3,5-Dinitro-*N*-(4'-benzo-15-crown-5)-benzamide Derivatives. Synthesis and Properties

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Abstract

Four new derivatives of benzo-15-crown-5 (**4** – **7**) were synthesized from 4'-amino-benzo-15-crown-5 (**3**) and 2-chloro-3,5-dinitrobenzoic acid (**1**) or its chloride (**2**): the amide **4** resulted from **2** and **3**, and the arylamine **5** from **1** and **3**. A compound with two crown ether cavities (**6**) resulted from **3** and **4**. Nucleophilic substitution with methoxyamine converted **4** into **7**. Structures were confirmed by ^{1}H-NMR, ^{13}C-NMR, and IR-ATR spectroscopy. Geometries of the the new compounds are presented. The hydrophobic character of **5**, **6**, and **7** was measured by reverse-phase thin-layer chromatography (RP-TLC). The yellow-orange compound **7,** in the solid state and in acetonitrile solution becomes deeper-colored in the presence of solid lithium or sodium hydroxides. Stability constants of the corresponding supramolecular complexes **8** (from **7** with LiOH or NaOH) were determined. The supramolecular complex **8** (with Na^{+}) was also obtained in solid state and was characterized by ^{1}NMR, IR-ATR and UV-vis spectroscopy.

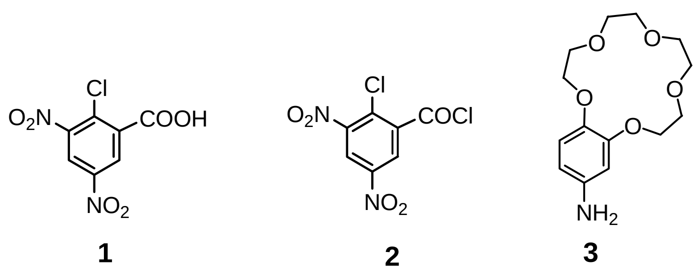
Keywords: 3,5-Dinitro-*N*-(4'-benzo-15-crown-5)-benzamide derivatives, Molecular geometry, Hydrophobic/hydrophilic balance, RP-TLC, Supramolecular complex

Introduction

Macrocyclic crown ethers have numerous applications due to their ionophoric properties.[1-3] An interesting molecular design, which was adopted in the present communication, involves a

benzo-crown moiety connected to a "core" moiety possessing reactive groups that can be used for anchoring the desired functions to the crown ether scaffold. An example is provided by derivatives possessing such ionophoric properties.[4-9] Moreover,` cytostatic activities were found for pyridine-dicarboxamides derived from benzo-15-crown-5.[10]

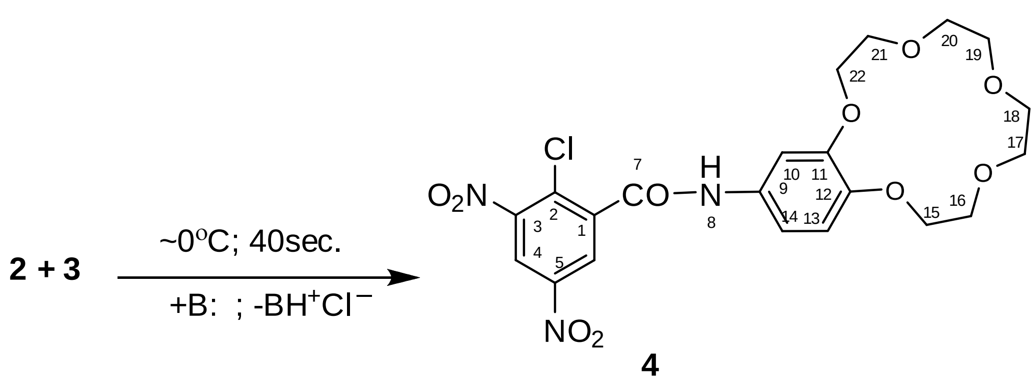
Starting from the commercially available 2-chloro-3,5-dinitrobenzoic acid (**1**) one can easily prepare 2-chloro-3,5-dinitrobenzoyl chloride (**2**).[11] The chlorine atom attached to the carbonyl group in **2** is more reactive (in S_N2 reactions),[12] and then the chlorine atom attached to the dinitrophenyl group can be substituted by an S_NAr process.[12,14] In the present paper we report the synthesis and properties of four new derivatives of benzo-15-crown-5 (**4** – **7**) with a dinitrophenyl core moiety to which we attached one or two crown ether groups having the amine scaffold 4'-aminobenzo-15-crown-5 (**3**), also commercially available. We will show the special ionophoric properties of the methoxyamino derivative **7** that is acidic enough to afford salts with sodium or lithium hydroxides, in which the alkali cation forms a complex with the crown ether.



Results and Discussion

Synthesis of compounds 4 - 7

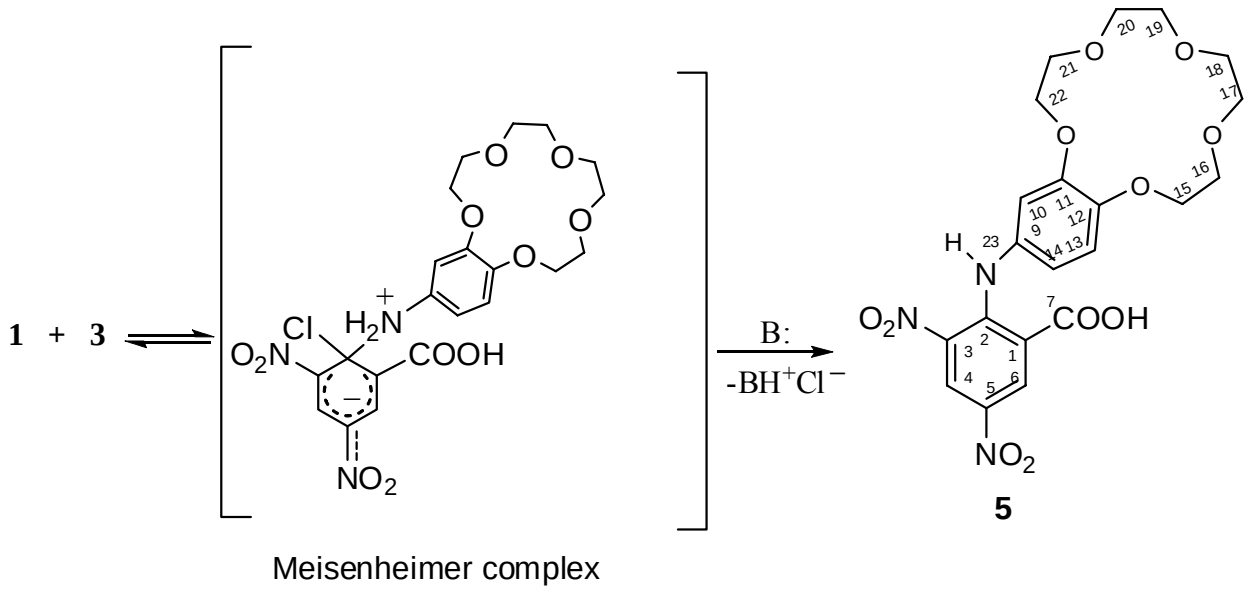
By means of a low temperature and short reaction time, compound **4** was obtained by combining compounds **2** and **3** and stopping the reaction by acidifying the reaction mixture (Scheme 1).



