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Fluorescent aza-cyclophanes derived from diethylenetriaminepentaacetic acid (DTPA), and their complexation with Gd(III)

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ABSTRACT

Chelating aza-cyclophanes were synthesized by reactions of diethylenetriaminepentaacetic acid (or DTPA) dianhydride with aromatic diamines, 4,4′-diaminobibenzyl (DAB) and 4,4′-bis(1,1′-biphenyl-4,4′-diyldioxy)dianiline (BPA). The former amine gave a 2:2-cyclization product bearing six –CH_2CO_2H arms, 2,12,29,39-tetraoxo-4,7,10,31,34,37-hexakis(carboxymethylene)-1,4,7,10,13,28,31,34,37,40-deca-aza-[13.2.13.2]ethylenparacyclophane, abbreviated as cy(*bis*dtpadab)H_6, whereas BPA yielded a 1:1-cyclization product carrying three –CH_2CO_2H arms, 2,12-dioxo-4,7,10-trakis(carboxymethylene)-1,4,7,10,13-pentaaza-20,33-dioxa[13.0.1]paracyclophane, abbreviated as cy(dtpabpa)H_3. Their protonation and complexation with Gd(III) were studied by fluorescence spectra, ^1H NMR and potentiometry. The macrocyclic framework of cy(dtpabpa)H_3 has a high rigidity; as a consequence, this ligand is incapable of forming a complex with Gd(III). In contrast, cy(*bis*dtpadab)H_6, which is moderately rigid, forms a binuclear Gd(III) complex, as confirmed by a sensitive quenching of the fluorescence upon complexation. On the basis of the pH dependence of the fluorescence spectra, the logarithmic overall formation constants were determined as $\log\beta_{M2L} = 28.3$, $\log\beta_{M2LH} = 31.9$, $\log\beta_{M2LH-1} = 21.0$, $\log\beta_{M2LH-2} = 9.8$. For the chelating cyclophanes, the rigidity is one of major controlling factors for the stability of their complexes. The sharp change in the fluorescence intensity upon complexation with Gd^{3+} ion suggests that the chelating cyclophane works potentially as fluorescent probes toward specific metal ions.

1. Introduction

Diethylenetriaminepentaacetic acid (or DTPA) and its derivatives form stable complexes with trivalent metal ions including rare-earth metals [1–5]; special interest has been directed to Gd(III) complexes because of their practical or potential usefulness as contrast enhancers of magnetic resonance imaging (or MRI) [6–12]. