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

Ana Cristina RĂDUŢIU,a Ion BACIU,b Miron T. CĂPROIU,c Constantin DRĂGHICI,c Adrian BETERINGHE,a Maria MAGANU,c Radu SOCOTEANU,a Titus CONSTANTINESCUa* and Alexandru T. BALABANd*

a Roumanian Academy, “Ilie Murgulescu” Institute of Physical Chemistry, Laboratory of Coordinative and Supramolecular Chemistry, Splaiul Independenţei 202, 060021, Romania
b University of Bucharest, Department of Organic Chemistry, Şoseaua Pandurii 90-92, Bucharest, Romania
c Roumanian Academy, “C. D. Nenitzescu” Institute of Organic Chemistry, NMR Department, Splaiul Independenţei 202 B, Bucharest, Romania
d Texas A&M University at Galveston, 5007 Ave. U, Galveston, TX, 77553-1675, USA

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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 SNAr 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).

Corresponding authors: e-mail: titelconstantinescu@yahoo.com or balabana@tamug.edu
Table 1
The new isomers 3a,b synthesized starting from compounds 1 and from the chloro isomers 2a,b, respectively

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Structure 1" /></td>
</tr>
<tr>
<td>2a,b</td>
<td><img src="image" alt="Structure 2a,b" /></td>
</tr>
<tr>
<td>3a,b</td>
<td><img src="image" alt="Structure 3a,b" /></td>
</tr>
</tbody>
</table>

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,\(^1\)\(^6\) starting from 1 and 2a,b (Table 1). The reactions were performed in acetonitrile, in the presence of Na_2CO_3, at 90°C, for three days. The red colour of the reaction mixture indicated the transient formation of the corresponding Meisenheimer complex (Scheme 1).\(^1\)\(^{0-15}\) 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 (\(^1\)H-NMR, \(^{13}\)C-NMR and IR).

NMR and IR Spectra of isomers 3a,b

The \(^1\)H-NMR and \(^{13}\)C-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 \(\delta\) 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 (CH_2) of the macrocycle moiety and (ii) vibrational frequencies for aromatic ring and for substituent groups (NO_2, 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, CF_3) 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
ArgusLab\textsuperscript{16} (Fig. 1). The following results were obtained: (i) the ground state for 3\textsubscript{a,b} is with the two aryl groups \textit{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 \textit{para}-carboxy isomer 3\textsubscript{a} is more planar than that of the \textit{ortho}-carboxy isomer 3\textsubscript{b}.

\begin{center}
\begin{align*}
\text{1} \quad \text{O}_2\text{N} & \quad \text{Cl} \quad \text{R}^1 \\
\text{2a,b} & \quad \text{O}_2\text{N} \quad \text{Cl} \quad \text{R}^1
\end{align*}
\end{center}

\begin{center}
\text{Meisenheimer Complex}
\end{center}

\begin{center}
\begin{align*}
-2\text{NaCl} & \quad -\text{H}_2\text{O} & \quad -\text{CO}_2 \\
& \quad \text{Na}_2\text{CO}_3
\end{align*}
\end{center}

\begin{center}
\text{Scheme 1. Synthesis of isomers 3\textsubscript{a,b} starting from compounds 1 and 2a,b.}
\end{center}

\textbf{Table 2}

\begin{center}
\begin{tabular}{|c|l|}
\hline
\textbf{Compound} & \textbf{NMR Spectra}\textsuperscript{a,b)} (\(\delta\) ppm; \(J\) Hz) \\
\hline
\textbf{3a} & \textit{H-NMR} (DMSO-d\textsubscript{6}, \(\delta\) ppm, \(J\) Hz): 8.46 (s, 2H, H-3',5'); 3.57 (t, 8H, sist. A\textsubscript{2}B\textsubscript{2}, H-2-6-11-15, 5.2); 3.50 (s, 8H, H-8-9-17-18); 3.24 (t, 8H, sist. A\textsubscript{2}B\textsubscript{2}, H-3-5-12-14, 5.2). \\
& \textit{C-NMR} (DMSO-d\textsubscript{6}, \(\delta\) 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). \\
\hline
\textbf{3b} & \textit{H-NMR} (DMSO-d\textsubscript{6}, \(\delta\) 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\textsubscript{2}B\textsubscript{2}, H-2-6-11-15, 6.2); 3.50 (s, 8H, H-8-9-17-18); 3.36 (t, 8H, sist. A\textsubscript{2}B\textsubscript{2}, H-3-5-12-14, 6.2). \\
& \textit{C-NMR} (DMSO-d\textsubscript{6}, \(\delta\) 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). \\
\hline
\end{tabular}
\end{center}

