

*Dedicated to the memory of
Professor Ecaterina Ciorănescu-Nenitzescu (1909–2000)*

TWO ISOMERIC BIS-DINITROCARBOXYPHENYL-KRYPTOFIX-22 DERIVATIVES: SYNTHESIS AND CHARACTERISTICS

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Two new isomers of Kryptofix-22-derivatives were synthesized, namely: 4N,13N-bis(2',6'-dinitro-4'-carboxyphenyl)-1,7,10,16-tetraoxa-4,13-diazacyclooctadecane (**3a**) and 4N,13N-bis(2',4'-dinitro-6'-carboxyphenyl)-1,7,10,16-tetraoxa-4,13-diazacyclooctadecane (**3b**). The isomers **3a,b** were characterized by their spectral analysis (¹H-NMR and ¹³C-NMR, UV-VIS, IR), by RP-TLC (for measuring their hydrophobic/hydrophilic character) and by structural theoretical investigation. The *ortho*-carboxy isomer **3b**, is more hydrophobic and absorbs a slightly higher wavelength than the *para*-carboxy isomer **3a**.

INTRODUCTION

The macrocycle **1** (1,7,10,16-tetraoxa-4,13-diazacyclooctadecane) known as *Kryptofix 22* (*K22*) has been used as starting material for the synthesis of *azacoronands* with different properties due to the substituents at the nitrogen atoms of macrocycle.¹⁻⁸ In a previous paper was presented the synthesis and physico-chemical properties of three isomeric pairs of bis-dinitrophenyl-derivatives of K22, with CN, CF₃ groups on the phenyl rings.⁹ Starting from **1** and 4-chloro-3,5-dinitrobenzoic acid (**2a**) or 2-chloro-3,5-dinitrobenzoic acid (**2b**), the present communication presents the synthesis (by a nucleophilic substitution *S_NAr* process) and the

properties of two new isomeric derivatives of K22, with a carboxyl group and two nitro groups, namely: 4N,13N-bis(2',6'-dinitro-4'-carboxyphenyl)-1,7,10,16-tetraoxa-4,13-diazacyclooctadecane (**3a**) and 4N,13N-bis(2',4'-dinitro-6'-carboxyphenyl)-1,7,10,16-tetraoxa-4,13-diazacyclooctadecane (**3b**), with formulas displayed in Table 1. The molecular design of isomers **3a,b** will lead to promising analytical application and starting materials for synthesis. The structures of isomers **3a,b** were confirmed by spectral analyses (¹H-NMR and ¹³C-NMR, IR, VIS). The hydrophobicity/hydrophilicity parameters have been investigated by reverse phase thin-layer chromatography (RP-TLC).

Table 1

The new isomers **3a,b** synthesized starting from compounds **1** and from the chloro isomers **2a,b**, respectively

Compound	Structure
1	
2a,b	<p>a R¹=NO₂; R²=COOH b R¹=COOH; R²=NO₂</p>
3a,b	<p>a R¹=NO₂; R²=COOH b R¹=COOH; R²=NO₂</p>

RESULTS AND DISCUSSION

Synthesis of the two isomers **3a,b**

The synthesis of the isomers **3a,b** was based on a classical process of S_NAr type,¹⁰ starting from **1** and **2a,b** (Table 1). The reactions were performed in acetonitrile, in the presence of Na₂CO₃, at 90°C, for three days. The red colour of the reaction mixture indicated the transient formation of the corresponding Meisenheimer complex (Scheme 1).¹⁰⁻¹⁵ These isomers were obtained in fairly good yields, 60% for **3a** and 75% for **3b**, respectively, and in pure state, as confirmed by TLC and NMR, needing no further purification. The identity of the isomers **3a,b** was confirmed by current methods and spectral techniques (¹H-NMR, ¹³C-NMR and IR).

NMR and IR Spectra of isomers **3a,b**

The ¹H-NMR and ¹³C-NMR data of the isomers **3a,b** (Table 2) confirm: (i) the presence of the carboxydinitrophenyl and macrocyclic moieties; (ii) the isomer structure by the different δ values for H-3'-5' for the COOH group, for carbons C-1',

C-4' and for carbon pairs C-2'-6' (denoted by **boldface** characters in Table 2).

IR spectra (FTIR through ATR-Pike and KBr pellet techniques), prove the structure of isomers **3a,b** by: (i) vibrational frequencies of the ether group (C-O-C) and methylene group (CH₂) of the macrocycle moiety and (ii) vibrational frequencies for aromatic ring and for substituent groups (NO₂, COOH). No significant differences were observed between the two isomers (see experimental part).