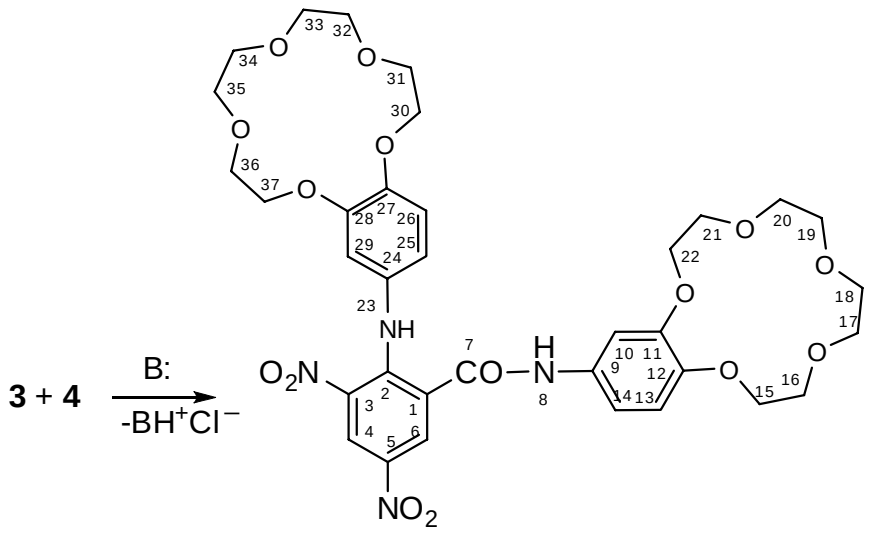
Scheme 1. Synthesis of compound **4**.

Compounds **5**, **6**, and **7** were prepared by S_NAr processes which involve the formation of Meisenheimer adducts, exemplified for **5**.[11,13,14] For compound **6**, a slightly better yield was achieved when the two steps were combined into a single one, starting from **2** and an excess of **3** in the presence of a tertiary amine.

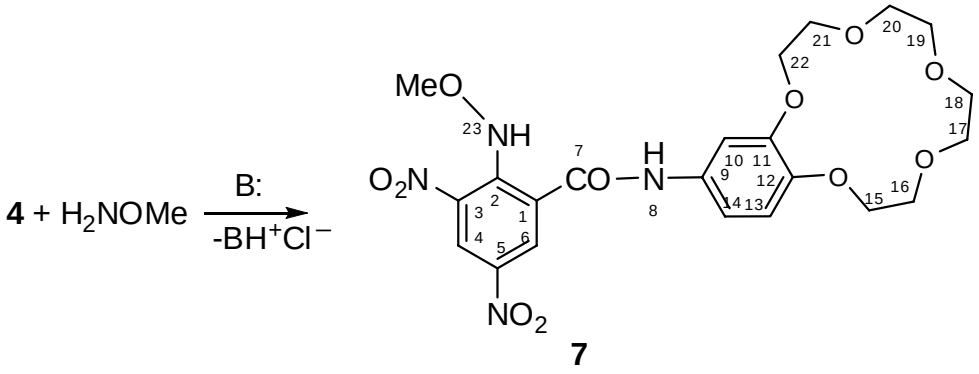
To facilitate NMR assignments, atoms are numbered in Schemes 1–4 consistently rather than systematically.



Scheme 2. Synthesis of compound **5**.



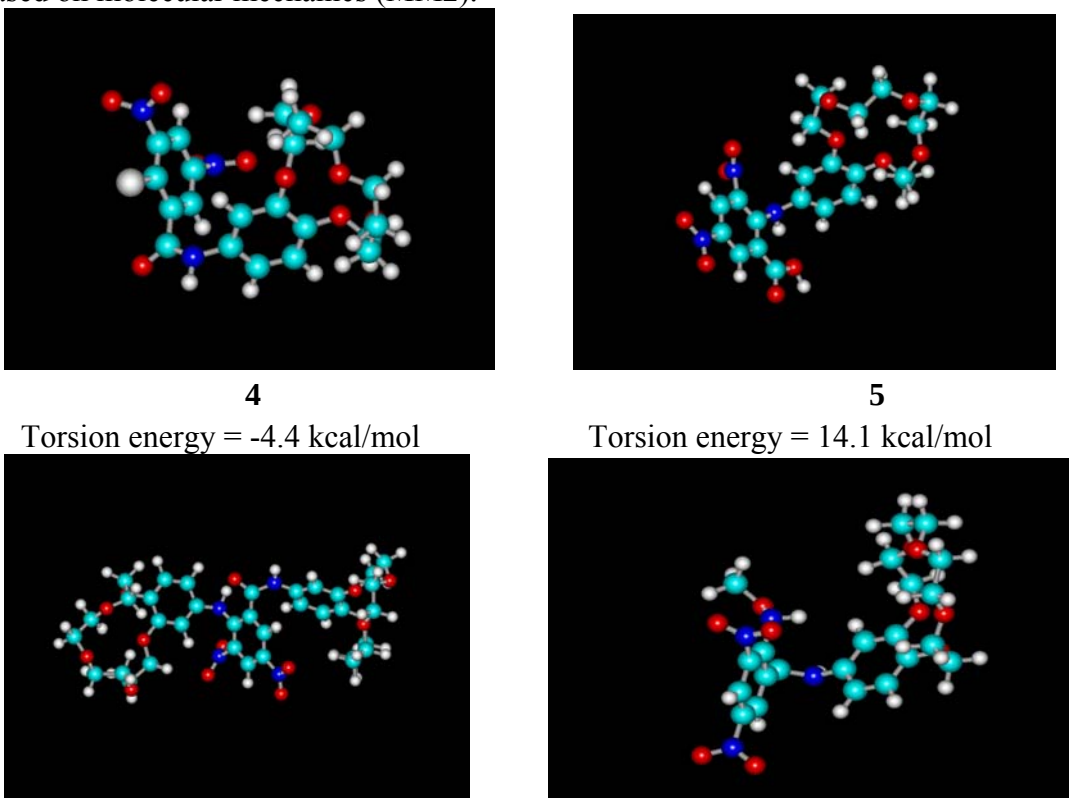
Scheme 3. Synthesis of compound **6**.



