ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 1, pp. 73–76. © Pleiades Publishing, Inc., 2006.
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Synthesis of Ion-Active Naphthalimide Derivatives

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Received November 18, 2004

Abstract—Crown ethers in which the macroring is fused to a naphthalimide fragment were synthesized. Their electron absorption spectra were found to depend on the solvent polarity and change as a result of complex formation.

DOI: 10.1134/S107042800601012X

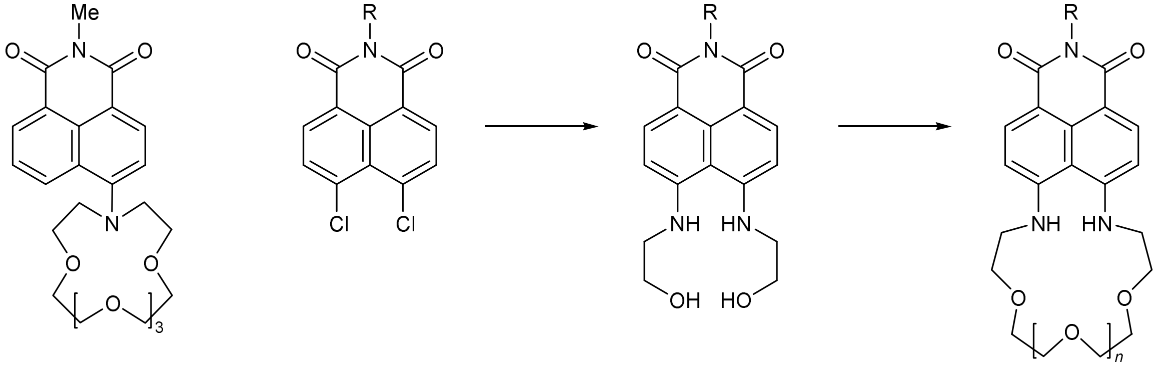
Derivatives of naphthalimide {1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione} are effective luminophores [1–5] and biologically active compounds [6]. Cosnard and Wintgens [7] synthesized crown ether **I** possessing a naphthalimide fragment; complex formation of **I** with metal ions is accompanied by blue shift of its absorption and luminescence maxima. Taking into account that the spectral properties of compound **I** are determined by the degree of conjugation of the nitrogen atom with the naphthalimide fragment and its participation in complex formation, we made an attempt to enhance these properties by fusion of an aza crown ether moiety to the naphthalimide fragment at the *peri* positions of the latter.

For this purpose, we synthesized three aza crown compounds **IVa**–**IVc** using 4,5-dichloro-*N*-octylnaphthalimide (**IIa**) and *N*-butyl-4,5-dichloronaphthalimide (**IIb**) as initial compounds. In the first stage, replacement of both chlorine atoms by 2-hydroxyethylamino groups gave diols **IIIa** and **IIIb** which were brought into reactions with di- and triethylene glycol bis(*p*-toluenesulfonates) to obtain target products **IVa**–**IVc** (Scheme 1). The synthesis of compounds **IVa**–**IVc** was performed in strongly dilute solutions in tetrahydrofuran in the presence of sodium hydroxide (**IVa**) or potassium *tert*-butoxide (**IVb**, **IVc**). When the reactions were carried out in dioxane instead of THF, the yields of compounds **IVa**–**IVc** were lower, and the fraction of oily impurities increased.

The structure of fused aza crown ethers **IVa**–**IVc** was confirmed by spectral data. The mass spectra of **IVa**–**IVc** contained peaks corresponding to their molecular ions. In the IR spectra of these compounds we observed absorption bands in the region 1600–1700 cm^{-1}, which are typical of stretching vibrations of the imide carbonyl groups. The N–H bonds gave rise to absorption in the region 3400–3440 cm^{-1}.

The ^{1}H NMR spectra of **IVa**–**IVc** were fully consistent with the assumed structure. A set of signals from aromatic protons was located at δ 6.7–8.5 ppm;

Scheme 1.



