the two drotaverin in the asymmetric unit except in the structure with maleinic acid (**2**) and *1,2,3,6-tetrahydro-7H-1,3-dimethyl-2,6-dioxopurine-7-acetate monohydrate (**5***).*

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Author Contributions

Experiments were designed by HT and MS and MC and were carried out by HT and MS. Crystallographic data collection were by HT under the supervision of MC. Structure analyses were done by MS and HT under supervision from MC. Data bank and further numeric analyses were by HT. The manuscript was written by HT and MC. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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■

DEDICATION

This paper is dedicated to the memory of Drs. K. Simon and I. Hermecz, pioneers of the structure studies of the drotaverin salts

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3.) Tiokarbamid-alapú organokatalizátorok szerkezetvizsgálata, különös tekintettel a szolvatált és a só formákban előállíthatóakra.

A kristályosítási és tervezési technika kiterjesztéseként hozzávetőleg három tucatnyi organokatalizátor só, illetve neutrális zárványkomplexeit állítottuk elő.

Ezek kimerítő részletezését és fölsorolását mellőzzük, csak egy áttekintő táblázatban mutatjuk az elvégzett munkák egy részét Az itt bemutatott 30 szerkezet csak a kinidin alapú organokatalizátorokat listázza.

krisalyok

	KDKAT térfogatok Kristályosodott		a	b	c	alfa	béta	gamma	térfogat	λ	T (K)	Mérés	R	SHEL
1a	KDK_Hftalát_aceton	P21	8.78	31.51	13.70	90	96.53	90	3764	Cu	108	>08.12.12	7.11	1
1b	KDK_Hftalát_aceton	P21	8.74	31.51	13.68	90	96.78	90	3744	Mo	93	>09.11.11	6.96	0.8
2	KDK_hHftalát_ftálsav	P1	8.60	13.89	19.49	69.79	86.17	84.27	2172	Cu	294	>09.08.08	5.98	0.95
3	KDK_hftalát_H2O	C2	36.97	13.85	8.85	90	90.72	90	4382	Mo	133	10.03.30	8.11	0.87
4	KDK_pirdisav_MeOH_H2O	P212121	18.36	19.07	42.61	90	90	90	14920	Mo	111	10.03.05	10.34	0.88
5	KDK_piridindisav_H2O	P212121	15.53	17.71	27.12	90	90	90	7460	Mo	121	10.03.27	7.27	0.84
6	CuCl2 /100/	P21	9.86	12.92	12.96	90	107.71	90	1573	Cu	110	09.02.24	7.97	0.95
7	CuCl2 /100/	P21	9.86	12.92	12.96	90	107.71	90	1573	Ag	136	09.03.25	7.42	1
8	CuCl2CuBr2 /83:17/	P21	9.93	13.19	13.08	90	108.1	90	1628.15	Ag	294	09.04.15	7.14	0.95
9	CuCl2FeCl2 /63:37/	P21	9.87	13.15	13.08	90	107.86	90	1616	Ag	294	09.07.09	5.24	0.92
10	CuCl2FeCl2 /62:38/	P21	9.86	12.91	12.95	90	107.66	90	1571	Ag	93	09.06.27	3.41	0.8
11	CuBr2FeCl2 /60:40/	P21	9.95	13.24	13.06	90	108.21	90	1634.6	Ag	294	09.07.09	7.25	1
12	CuBr2FeCl2 /34:66/	P21	9.95	13.03	12.98	90	107.94	90	1601	Ag	94	09.07.14	9.14	0.93
13	CuCl2FeCl2 /92:8/	P21	9.91	13.10	13.13	90	107.93	90	1620	Cu	294	09.08.05	3.89	0.8
14	CuCl2FeCl2 /62:38/	P21	9.93	13.14	13.12	90	107.87	90	1629	Mo	294	09.11.03	4.36	0.87
15	CuCl2FeCl2 /63:37/	P21	9.86	12.9	12.97	90	107.54	90	1578	Mo	113(7)	09.11.03	3	0.8
16	CuCl2FeCl2 +Hcl/63:37/	P21	9.87	12.9	12.99	90	107.74	90	1575	Mo	96	09.11.04	6.45	0.88
17	CuCl2FeCl3 /75:25/	P21	9.9	13.11	13.09	90	107.93	90	1617.23	Mo	295	10.08.23	4.1	0.76
18	CuCl2FeCl2 /25:75/	P21	9.9	13.01	13.22	90	107.85	90	1620.18	Mo	295	10.08.25	7.1	0.95
	CuBr2 100%	-	-	-	-	-	-	-	iker	Mo	93			iker
19	KDK_MeOH	P212121	9.41	13.55	24.28	90	90	90	3096	Cu	148	2008.12.10	4.62	0.82
20	KDK_EtOH	P212121	9.70	12.91	25.42	90	90	90	3183	Cu	93	2008.12.03	5.96	0.84
21	KDK_etglik	P212121	9.64	13.75	25.45	90	90	90	3319	Ag	293	2009.06.19	7.8	1.08
22	KDK_nPrOH	P212121	9.88	13.96	25.13	90	90	90	3468	Mo	21	09.02.05	4.47	0.93
23	KDK_iPrOH_H2O	P212121	10.23	11.45	28.9	90	90	90	3385	Mo	93	09.03.01	5.87	0.84
24	KDK_1H2O	R3	26.67	26.67	10.44	90	90	120	6431	Cu	93	11.01.11	3.23	1.01
25	KDK_2H2O	P212121	9.95	13.36	23.78	90	90	90	3158	Mo	294	10.09.26.	7.24	1
26	KDK_EtAc_1H2O	P212121	21.18	24.19	24.44	90	90	90	12521	Mo	93	10.04.30	iker	iker
27	KDK_acac_1H2O	C2221	10.69	24.46	24.94	90	90	90	6518	Cu	294	11.11.26	5.93	1.05
28	KDK_acac_1H2O	C2221	10.55	24.13	24.64	90	90	90	6273	Cu	93	11.01.17	5.4	0.84