Scheme 4. Synthesis of compound **7**.

The new compounds **4** – **7** were purified by preparative TLC, and their purity was attested by single spots in TLC. For compound **6** that has two crown ether moieties, the ^{1}H-NMR and ^{13}C-NMR spectra were repeated at a higher temperature (55 ºC) but no significant differences were observed relatively to room temperature NMR. Fourier transform infrared (FTIR) spectra were performed in the attenuated total reflection (ATR) mode.

Optimized geometries for compounds **4**-7 were calculated using the ArgusLab program (Fig. 1) based on molecular mechanics (MM2).[15-17]



4
Torsion energy = -4.4 kcal/mol

5
Torsion energy = 14.1 kcal/mol

6
Torsion energy = 40.8 kcal/mol

7
Torsion energy = 9.6 kcal/mol

Figure 1. Optimized geometry by the ArgusLab program [15,17] for compounds **4–7**.

Optimized geometries of compounds **4** – **7** (Fig. 1) lead to the following conclusions: (i) energies are influenced by the torsion energies which are lowest for **4** and highest for **6**; (ii) compound **4** followed by **7** presents the closest proximity between the dinitrophenyl and crown rings; (iii) the carboxy group of **5** has the closest vicinity to the macrocyclic ring. In solution one expects various mobile conformations for **4** and **7** having two moieties connected by the CO–NH bridge group, for **5** with two moieties connected by the NH bridge, and for **6** with three cyclic blocks connected by both types of bridges.

Hydrophobicity of compounds 5–7

The hydrohobic/hydrophilic properties determine how easily substances are able to cross biomembranes. One can estimate the octanol-water partition factor (logP) by computational methods using the molecular fragment approach,[18] but experimental determinations of hydrophobicity by means of reversed-phase thin-layer chromatography (RP-TLC) are more trustworthy for obtaining the molecular hydrophobicity (R_{M0}) due to their ease and precision.[19-24] In Table 1 we present experimental results for R_f values in ethanol-water mixtures of various concentrations and the calculated molecular hydrophobicity (R_{M0}) according to equations (1) and (2),[19-24] as well as the calculated values for the *log P* parameter.[18] The determinations included compounds **1**, **3** – **7**.

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

$$R_M = R_{M0} + b\mathrm{K} \quad (2)$$

The molecular hydrophobicity, R_{M0}, is the R_M value extrapolated to zero concentration of organic component in the alcohol-water mixture; 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 involved the correlation coefficient (R), the Fisher parameter (F), and the standard deviation (SD).[25]

Table 1. Experimental hydrophobicity (R_{M0} and b) and calculated *log P* [18] for compounds **1**, **3**–**7**

No	Experimental and calculated data [a]									Calc. *log P*
	R_f in aqueous ethanol, conc.(v/v)				R_{M0}	b	Statistical parameters			
	A	B	C	D			R	F	SD	
1	0.937	0.919	0.909	0.900	–0.582	–0.007	–0.975	39.89	0.025	-0.76
3	0.387	0.370	0.354	0.343	0.424	–0.002	–0.995	238.1	0.004	3.10
4	0.806	0.677	0.580	0.406	1.417	–0.025	–0.995	220.1	0.038	4.64
5	0.953	0.959	0.924	0.871	–0.031	–0.017	–0.905	9.081	0.127	1.68
6	0.406	0.424	0.459	0.578	–0.569	0.009	0.922	11.38	0.064	1.06
7	0.838	0.806	0.709	0.578	0.812	–0.019	–0.983	57.39	0.057	3.40

[a]Five determinations on silica gel RP-18F_{254} (Merck), with per cent of ethanol in the mixture ethanol–water: A = 80%, B = 70%, C = 60%, D = 50%; R_{M0} = molecular hydrophobicity (eq. 2).

Analysis of Table 1 reveals satisfactory values of statistical indicators, and points to the following order of hydrophobicity (R_{M0}): **4**>**7**>**3**>**5**>**6**>**1**. On correlating the calculated log *P* values with the experimentally-based molecular hydrophobicity R_{M0} for all compounds possessing benzo-15-crown-5 moieties (**3-7**), a statistically significant correlation with R^2 = 0.976 was found (Fig. 2).

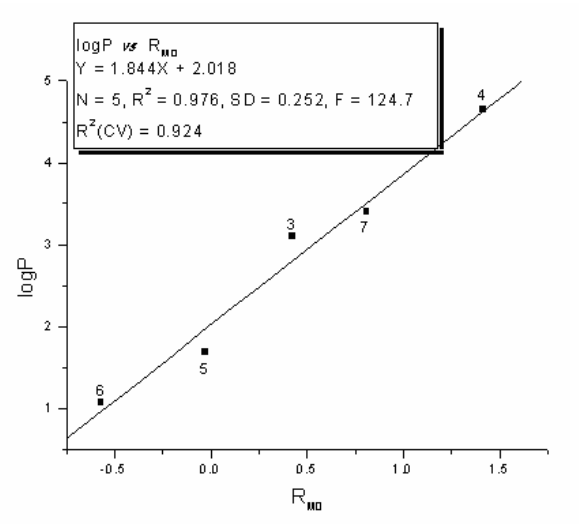


Figure 2. R_{M0} *vs* log *P* for compounds **3**–**7**.

Electronic absorption spectra of compounds 5–7

In crystalline state, compounds **5–7** are yellow-orange and their solutions are colored in yellow-orange (**6**) or red-orange (**5, 7**).

We selected acetonitrile as a water-miscible solvent for investigating the complexing abilities of the new compounds, and therefore we report in Table 2 the electronic absorption data in this solvent. The bathochromic effect of the 1-amino nitrogen attached to the 2-carbonyl-4,6-dinitrophenyl group decreases in the order **7>6**>**5**.

Table 2. UV-Vis values (λ_{max} and ε) in acetonitrile for compounds **5–7**

Compound	λ_{max} (nm)	$\varepsilon\times10^{-4}$ (L·mol^{-1}·cm^{-1})
5	404	1.478
6	386	1.390
7	344	1.536
8	439	1.600

An interesting behavior of **7** was observed in various solvents. The λ_{max} value reported in Table 2 refers to HCl-containing acetonitrile. Similarly, in methylene chloriide or dioxane,compound **7** presents only one absorption band at 340 or 344 nm, respectively. In

acetonitrile without HCl, in methanol, or dimethylsulfoxide, partial ionization of **7** leads to the appearance of a shoulder around 430 nm ($\varepsilon = 1.410$ L·mol^{-1}·cm^{-1}).