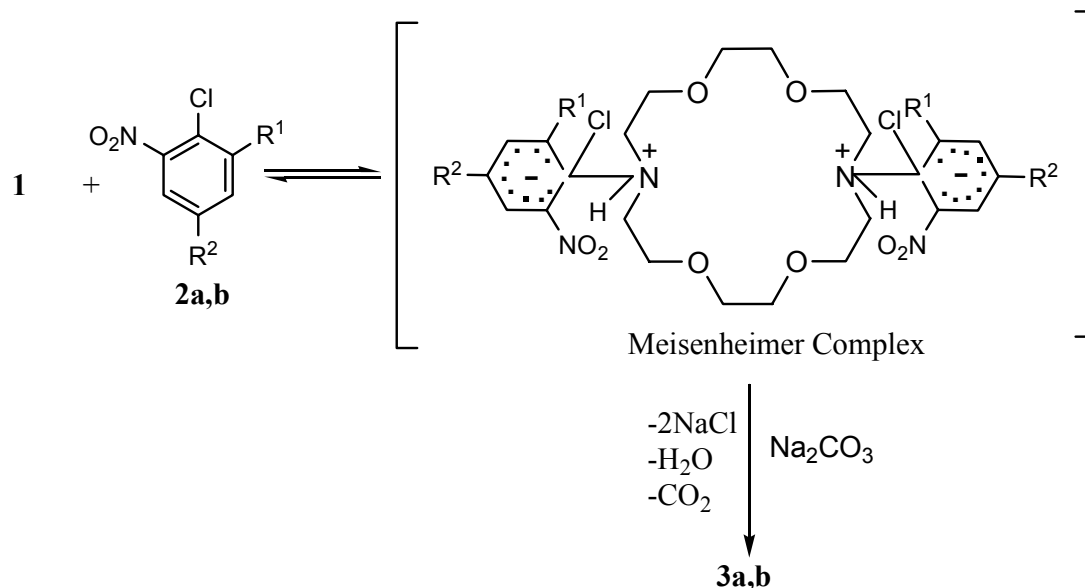
Structure of isomers **3a,b**. Theoretical investigation

Compounds **3a** and **3b** differ by an interchange between a nitro and a carboxy group: **3a** is the *para*-carboxy isomer, and **3b** is the *ortho*-carboxy isomer. Previously it was observed that when the COOH group was interchanged with other substituents (H, CN, CF₃) several properties differed,⁹ and therefore we investigated if there were such differences between the present isomers **3a** and **3b**.

The geometry of these isomers in solid state was studied theoretically using the program

ArgusLab¹⁶ (Fig.1). The following results were obtained: (i) the ground state for **3a,b** is with the two aryl groups *trans* it respect to the macrocycle, but of course the inversion barrier for tertiary

amines is very low and (ii) comparatively, the structure of the *para*-carboxy isomer **3a** is more planar than that of the *ortho*-carboxy isomer **3b**.



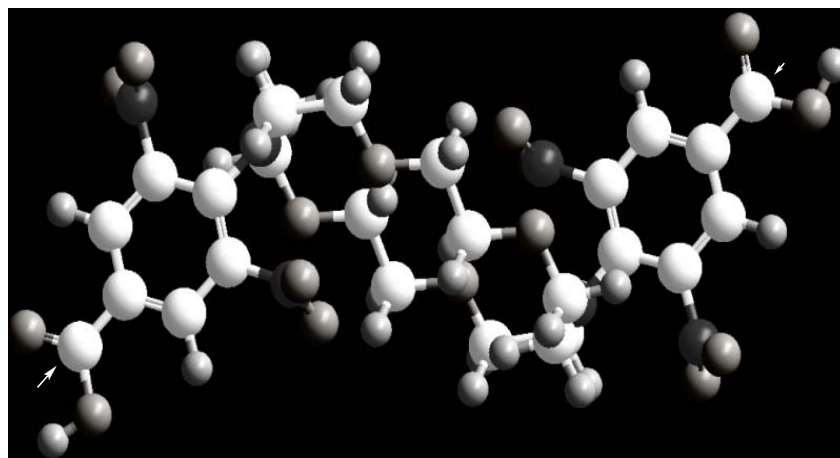
Scheme 1. Synthesis of isomers **3a,b** starting from compounds **1** and **2a,b**.