Külön említendők a 6-18 sorszám alatt listázott rézkomplexek. Azon túl, hogy ezek egy új, véletlenül fölfedezett reakcióban állíthatók elő, egyben a tudatos kristály növesztés szép példái is.

További *több mint 15*, a témához tartozó kinin, illetve borkősav bázist használó illetve a Takemoto típushoz tartozó katalizátor szerkezetet nem sorolunk föl. Ugyancsak hiányzik a jelenleg is földolgozás alatt álló, szinkrotron adatgyűjtések adatait bemutató adatsor. Ezek némelyike az egyedülálló méréstechnikai lehetőségek mellett is jelentős kémiai és krisztallográfiai problémahalmazt jelent, amelyeknek sem a földolgozása, sem a megoldása messze túl van a szokásos nehézségeken.

E vizsgálatokkal kapcsolatban egy kézirat előrehaladottab állapotban van, továbbiak elkészülte 2014 és 2015 folyamán várható.

4.) “Ad hoc” alkalmazások és szerkezetvizsgálatok

Ezeknek a munkáknak jelentős részét együttműködésben már közöltük, és azok a közleménylistán is szerepelnek.
A projekt során szerzett ismeretek számos kooperatív kutatási alkalmazást is nyertek, például új vegyületek kristályosításával, illetve a mérésre alkalmatlan zárványok újrakristályosítása utáni adatgyűjtéssel.
A széles, szerves és szervetlen vegyületek kristályait is átfogó munkák az utóbbi esetre két különös, magával a Reinecke-só szerkezetével szerzett ismeretekre is támaszkodó publikációt képviselnek.
A *Wulfenit*, a Reinecke-sóhoz hasonlatosan, egy klasszikus ásvány tankönyvi szimmetriától való alaki és belső eltérését igazolta.
Ez a dolgozatunk bekerült az *Acta Crystallographica C* “abszolút szerkezetek” - a terület elsőszámú szakértője, Prof. H.D. Flack válogatta - open access virtuális kötetébe (doi:10.1107/S0108270111015769, Acta Cryst. (2011). C67, i33–i35).
A másik eset egy hasonló, kation – szennyezéses probléma volt, ahol gadolinium aluminum borát kristályok Tb és Eu szennyezésének módosító hatásait derítettük föl.

Egy ipari alkalmazásra is kísérletet végeztünk, részleges eredménnyel. A feladat itt egy addig kristályosíthatatlan és nem egyértelműen jellemzett statin származék kristályosítása, majd szerkezetmeghatározása volt. Az átadott mintából a biológiai körülményekhez hasonló föltételek mellett kristályosodott két szem, pár 10 mikronos méretű kristálykákból választott egyed szerkezetmeghatározása az anyag egy eddig ismeretlen bomlástermékét mutatta.

Ezeknek a vegyületknek jó része kisebb-nagyobb problémát jelentett a "közönséges" szerveskémiai praktikum számára.

Összegezve, a projekt támogatási ideje alatt elvégeztük *mintegy tucatnyi Reinecke-só származék* előállítását és vizsgálatát, *másfél tucatnyi No-SPA® asszociátum* kristály szerkezetfölderítését, több mint *3 tucatnyi organo-katalizátor* kristályosítását és szerkezetvizsgálatát, kiterjesztve ezeket szinkrotron-forrással végzett munkákra is. További legalább *tucatnyi* olyan külső kooperációs munkát folytattunk, ahol az anyaprojekt mellékes nyereségeként lehetővé vált nem rutin problémák földerítése.

Mindezt amellett, hogy a 2012-ben megkezdett, 2014- ben záródó átszervezés előzményei és utóhatásai jelentősen befolyásolták a projekt személyi feltételeit.

Összeségében tehát e projekt lehetővé tette legalább 80 olyan kristály – és molekulaszerkezet földerítését, amelyek jó része a standard megközelítések és kezelésmódok számára elérhetetlen lett volna.