Using the MOPAC-2007 program,[16] the net atomic charge on the aminic nitrogen atom (NAC_N) was calculated, and by assuming an inverse correlation with the experimental longest-wavelength absorption band, the calculated λ_{max} values according to eq. (3) present a reasonable correlation with the experimental λ_{max} values (Table 3). Because only three points are involved, statistical data are mainly for orientation.

$$\lambda_{max}(\text{calc.}) = -332.9NAC_N + 872.1 \quad (3)$$

$N = 3$, $R^2 = 0.945$, $SD = 3.187$, $F = 17.37$, $R^2(CV) = 0.891$, $Q = 0.305$

Table 3. Net atomic charges on the amino nitrogen (NAC_N), experimental and calculated λ_{max} (with eq. 3, in nm) for compounds **5–7** in acetonitrile

Compound	NAC_N	λ_{max} (nm)		
		Experimental	Calculated	Residual
5	1.427	404	397.1	6.9
6	1.438	386	393.4	-7.4
7	1.588	344	343.5	0.5

A more complete explanation for the λ_{max} presented in Table 2 would require an elaborate quantum-chemical calculation of HOMO-LUMO values.

Reaction of compounds 5–7 with alkali metal hydroxides

Only compound **7** presented an interesting behavior in the presence of LiOH and NaOH. We had designed compound **7** so that in addition to the benzo-15-crown-5 moiety, it possesses the N-methoxypolynitroaniline group,[26-30] endowing it with hydrophobicity, acidity, and ability to react *via* redox processes with 2,2-diphenyl-1-picrylhydrazyl yielding intensely-colored blue-violet betainic compounds, which will be reported separately. Understandably, the MeO-NH-Ar proton is more acidic than an Ar-NH-Ar' proton, when Ar is a 2,4-dinitro-6-benzamido group.

On treatment with increasing amounts of powdered LiOH or NaOH, compound **7** undergoes gradual changes in its electronic absorption spectrum illustrated in Fig. 3, which reveals isosbestic points (388 nm for LiOH in Fig. 3A, and 386 nm for NaOH in Fig. 3B).

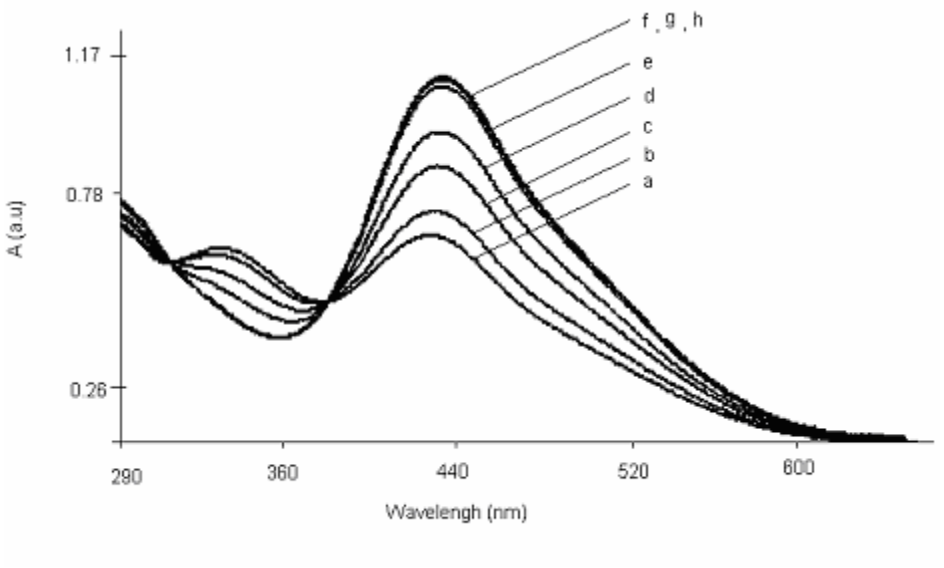


Figure 3A. Electronic absorption spectra of **7** (concentration 2.95×10^{-5} M) on adding successively 0.5 mg of powdered LiOH, starting with curve (a).

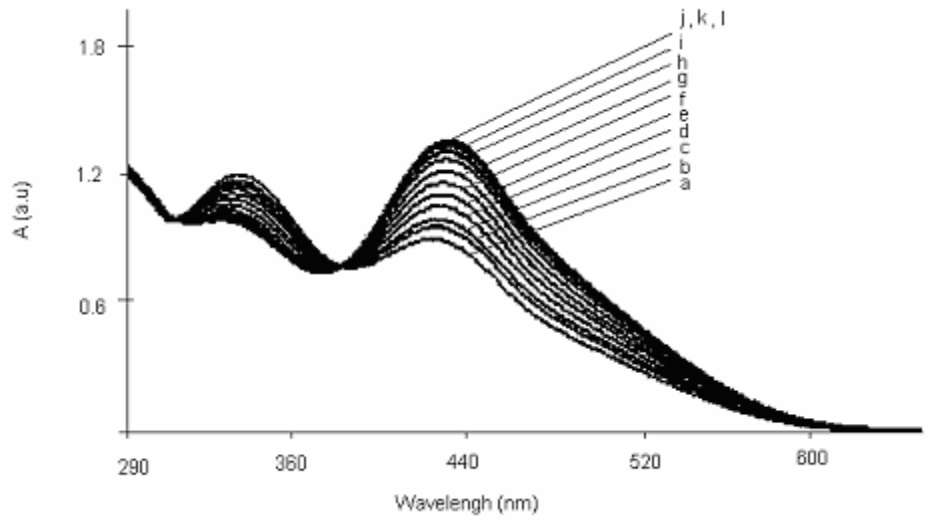
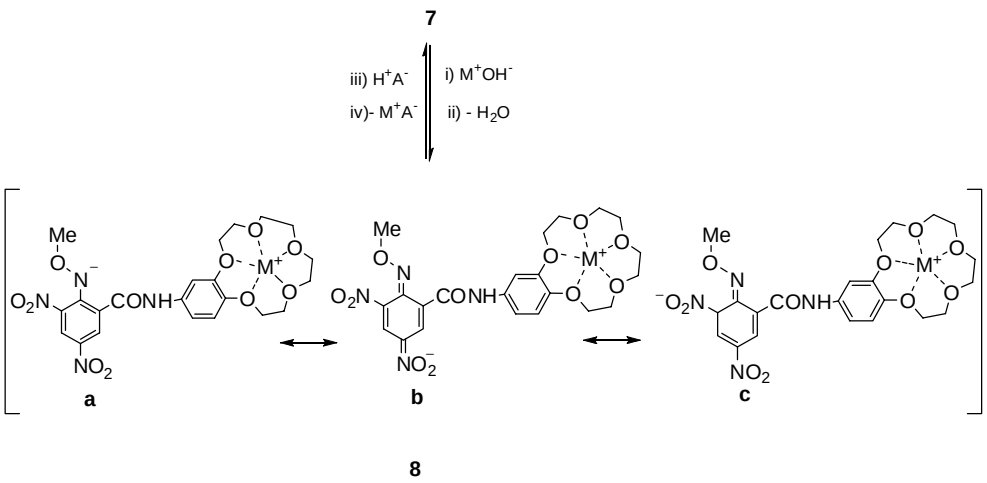