I **IIa**, **IIb** **IIIa**, **IIIb** **IVa**–**IVc**

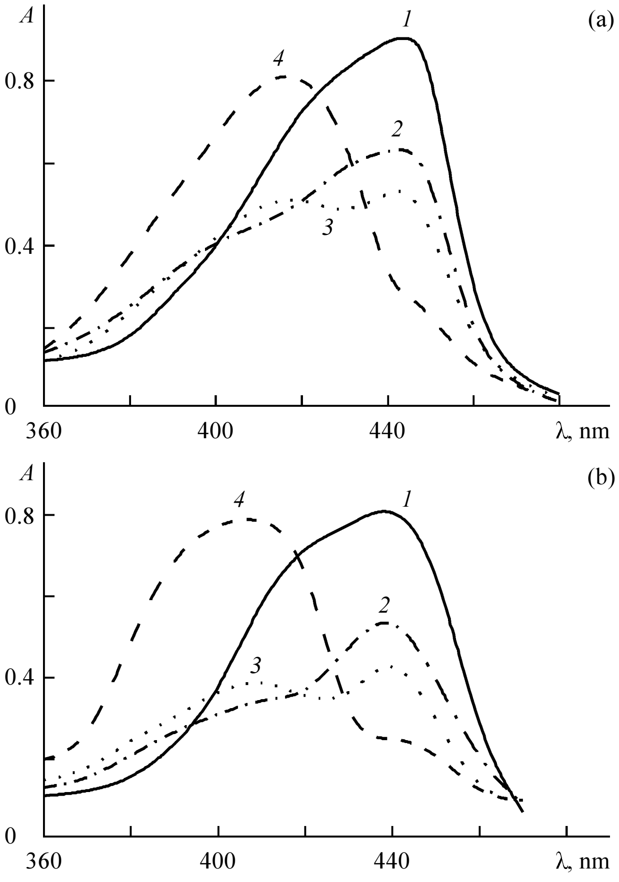
II, **III**, R = n-C_8H_{17} (**a**), n-C_4H_9 (**b**); **IV**, R = n-C_8H_{17} (**a**, **b**), n-C_4H_9 (**c**); n = 1 (**a**), 2 (**b**, **c**).

Absorption maxima in the electron spectra of compounds **IVa** and **IVb** in different solvents

Comp. no.	λ_{max}, nm				
	hexane	chloroform	dioxane	acetonitrile	ethanol
IVa	424	433	435	443	452
IVb	425	435	436	445	450

the 4-H and 5-H signals appeared as doublets with coupling constants typical of naphthalimide derivatives. The δ region 3.4–3.9 ppm contained signals from aliphatic protons in the polyether fragment of molecules **IVa**–**IVc**, and protons in the alkyl groups on the imide nitrogen atom resonated in the δ range from 0.8 to 4.2 ppm.

Lone electron pairs on the nitrogen atoms on C^6 and C^7 in the 2,3-dihydro-1*H*-benzo[*de*]isoquinoline-1,3-dione system (C^4 and C^5 in naphthalimide) are involved in conjugation with the aromatic fragment, which leads to appearance of a broad absorption band in the visible region of the electron spectra of all compounds **IVa**–**IVc**. The absorption maxima in the spectra of **IVa** and **IVb** shift to longer wavelengths as the solvent polarity increases (see table); obviously, their excited states are better stabilized by more polar solvents. In going from hexane to ethanol, the red shift is 25–28 nm, while the corresponding shift observed for compound **I** is only 11 nm [7].



Electron absorption spectra of compounds (a) **IVb** and (b) **IVa** (*1*) in the absence and in the presence of $NaClO_4$ at a $NaClO_4$-to-**IV** ratio of (*2*) 1 : 3, (*3*) 1 : 2, and (*4*) 1 : 1; concentration of **IV** 3.50×10^{-5} M.

We also examined the ability of aza crown ethers **IV** to change their spectral properties as a result of complex formation. For this purpose, we recorded the electron absorption spectra of compounds **IVa** and **IVb** in acetonitrile in the presence of sodium perchlorate (see figure). It is seen that the absorption maxima of the complexes with sodium ion are located at shorter wavelengths as compared to the initial compounds. The blue shifts are 24 and 36 nm for crown ethers **IVb** and **IVa**, respectively. The larger blue shift observed for compound **IVa** may be rationalized in terms of better correspondence in size between the cavity in **IVa** and sodium cation. It should be noted that complex formation of crown ether **I** (whose cavity has a similar size) with sodium ion is characterized by a blue shift of 14 nm [7].