Table 2

¹H-NMR and ¹³C-NMR data of isomers **3a,b**

Compound	NMR Spectra ^{a,b)} (δ ppm; J Hz)
3a	¹ H-NMR (DMSO-d ₆ , δ ppm, J Hz): 8.46 (s, 2H, H-3'5') ; 3.57 (t, 8H, sist. A ₂ B ₂ , H-2-6-11-15, 5.2); 3.50 (s, 8H, H-8-9-17-18); 3.24 (t, 8H, sist. A ₂ B ₂ , H-3-5-12-14, 5.2). ¹³ C-NMR (DMSO-d ₆ , δ ppm): 164.03 (COO) ; 146.55 (C-2'-6') ; 141.34 (C-1') ; 129.72 (C-3'-5'); 125.01 (C-4') ; 70.12 (C-8-9-17-18); 69.35 (C-2-6-11-15); 52.52 (C-3-5-12-14).
3b	¹ H-NMR (DMSO-d ₆ , δ ppm, J Hz): 8.71 (d, 1H, H-3', 2.7) ; 8.48 (d, 1H, H-5', 2.7) ; 3.60 (t, 8H, sist. A ₂ B ₂ , H-2-6-11-15, 6.2); 3.50 (s, 8H, H-8-9-17-18); 3.36 (t, 8H, sist. A ₂ B ₂ , H-3-5-12-14, 6.2). ¹³ C-NMR (DMSO-d ₆ , δ ppm): 166.34 (COO) ; 148.24 (C-2') ; 144.53 (C-4') ; 139.30 (C-1') ; 130.63 (C-6') ; 129.00 (C-5'); 123.85 (C-3'); 70.12 (C-8-9-17-18); 69.18 (C-2-6-11-15); 52.87 (C-3-5-12-14).

^{a)} At about 295 K and with TMS as internal standard; ^{b)} Numbering of atoms in isomers **3a,b** as shown in Table 1.



3a

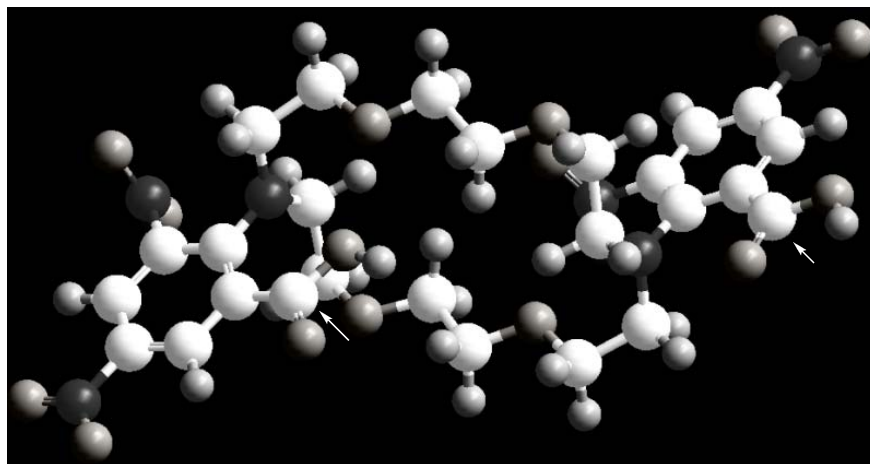
**3b**

Fig. 1 – Optimized geometry for isomers **3a,b** in solid state (white for C, black for N, dark grey for O and light grey for H).

The programs PCGamess¹⁷ and MOPAC,¹⁸ except for torsion energy, did not reveal significant differences between isomers **3a,b** in solid state (Table 3). The somewhat larger torsion energy of the *ortho*-carboxy isomer **3b** than that of the *para*-carboxy isomer **3a** is responsible for the non-planarity of the **3b** isomer, as seen in Fig. 1.

UV-VIS Spectra of isomers **3a,b**

The isomers **3a,b** have different colours in solid state and in solution: **3a** is yellow and **3b** is orange. The isomers **3a,b** dissolve very slightly in water, but relatively easily in organic solvents (dimethylsulfoxide, methanol, acetone, acetic acid), with the highest solubility in dimethylsulfoxide. In

Table 4 are presented the visible electronic spectral data for the isomers **3a,b** using dimethylsulfoxide as solvent. A bathochromic shift (by 12 nm) was observed for the *ortho*-carboxy isomer **3b**, (Table 4) probably due to electronic and steric effects: (i) the electron-withdrawing effect is higher for NO₂ than for COOH; (ii) the different relative positions of the NO₂ groups (next to each other and to the nitrogen of the macrocycle) will lead to differences in the relative weight of quinonoid resonance structures with different planarity requirements and, (ii) the intramolecular hydrogen bond of the *ortho*-carboxy isomer **3b** (Fig. 1) may also play a part in this bathochromic shift.