Figure 3B. Electronic absorption spectra of **7** (concentration 4.21×10^{-5} M) on adding successively 0.5 mg of powdered NaOH, starting with curve (a).

On applying Job's method,[31-33] it was found that the alkali metal cation and the anion of compound **7** form equimolar complexes **8** in which the ratio **7 :** M^+ is 1:1 for M^+= Li^+, Na^+. Visually, on acidifying complexes **8,** the red-orange color becomes less intense due to the reformation of compounds **7** (Scheme 5), which were identified by TLC.



Scheme 5. Reversible reaction of **7** with M^+OH^- (where $M^+ = Li^+$ or Na^+) leading to the reversible formation of complex **8**.

By using the Benesi-Hildebrand method,[34] stability constants (log K_S) were determined in acetonitrile at room temperature for the two supramolecular complexes **8**. Both have similar stability constants, as seen from Table 4, resulting from five determinations at room temperature. The order K_S (Na^+) > K_S(Li^+) agrees with the closeness between the diameters of the cation and of the macrocyclic cavity, believed to be similar to that of 15-crown-5, namely 1.7 – 2.2 Å.[35,36]

Table 4. Stability constants of supramolecular complexes **8** formed by **7** and M^+OH^-

Cation (M^+)	Cation diameter (Å) [35]	Complexing ratio	log K_S
Li^+	1.36	1:1	3.59 (± 0.04)
Na^+	1.94	1:1	3.85 (± 0.02)

The supramolecular complex **8** (M^+= Na^+) was also obtained in solid state and was characterized by UV-Vis (λ_{max}=439 nm, ε=1.6 x10^{-4} L·mol^{-1}·cm^{-1}), ^{1}H-NMR and IR-ATR spectra (see experimental part). This solid complex **8** in acetonitrile with hydrochloric acid led back to **7** as proved by UV-Vis and TLC experiments.

A similar treatment of **7** with solid potassium hydroxide did not result quantitatively in complexation probably because the cavity of the 15-crown-5 macrocycle is smaller than the diameter of the potassium cation (2.66 Å).[35,36] This cation can be properly accommodated by the larger cavity of the 18-crown-6 ethers.[2,3,35,36]

On shaking a dichloromethane solution of **7** with aqueous LiOH or NaOH, the organic layer becomes red, and the aqueous solution stays colorless, proving that the alkali cations are extracted into the organic layer. The process becomes reversible on acidification, as indicated by spectrophotometry. A similar complexation takes place between dichloromethane solutions of **7** which become red on treatment with aqueous sodium chloride, nitrite, or nitrate.

On shaking the orange-red solution of **7** in methylene chloride with an aqueous solution of a basic amino acid (lysine, ornithine or arginine), the organic layer loses its color and the aqueous layer becomes red, evidencing the extraction of **7** as an anion into the aqueous layer which now contains also the conjugate acid of lysine, ornithine or arginine. An aqueous solution of bovine serum albumin or chitosane becomes red on treatment with a solution of **7** in methanol, due to a similar protolytic equilibrium. In the absence of water, on treating a dichloromethane solution of **7** with these solid amino acids (lysine, ornithine or arginine), an intense red color appears; if, after filtering this solution, low-boiling petroleum ether is added (fraction with NBP 30-60° C), brick-red crystals are formed, leaving a colorless solution. Details about these processes will be reported separately.

Conclusions

Using as starting materials the carboxylic acid **1**, the acid chloride **2**, and the amine **3**, compounds **4**–**7** were synthesized by nucleophilic substitutions of chlorine atoms. Experimental determinations of the molecular hydrophobicity R_{M0} by means of RP-TLC and theoretical calculations of log *P* for compounds **5**–**7** showed that the hydrophobicity decreases in the order **7**>**5**>**6**. Electronic absorption spectra indicated the formation of a supramolecular complex **8** of compound **7** with an equimolar amount of LiOH or NaOH. The stability constants K_S of these complexes in acetonitrile at room temperature are similar (log $K_S Li^+$= 3.59, log $K_S Na^+$= 3.85); these complexes are also formed in a biphasic dichloromethane/water system, and their formation becomes reverted on acidification. The supramolecular complex **8** (M^+= Na^+) was also obtained in solid state. With solid LiOH, NaOH, or basic amino acids (either solid or in aqueous solution) dichloromethane solutions of **7** also yield molecular complexes. The fact that **7** has an acidic proton and presents ionophoric and chromogenic properties recommends it as an analytical and bioanalytical reagent.

Experimental Section

General Procedures. Commercial materials were used: compounds **1** (Aldrich), **2**,[11] **3** (Fluka), O-methylhydroxylamine hydrochloride (Aldrich), $LiClO_4$ (Pierce Erochimie), $NaClO_4 \cdot H_2O$ (Aldrich), silica gel GF 254 and silica gel plates RP-18 F_{254S} for RP-TLC (Merck). ^{1}H- and ^{13}C-NMR spectra were recorded with a Varian Gemini 300 BB spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively). IR spectra were recorded with a Bruker FTIR Spectrophotometer Vertex 70, using the attenuated total reflection (ATR) technique. UV-Vis spectra were recorded with UV-Vis Analitik Jena SPECORD 200. Melting points were determined in open capillary with Electrothermal's IA 9000Series of digital melting point instruments.