Our results confirm the existence of a strong relation between spectral properties of crown-fused naphthalimides and specificity of complex formation with participation of the aza crown ether moiety. Further more detailed study on complex formation between compounds **IVa**–**IVc** and different metal ions seems to be promising.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker WM-300 spectrometer. The UV spectra were measured on a Specord UV-Vis spectrophotometer. The IR spectra were obtained in KBr on a Mattson FTIR-1001 instrument. The mass spectra (electron impact, 70 eV) were recorded on a Varian MAT-311A mass spectrometer with direct sample admission into the ion source heated to 200°C. The progress of reactions and the purity of products were monitored by thin-layer chromatography on Silica gel 60 F_{254} plates (Merck); spots were visualized under UV light.

The solvents were purified by standard procedures [8]. *N*-Butyl-4,5-dichloronaphthalimide (**IIb**) and 4,5-dichloro-*N*-octylnaphthalimide (**IIa**) were prepared by the procedure reported in [9], and *N*-octyl-4,5-bis-(2-hydroxyethylamino)naphthalimide (**IIIa**) was synthesized as described in [10].

2-Butyl-6,7-bis(2-hydroxyethylamino)-2,3-dihydro-1*H*-benzo[*de*]isoquinoline-1,3-dione (IIIb). A mixture of 3.2 g (0.01 mol) of *N*-butyl-4,5-dichloronaphthalimide (**IIb**) and 6.1 g (0.1 mol) of 2-aminoethanol in 50 ml of chlorobenzene was heated for 20 h under reflux. The solvent was removed by steam distillation, the solid product was dissolved in 800 ml of chloroform, and the solution was washed with water until neutral washings, dried over sodium sulfate, and evaporated to obtain 3.1 g of crude product **IIIb** which was purified by recrystallization from acetone. Yield 2.5 g, golden plates, mp 188–189°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.85 t (3H, CH_3), 1.22–1.74 m (4H, CH_2), 3.98 t (2H, NCH_2, J = 7.5 Hz), 7.24–7.28 m (2H, NH), 3.39–3.44 m (4H, $NHC\mathbf{H}_2$), 3.75–3.79 m (4H, $C\mathbf{H}_2OH$), 4.98 t (2H, OH, J = 5.4 Hz), 8.38 d (2H, 4-H, J = 8.4 Hz), 6.76 d (2H, 5-H, J = 8.4 Hz). Electron absorption spectrum (*i*-PrOH), λ_{max}, nm (logε): 342 (3.67), 448 (4.29). Found, %: C 64.60, 64.56; H 6.80, 6.98; N 11.30, 11.41. $C_{20}H_{25}N_3O_4$. Calculated, %: C 64.67; H 6.78; N 11.31.

2-Octyl-6,7-(1,16-diaza-4,7,10,13-tetraoxahexadecamethylene)-2,3-dihydro-1*H*-benzo[*de*]isoquinoline-1,3-dione (IVb). A solution of 1.06 g (2.5 mmol) of compound **IIIa** in 60 ml of tetrahydrofuran and a solution of 1.15 g (2.5 mmol) of triethylene glycol bis(*p*-toluenesulfonate) in 60 ml of tetrahydrofuran were added dropwise over 2 h under vigorous stirring to a hot solution of 0.56 g (5 mmol) of potassium *tert*-butoxide in 30 ml of *tert*-butyl alcohol. The mixture was heated for 48 h under reflux, diluted with 2 volumes of water, and extracted with 400 ml of chloroform. The extract was dried over sodium sulfate, and the solvent was distilled off to obtain 1.5 g of an oily material which was subjected to column chromatography using chloroform–acetone (5:1) as eluent. Recrystallization from hexane gave 0.32 g (25%) of compound **IVb** as orange plates with mp 136–137°C. IR spectrum, ν, cm^{-1}: 1117, 1352, 1408, 1593, 1634, 1677, 2851, 2924, 3439. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 t (3H, CH_3), 1.20–1.76 m (12H, CH_2), 4.12 t (2H, NCH_2, J = 7.5 Hz), 3.47–3.51 m (4H, $NHC\mathbf{H}_2$), 3.85 t (4H, $NHCH_2C\mathbf{H}_2O$, J = 5.4 Hz), 3.64–3.74 m (12H, CH_2O), 8.40 d (2H, 4-H, J = 8.4 Hz), 6.74 d (2H, 5-H, J = 8.4 Hz). Electron absorption spectrum (*i*-PrOH), λ_{max}, nm (logε): 283 (3.95), 343 (3.69), 453 (4.36). Mass spectrum, *m*/*z* (I_{rel}, %): 542 (34), 541 (100) $[M]^+$, 526 (19), 364 (11), 252 (15), 238 (11). Found, %: C 66.50, 66.62; H 8.30, 8.32; N 7.59, 7.63. $C_{30}H_{43}N_3O_6$. Calculated, %: C 66.52; H 8.00; N 7.76.