Table 3

Energies of isomers **3a,b** in solid state (kcal/mol)

Energy	3a	3b
Stretch	6.289	5.927
Bend	50.670	49.408
Stretch-Bend	-2.640	-4.324
Torsion	15.525	18.753
Non-1,4 Van-der-Waals	-21.083	-22.349
1,4 Van-der-Waals	20.228	20.731
Dipole/dipole	6.769	6.513
Total	75.758	74.659

Table 4

UV-VIS spectral data (in dimethylsulfoxide) of isomers **3a,b**

Compound	λ_{\max} (nm)	ϵ (L \times mole ⁻¹ \times cm ⁻¹)
3a	388	4059
3b	400	3664

The qualitative experiments, using solvents with different Dimroth-Reichardt parameters $E_T(30)^{19}$ (Table 5), do not show a correlation of λ_{\max} values with this parameter. However, one may

observe that $\lambda_{\max}(\mathbf{3b}) > \lambda_{\max}(\mathbf{3a})$ for all solvents, and that the difference $\Delta\lambda = \lambda(\mathbf{3b}) - \lambda(\mathbf{3a})$ is larger for polar solvents with hydroxy groups than for less polar solvents.

Table 5

UV-VIS spectra data of isomers **3a,b** in four solvents with different $E_T(30)$ values

Solvent	$E_T(30)^{19}$	λ_{\max} (nm)	
		3a	3b
Acetone	42.2	378	390
Dimethylsulfoxide	45.1	388	400
Acetic acid	51.2	370	379
Methanol	55.5	379	389

Hydrophobicity/hydrophilicity of isomers **3a,b**

The hydrophobicity/hydrophilicity balance of isomers **3a,b** is very important for any future applications, influencing the partition between different phases. The partition coefficient (P) between 1-octanol and water and its logarithm ($\log P$) are the usual parameters for estimating quantitatively these characteristics,²⁰ and they can be measured or computed. This property for isomers **3a,b** was studied experimentally by reversed phase thin-layer chromatography (RP-TLC), using precoated C_{18} -chain layers as stationary phases and acetonitrile-water mixtures in different ratios as mobile phases (Table 6). The

hydrophobicity was appreciated as a result of experimental data depending on R_{M0} values calculated²¹⁻²⁴ with eqs. 1 and 2 (where the molecular hydrophobicity R_{M0} is the R_M value extrapolated to zero concentration of organic component in the acetonitrile-water mixture, and b is the change in the R_M value caused by increasing the concentration (K) of the organic component in the mobile phase). Statistical analysis (Table 6) involved the correlation coefficient (r), the Fisher parameter^{25,26} (F), and the standard deviation²⁷ (SD).

$$R_M = \log(1/R_f - 1) \quad (1)$$

$$R_M = R_{M0} + bK \quad (2)$$

Table 6

R_f values and hydrophobic characteristics (R_{M0} and b) of isomers **3a,b** and RP-TLC results for four mixtures of acetonitrile with water (A-D)^{a,b}

Comp.	R_f				Hydrophobic characteristics		Statistical parameters		
	A	B	C	D	R_{M0}	b	r	F	SD
3a	0.923	0.885	0.833	0.741	0.551	0.020	0.998	551.03	0.019
3b	0.918	0.857	0.787	0.677	0.884	0.024	0.998	756.81	0.019

^a Four determinations on silica gel plates RP-18F_{254S} (Merck), with percent of acetonitrile in the mixture of acetonitrile with water: A = 80, B = 70, C = 60, D = 50%; ^b R_{M0} , b , r , F and SD are defined by the preceding text by eqs. 1 and 2.

The data presented in Table 6 concerning the molecular hydrophobicity R_{M0} of the isomeric pair **3a,b** allowed the following observation: $R_{M0}(\mathbf{3b}) > R_{M0}(\mathbf{3a})$, i. e. the *ortho*-carboxy isomer is more hydrophobic than the *para*-carboxy isomer due probably to intramolecular hydrogen bonding and steric effects, as shown in Fig. 1.