Syntheses and Spectra. General Procedure

Compound 4. The amine **3** and the acid chloride **2** (molar ratio **3**:**2** = 2.2) were combined,[11] observing strict temperature and duration conditions. One gram of **3** was dissolved in 15 mL of water-acetone mixture 3:2 v/v (15 mL/ g of **3**), and the solution was cooled in an ice-salt bath. Under external cooling and rapid stirring a pre-cooled solution of **2** in acetone (5 mL/g of **2**) was added rapidly in one portion. After 40-45 seconds, 50 mL of cooled 1M hydrochloric acid were added in one portion for stopping the reaction. Stirring was continued under cooling for complete precipitation. The precipitate was filtered off (glass filter G3) and washed on the filter with 1M hydrochloric acid and then with water. The solid product was dissolved in methylene chloride and the solution was stirred for one hour with a 10% solution of sodium hydrogen carbonate. The organic layer was washed twice with a saturated solution of sodium chloride in 1M hydrochloric acid, then after drying with anhydrous sodium sulfate the solvent was removed under reduced pressure. The crude **4** was purified by preparative TLC (silica gel GF 254, methylene chloride/methanol 9:1 v/v, twice). The yellow zone was then extracted (Soxhlet), with a methylene chloride/methanol mixture 8:2 v/v, and the solvent mixture was removed under vacuum, affording the pure **4** which gives a single spot by TLC (methylene chloride/methanol mixture 9:1 v/v, twice).

2-Chloro-3,5-dinitro-N-(4'-benzo-15-crown-5)-benzamide (**4**). 55% yield, yellow solid, m. p. 177-178 °C; Anal.: Calcd. for $C_{21}H_{22}ClN_3O_{10}$: C 49.28; H 4.33; N 8.21; found C 49.20; H 4.28; N 8.15%; ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T = 35ºC): 8.60 (bs, 2H, H-4-6); 7.32 (bs, 1H, H-14); 7.03 (bs, 1H, H-13); 6.78 (bs, 1H, H-10); 4.10 (bs, 4H, H-15-22); 3.87 (bs, 4H, H-16-21); 3.73 (bs, 8H, H-17-18-19-20); ^{13}C-NMR ($CDCl_3$, δ ppm): 160.87 (C-7); 148.89 (Cq); 146.89 (Cq); 146.84 (Cq); 146.00 (Cq); 140.41 (Cq); 130.93 (Cq); 130.43 (Cq); 126.58 (CH-14); 121.00 (CH-13); 114.57 (CH-4 or CH-6); 113.58 (CH-6 or CH-4); 107.79 (CH-10); 70.85 (CH_2); 70.34 (CH_2); 69.44 (CH_2); 69.15 (CH_2).

Compound 5. An equimolar mixture of **1** and **3** in acetonitrile (20 mL/1 g mixture) was stirred for 2 hrs at 90° C in the presence of an excess of powdered sodium carbonate. An orange-red precipitate was formed. To this mixture 1M hydrochloric acid was added till a pH = 2 was reached. After cooling the mixture to 5 °C, the precipitate was filtered off on a G3 glass filter and washed thrice on the filter with 1M hydrochloric acid. Then this first batch of crude **5** was dried on $CaCl_2$ in a desiccator. A second batch was obtained by extracting the filtrate with dichloromethane, separating the organic phase and evaporating the solvent under reduced pressure for another crop of **5**. The combined crude **5** was purified by preparative TLC (silica gel GF 254, methylene chloride/methanol 9:1 v/v, twice). The orange-red zone was then extracted (Soxhlet) with a methylene chloride/methanol mixture 8:2 v/v and the solvent mixture was removed under vacuum, affording the pure **5** which gives a single spot by TLC (silica gel GF 254, methylene chloride/methanol mixture 9:1 v/v, twice).

3,5-Dinitro-N-(4'-benzo-15-crown-5)-anthranylic acid (5). 65% yield, yellow crystals, m. p. 144-146° C; Anal.: Calcd. for $C_{21}H_{23}N_3O_{11}$: C 51.12; H 4.70; N 8.52; found C 51.09; H 4.78; N

8.45%. IR (ATR), cm^{-1}: 1512 (NO_2), 1637 (CO), 2878, 2880 (CH, CH_2), 3390, 3574 (COOH, NH); ^{1}H-NMR (dmso-d_6, δ ppm, *J* Hz): 10.87 (s, 1H, H-23); 8.81 (d, 1H, H-4, 1.7); 8.74 (d, 1H, H-6, 1.7); 6.87 (d, 1H, H-13, 8.5); 6.77 (d, 1H, H-10, 2.0); 6.66 (dd, 1H, H-14, 2.0, 8.5); 4.04-3.92 (m, 4H, H-15-22); 3.74 (bs, 4H, H-16-21); 3.61 (s, 8H, H-17-18-19-20); ^{13}C-NMR (dmso-d_6, δ ppm): 167.68 (C-7); 148.69 (Cq); 146.49 (Cq); 144.58 (Cq); 136.82 (Cq); 135.18 (Cq); 132.59 (Cq); 130.81 (C-4); 127.11 (C-6); 117.96 (Cq-1); 113.71 (C-13);113.36 (C-14); 106.96 (C-10); 70.48 (C-17 or C-20); 70.43 (C-20 or C-17); 69.72 (C-18 or C-19); 69.65 (C-19 or C-18); 68.79 (C-16 or C-21); 68.59 (C-21 or C-16); 68.55 (C-15 or C-22); 68.27 (C-22 or C-15).

Compound 6. Variant A. A solution of compounds **3** and **4** (molar ratio **3**:**4 =** 2.5) in a mixture (9:1 v/v) of methylene chloride and methanol (10 mL solvent mixture for one gram of mixture **3**+**4**) was stirred at room temperature for four days in a closed container in the presence of triethylamine (5 mL for one gram of mixture **3** +**4**). Then 10 mL of methylene chloride were added to the red reaction mixture, and this mixture was extracted twice with 1M hydrochloric acid. The organic phase was dried on anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude **6** was purified by preparative TLC (silica gel GF 254, toluene/methylene chloride/methanol 4:5:1 v/v, twice). The yellow zone was then extracted (Soxhlet) with a methylene chloride/methanol mixture 8:2 v/v and the solvent mixture was removed under vacuum, affording the pure **6** which gave a single spot by TLC (silica gel GF 254, toluene/dichloromethane/methanol mixture 4:5:1 v/v, three times).

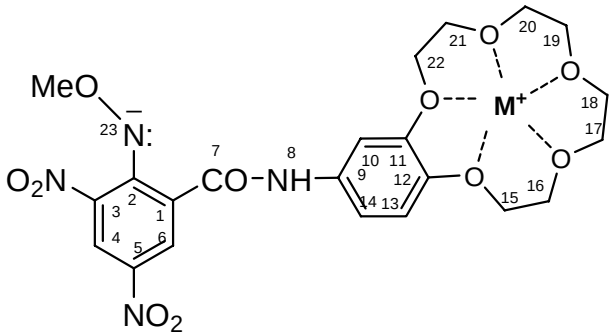
Variant B. A mixture of compounds **2** and **3** (molar ratio **3**:**2**=2.5) in methylene chloride (15 mL for one gram of mixture **2**+**3**), in the presence of triethylamine (5 mL for one gram of mixture **2** +**3**) was stirred for five days at room temperature in a closed container. Then the work-up was as in the previous variant.