2-Butyl-6,7-(1,16-diaza-4,7,10,13-tetraoxahexadecamethylene)-2,3-dihydro-1*H*-benzo[*de*]isoquinoline-1,3-dione (IVc) was synthesized as described above for **IVb** using 0.92 g (2.5 mmol) of imide **IIIb** in 60 ml of tetrahydrofuran, 1.15 g (2.5 mmol) of triethylene glycol bis(*p*-toluenesulfonate) in 60 ml of tetrahydrofuran, and 0.56 g (5 mmol) of potassium *tert*-butoxide in 30 ml of *tert*-butyl alcohol. The reaction mixture was heated for 40 h under reflux. Yield 0.3 g (25%), orange plates, mp 102–104°C (from hexane). IR spectrum, ν, cm^{-1}: 1092 w, 1239, 1386, 1404 w, 1586, 1645, 1688, 2870, 2955, 3452. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.96 t (3H, CH_3), 1.24–1.50 m (4H, CH_2), 4.14 t (2H, NCH_2, J = 7.5 Hz), 3.56–3.62 m (4H, $NHC\mathbf{H}_2$), 3.85 t (4H, $NHCH_2C\mathbf{H}_2O$, J = 5.4 Hz), 3.68–3.76 m (12H, CH_2O), 8.41 d (2H, 4-H, J = 8.4 Hz), 6.76 d (2H, 5-H, J = 8.4 Hz). Electron absorption spectrum (*i*-PrOH), λ_{max}, nm (logε): 283 (3.94), 342 (3.71), 452 (4.38). Mass spectrum, *m*/*z* (I_{rel}, %): 486 (30), 485 (100) $[M]^+$, 470 (21), 322 (13), 308 (18), 294 (10), 252 (15), 238 (11). Found, %: C 64.40, 64.47; H 7.29, 7.40; N 8.65, 8.81. $C_{26}H_{35}N_3O_6$. Calculated, %: C 64.31; H 7.27; N 8.65.

6,7-(1,13-Diaza-4,7,10-trioxatridecamethylene)-2-octyl-2,3-dihydro-1*H*-benzo[*de*]isoquinoline-1,3-dione (IVa) was synthesized as described above for compound **IVb** using 1.00 g (2.34 mmol) of imide **IIIa** in 60 ml of tetrahydrofuran, 0.97 g (2.34 mmol) of diethylene glycol bis(*p*-toluenesulfonate) in 60 ml of tetrahydrofuran, and a suspension of 1 g (2.5 mmol) of sodium hydroxide in 30 ml of tetrahydrofuran. The mixture was heated on an oil bath for 37 h under reflux with stirring. Yield 0.35 g (30%), yellow–green plates, mp 152–153°C (from hexane). IR spectrum, ν, cm^{-1}: 1129, 1249 w, 1358 w, 1406, 1603, 1633, 1675, 2855, 2922, 3402. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 t (3H, CH_3), 1.20–1.76 m (12H, CH_2), 4.12 t (2H, NCH_2, J = 7.5 Hz), 3.45–3.49 m (4H, $NHC\mathbf{H}_2$), 3.90 t (4H, $NHCH_2C\mathbf{H}_2O$, J = 4.8 Hz), 3.7–3.74 m (8H, CH_2O), 8.42 d (2H, 4-H, J = 8.4 Hz), 6.74 d (2H, 5-H, J = 8.4 Hz). Electron absorption spectrum (*i*-PrOH), λ_{max}, nm (logε): 284 (4.01), 344 (3.79), 450 (4.44). Mass spectrum, *m*/*z* (I_{rel}, %): 498 (32), 497 (100) $[M]^+$, 482 (14), 480 (10), 252 (15), 238 (12), 86 (10), 84 (17), 49 (13). Found, %: C 67.39, 67.43; H 7.99, 8.10; N 8.40, 8.42. $C_{28}H_{39}N_3O_5$. Calculated, %: C 67.58; H 7.90; N 8.44.

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