\textsuperscript{a)} At about 295 K and with TMS as internal standard; \textsuperscript{b)} Numbering of atoms in isomers 3\textsubscript{a,b} as shown in Table 1.
The programs PCGamess\(^{17}\) 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 \textit{ortho}-carboxy isomer \(3b\) than that of the \textit{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 bathocromic shift (by 12 nm) was observed for the \textit{ortho}-carboxy isomer \(3b\), (Table 4) probably due to electronic and steric effects: (i) the electron-withdrawing effect is higher for NO\(_2\) than for COOH; (ii) the different relative positions of the NO\(_2\) 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 \textit{ortho}-carboxy isomer \(3b\) (Fig. 1) may also play a part in this bathocromic shift.

![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).](image)
The qualitative experiments, using solvents with different Dimroth-Reichardt parameters $E_T(30)^{19}$ (Table 5), do not show a correlation of $\lambda_{\text{max}}$ values with this parameter. However, one may observe that $\lambda_{\text{max}}(3b) > \lambda_{\text{max}}(3a)$ for all solvents, and that the difference $\Delta \lambda = \lambda(3b) - \lambda(3a)$ 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

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$E_T(30)^{19}$</th>
<th>$\lambda_{\text{max}}$ (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>Acetone</td>
<td>42.2</td>
</tr>
<tr>
<td>Dimethylsulfoxide</td>
<td>45.1</td>
<td>388</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>51.2</td>
<td>370</td>
</tr>
<tr>
<td>Methanol</td>
<td>55.5</td>
<td>379</td>
</tr>
</tbody>
</table>

**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, 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 calculated 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 ($F$), and the standard deviation ($SD$).

$$R_M = \log\left(\frac{1}{R_f}-1\right) \quad (1)$$
$$R_M = R_{M0} + bK \quad (2)$$

**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)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>$R_f$</th>
<th>Hydrophobic characteristics</th>
<th>Statistical parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>$3a$</td>
<td>0.923</td>
<td>0.885</td>
<td>0.833</td>
</tr>
<tr>
<td>$3b$</td>
<td>0.918</td>
<td>0.857</td>
<td>0.787</td>
</tr>
</tbody>
</table>

* Four determinations on silica gel plates RP-18F$_{254}$ (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: $R_{M0}(3b) > R_{M0}(3a)$, i.e. the ortho–carboxy isomer is more hydrophobic than the para–carboxy isomer due probably ho intramolecular hydrogen bonding and steric effects, as shown in Fig. 1.

**CONCLUSIONS**

Starting from 1 (Kryptofix K22) and chloro-derivatives $2a,b$ it was easy to obtain, using the classical reaction of S$_2$Ar type, the new isomers $3a$ ($para$-carboxy) and $3b$ ($ortho$-carboxy). The isomers $3a,b$ were characterized by spectral
analyses (H- and 13C-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 and 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-18F254S (for RP-TLC) were from Merck; 2a and 2b were from Aldrich.

H-NMR and 13C-NMR spectra were recorded with a Varian Gemini 300 BB (300 MHz for 1H and 75 MHz for 13C, respectively); IR spectra were recorded with Brucker Vector 33 for FTIR (ATR-Pike method) and Carl Zeiss Jena (KBr pellets method); VIS spectra were recorded with a UV-VIS Spectord 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: Na2CO3: 2a,b = 1:6:2) was dissolved by stirring in acetone/tirle (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; for UV-VIS see Table 4; for RP-TLC (hydrophobicity data) see Table 6.

**REFERENCES**