3,5-Dinitro-N,N'-bis-(4'-benzo-15-crown-5)-anthranylamide (**6**).Yield 40% for variant A and 53% for variant B, brick-red crystals, m. p. 147-149° C; Anal.: Calcd. for $C_{35}H_{42}N_4O_{15}$: C 55.41; H 5.58; N 7.38; found C 55.38; H 5.60; N 7.30%; IR (ATR), cm^{-1}: 1507 (NO_2), 1653 (CO), 2865, 2922 (CH, CH_2), 3300, 3530 (CONH, NH). Two temperatures were used for ^{1}H-NMR spectra for checking whether geometry changes may occur, but at the higher temperature only slightly better resolution was achieved; ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 10.27 (s, 1H, H-23); 8.91 (d, 1H, H-4, 2.6); 8.67 (bs, 1H, H-8, deuterable); 8.56 (d, 1H, H-6, 2.6); 6.95 (bs, 1H, H-10); 6.79 (d, 1H, H-14, 8.5); 6.72 (d, 1H, H-13, 8.5); 6.58-6.65 (m, 3H, H-25-26-29); 4.10-3.68 (m, 32H, H_2C-O); ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz, T=55° C): 10.13 (s, 1H, H-23); 8.95 (d, 1H, H-4, 2.6); 8.88 (d, 1H, H-6, 2.6); 8.20 (bs, 1H, H-8, deuterable); 6.96 (bs, 1H, H-10); 6.77 (dd, 1H, H-14, 1.6, 8.7); 6.73 (d, 1H, H-13, 8.7); 6.68 (d, 1H, H-26, 8.6); 6.64 (d, 1H, H-29); 6.62 (dd, 1H, H-25, 2.1, 8.6); 4.10-3.68 (m, 32H, H_2C-O); ^{13}C-NMR ($CDCl_3$, δ ppm): 163.29 (C-7); 149.59 (Cq); 148.89 (Cq); 147.62 (Cq); 146.28 (Cq); 143.92 (Cq); 136.48 (Cq); 135.58 (Cq); 132.49 (Cq); 130.85 (Cq); 125.93 (Cq);130.00(CH); 125.15 (CH); 114.73 (CH); 114.26 (CH); 113.98 (CH); 113.35 (CH); 108.64 (CH); 107.37 (CH); 70.82 (CH_2); 70.29 (CH_2); 69.34 (CH_2); 69.22 (CH_2); 68.76 (CH_2); 68.69 (CH_2);

Compound 7. A solution of compound **4** (1 g) in 10 mL of warm ethanol was mixed with a solution of an excess (molar ratio **4**:$H_3CO–NH_3^+$ $Cl^–$ = 4.5) of O-methylhydroxylamine hydrochloride in a mixture of dioxane–water (3:2 v:v) (5 mL for one gram of mixture) with sufficient sodium carbonate for neutralizing all the hydrochloric acid. The solution was kept at pH around 8 by adding Na_2CO_3, and was stirred at 50 °C for six days. To the resulted red solution an equal volume of dichloromethane was added, and the mixture was extracted with a saturated solution of sodium chloride in 1M hydrochloric acid. The orange-colored organic phase was dried on Na_2SO_4 and the solvent was removed under reduced pressure. The crude **7** was purified by preparative TLC (silica gel GF 254, toluene/dichloromethane/methanol mixture 4:5:1 v/v, twice). The orange-red zone was then extracted (Soxhlet) with a methylene chloride/methanol mixture 8:2 v/v and the solvent mixture was removed under vacuum, affording the pure **5** which gave a single spot by TLC (silica gel GF 254, toluene/dichloromethane/methanol mixture 4:5:1 v/v, twice).

2-Methoxyamino-3,5-dinitro-N-(4'-benzo-15-crown-5)-benzamide (**7**). 51% yield, red-brown crystals, m. p. 76-77°C; Anal.: Calcd. for $C_{22}H_{26}N_4O_{11}$: C 50.57; H 5.02; N 10.72; found C 50.50; H 4.95; N 10.68% IR (ATR), cm^{-1}: 1511 (NO_2), 1604 (CO), 2870, 2925, 3100 (CH, CH_2, CH_3), 3281 (CONH); ^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 10.54 (s, 1H, NH probably for NH-O-CH_3); 8.83 (d, 2.0, 1H, H-4);8.40 (d, 2.0, 1H, H-6); 7.20 (s, 1H, NH probably amidic); 7.16 (d, 2.0, 1H, H-10); 7.02 (dd, 8.3, 2.0, 1H, H-14); 6.79 (d, 8.3, 1H, H-13); 4.10 (m, 4H, H-15, H-22); 3.88 (m, 4H, H-16, H-21); 3.77 (s, 3H, OCH_3); 3.74 (s, 8H, H-17-18-19-20); ^{13}C-NMR ($CDCl_3$, δ ppm, *J* Hz): 163.93 (C-7); 149.13 (Cq-2); 146.17 (Cq-12); 137.46 (Cq-5); 131.98 (Cq-3); 131.38 (Cq-9); 128.90 (C-6); 124.96 (Cq-1); 123.62 (C-4); 114.24 (C-13); 112.90 (C-13); 112.90 (C-14); 107.05 (C-10); 70.78 (C-15, C-22); 70.30 (C-16,C-21); 70.24 (C-16,C-21); 69.41 (CH_2); 69.29 (CH_2); 69.20 (CH_2); 68.78 (CH_2); 64.32 (OCH_3).

Supramolecular complex 8 (M^+= Na^+). Compound **7** was treated with a methanol solution of sodium hydroxide (molar ratio NaOH:**7** = 1.1); 3 mL of methanol was used for one gram of mixture NaOH + **7**. The clear red-colored solution was diluted with an equal volume of dichloromethane and then petroleum ether was gradually added, scratching the walls of the contained with a glass rod for initiating crystallization. After 20 minutes at 5 ºC, the red-brown precipitate (**8**) was filtered off from the colorless solution. Compound **8** was dried over anhydrous $CaCl_2$ in a vacuum desiccator. Yield 95%. By titration with HCl 1N and UV-Vis spectrophotometry it was confirmed that **7** was re-obtained and that the stoichiometry of the complex was **7**:Na^+ = 1:1.