CONCLUSIONS

Starting from **1** (Kriptofix K22) and chloro-derivatives **2a,b** it was easy to obtain, using the classical reaction of S_NAr type, the new isomers **3a** (*para*-carboxy) and **3b** (*ortho*-carboxy). The isomers **3a,b** were characterized by spectral

analyses (^1H - and ^{13}C -NMR, IR, UV-VIS), RP-TLC for hydrophobic/hydrophilic balance, and by structural theoretical investigation. The *ortho*-carboxy isomer **3b** is more hydrophobic and absorbs at a slightly higher wavelength than the isomer **3a** with *para*-carboxyphenyl groups.

EXPERIMENTAL

Starting compounds for synthesis and materials: **1**, silica gel plates 60GF₂₅₄ (for TLC) and silica gel plates RP-18F_{254S} (for RP-TLC) were from Merck; **2a** and **2b** were from Aldrich.

^1H -NMR and ^{13}C -NMR spectra were recorded with a Varian Gemini 300 BB (300 MHz for ^1H and 75 MHz for ^{13}C , respectively); IR spectra were recorded with Bruker Vector 33 for FTIR (ATR-Pike method) and Carl Zeiss Jena (KBr pellets method); VIS spectra were recorded with a UV-VIS Specord M 400 Carl Zeiss Jena.

Synthesis of isomers **3a,b**. Typical procedure.

A mixture of Kryptofix-22 (**1**), solid sodium carbonate and chloro-derivative **2a,b** (molar ratio **1**: Na_2CO_3 : **2a,b** = 1:6:2) was dissolved by stirring in acetonitrile (50 mL for 1g **2a,b** derivative). The mixture was heated under stirring at 90°C for three days. After cooling, the solution was treated with an excess of 1N hydrochloric acid under stirring at room temperature. The resulted suspension was cooled at 5°C (for 24 hrs), the precipitate was filtered off (fritted glass G-3), washed with 1N HCl (three times), then with water (three times) and then it was kept in the desiccator over calcium chloride. The product obtained is pure (TLC analysis, silica gel GF₂₅₄ with methylene chloride: glacial acetic acid 9:1 v/v and NMR spectra).

3a (4*N*,13*N*-bis(2',6'-dinitro-4'-carboxyphenyl)-1,7,10,16-tetraoxa-4,13-diazacyclooctadecane), 60% yield; yellow solid, m. p. 237-238°C; Anal.: Calc.% for $\text{C}_{26}\text{H}_{30}\text{N}_6\text{O}_{16}$: C 45.75; H 4.42; N 12.31; found% C 45.53; H 4.27; N 12.10; for ^1H - and ^{13}C -NMR data see Table 2; IR: a) FTIR (ATR-Pike method), cm^{-1} : 1100 ($\nu_{\text{C-O-C}}$); 1349, 1536 (ν_{NO_2}); 1719 (ν_{CO}); 2875, 2922 (ν_{CH} and ν_{CH_2}); 3500 u (ν_{OH} from COOH); b) KBr pellets, cm^{-1} : 1120 ($\nu_{\text{C-O-C}}$); 1330, 1355 (ν_{NO_2}); 1720 (ν_{CO}); 2950, 3170 (ν_{CH} , ν_{CH_2}); 3550 u (ν_{OH} from COOH); R_f = 0.44 (silica gel GF₂₅₄; methylene chloride: glacial acetic acid 9:1 v/v); for UV-VIS see Table 4; for RP-TLC (hydrophobicity data) see Table 6.

3b (4*N*,13*N*-bis(2',4'-dinitro-6'-carboxyphenyl)-1,7,10,16-tetraoxa-4,13-diazacyclooctadecane), 75% yield; orange solid, m. p. 202-203°C; Anal.: Calc.% for $\text{C}_{26}\text{H}_{30}\text{N}_6\text{O}_{16}$: C 45.75; H 4.42; N 12.31; found% C 45.62; H 4.30; N 12.18; for ^1H - and ^{13}C -NMR data see Table 2; IR: a) FTIR (ATR-Pike method), cm^{-1} : 1100 ($\nu_{\text{C-O-C}}$); 1349, 1533 (ν_{NO_2}); 1729 (ν_{CO}); 2876, 2922 (ν_{CH} and ν_{CH_2}); 3500 u (ν_{OH} from COOH); b) KBr pellets, cm^{-1} : 1120 ($\nu_{\text{C-O-C}}$); 1330, 1360 (ν_{NO_2}); 1720 (ν_{CO}); 2800, 3140 (ν_{CH} , ν_{CH_2}); 3430 u (ν_{OH} from COOH); R_f = 0.20 (silica gel GF₂₅₄; methylene chloride: glacial acetic acid 9:1 v/v); for UV-VIS see Table 4; for RP-TLC (hydrophobicity data) see Table 6.

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