8 (M^+=Na^+)

^{1}H-NMR (acetone-d6, δ ppm, *J* Hz): 12.02 (s, 1H, H-8); 8.68 (d, 1H, H-4, 2.8); 8.22 (d, 1H, H-6, 2.8); 7.78 (d, 1H, H-10, 2.1); 7.13 (dd, 1H, H-14, 8.8, 2.1); 7.02 (d, 1H, H-13, 8.8); 4.28 (m, 2H, H-22); 4.23 (m, 2H, H-15); 3.98 (m, 2H, H-21); 3.94 (m, 2H, H-16); 3.81 (s, 3H, OCH_3); 3.78 (m, 8H, H-17-18-19-20). The ethylene group protons H-15, H16 and H-21, H-22 appear as A_2B_2 systems; FT-IR (ATR in solid state, ν cm^{-1}): 2939; 2877; 2819; 1643; 1614; 1559; 1504; 1461; 1424; 1361; 1307; 1229; 1113; 1043; 994; 967; 944; 920; 850; 822; 745; 719; 675; 591; 543; 494; 461.

References

1. Lehn, J. M. *Supramolecular Chemistry. Concepts and Perspectives*, VCH, Weinheim, 1995.
2. Vögtle, F. *Supramolecular Chemistry*, Wiley, Chichester, 1991.
3. Weber, E.; Toner, J. L.; Goldberg, I.; Vögtle, F.; Laideer, D. A.; Stoddart, J. F.; Bartsch, R. A.; Liotta, C. L. *Crown Ethers and Analogs*, Wiley, Chichester, 1989.
4. Takagi, M.; Nakamura, H.; Ueno, K. *Anal. Lett*. **1977**, *10*, 1115.
5. Bubnis, B. P.; Steger, J. L.; Wu., Y. P.; Meyers, L. A.; Pacey, G. E. *Anal. Chim. Acta,* **1982**, *139*, 307.
6. Bubnis, B. P.; Pacey, G. E. *Talanta*, **1984**, *31*, 1149.
7. Fux, P.; Lagrange, J.; Lagrange, P. *Anal. Chem.*, **1984**, *56*, 160.
8. Dubonosov, A. D.; Minkin, V. I.; Bren, V. A.; Popova, L. L.; Rybalkin, V. P.; Shepelenko, E. N.; Tkalina, N. N.; Tsukanov, A. V. *ARKIVOC* **2003**, (*xiii)*, 12.
9. Fedorova, O. A.; Andryukhina, E. N.; Mashura; M. M.; Gromov, S. P. *ARKIVOC* **2005**, (*xv),* 12.
10. Hadden, M. K.; Blagg, B.S.J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5063.
11. Tudose, M.; Ionita, P.; Dumitrascu, F.; Draghici, C.; Caproiu, M. T.; Covaci, I. C.; Constantinescu, T.; Banciu, M. D.; Balaban, A. T. *ARKIVOC* **2005**, (*iv*), 225.
12. Gould, E. S. *Mechanism and Structure in Organic Chemistry*, Holt, New York, 1959, p. 251.
13. Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam, 1968.

14. Terrier, F. *Nucleophilic Aromatic Displacement*, VCH, New York, 1991.
15. http://www.arguslab.com.
16. Stewart, J. J. P. MOPAC-2007, Stewart ComputationalChemistry, Version 8.032W web: HTTP://OpenMOPAC.net.
17. http://scistore.cambridgesoft.com/software/product.cfm?pid=4013.
18. Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York, 1979.
19. Kossoy, A. D.; Risley, D. S.; Kleyle, R. M.; Nurok, D. *Anal. Chem.,* **1992**, *64*, 1345.
20. Soczewinski, E. *Anal. Chem.* **1969**, *41*, 179.
21. Cserhati, T.; Forgacs, E. *J. Chromatogr. A* **1994**, *660*, 313.
22. Radutiu, A. C.; Baciu, I.; Caproiu, M. T.; Draghici, C.; Nicolae, A.; Constantinescu, T.; Balaban, A. T. *ARKIVOC* **2007**, (*xiii)*, 8.
23. Beteringhe, A.; Radutiu, A. C.; Bem, M.; Constantinescu, T.; Balaban, A. T. *Internet Elecronic J. Mol. Des.* **2006**, *5*, 237.
24. Bem, M.; Badea. F.; Draghici, C.; Caproiu, M. T.; Vasilescu, M.; Voicescu, M.; Beteringhe, A.; Caragheorgheopol, A.; Maganu, M.; Constantinescu, T.; Balaban, A. T. *ARKIVOC* **2007**, (*xiii)*, 87.
25. Draper, N. R.; Smith, H. *Applied Regression Analysis*, Wiley, New York, 1981.
26. Covaci, I.; Constantinescu, T.; Caproiu, M. T.; Dumitrascu, F.; Luca, C.; Balaban, A. T. *Rev. Roum. Chim*. **1999**, *44*, 531.
27. Covaci, I. C.; Constantinescu, T.; Caproiu, M. T.; Draghici, C.; Ionita, P.; Luca, C.; Stanciuc, G.; Maganu, M.; Balaban, A. T. *Rev. Roum Chim.* **1999**, *44*, 333.
28. Covaci, I. C.; Constantinescu, T.; Caproiu, M. T.; Luca, C.; Balaban, A. T. *Eur. J. Org. Chem*. **2000**, 3569.
29. Constantinescu, T.; Caproiu, M. T.; Zarna, N.; Caragheorgheopol, A.; Caldararu, H.; Stanciuc, G.; Radu, M.; Badescu, V.; Balaban, A. T. *New J. Chem*. **1997**, *21*, 575.
30. Covaci, I. C.; Constantinescu, T.; Caproiu, M. T.; Caldararu, H.; Ionita, P.; Balaban, A. T. *Polish J. Chem*. **2001**, *75*, 1427.
31. Cartwright, H. M. *Microchem. J*. **1986**, *34*, 313.
32. Krunz, M. M., Pfendt, L. B. *Microchem. J*. **1983**, *28*, 162.
33. Job, P. *Ann. Chim*. **1928**, *10*, 9.
34. Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc*. **1949**, *71*, 2703.
35. Bourson, J.; Pouget, J.; Valeur, B. *J. Phys. Chem*. **1993**, *97*, 4552.
36. Hilgenfeld, R.; Saenger, W.; Paintel, G. R.; Pressman, B. C.; Kellogg, R. M.; Montanari, F.; Landini, D.; Rolla, F. *Host-Guest Complex Chemistry II*, Akadämie-Verlag, Berlin, 1982 , p. 42.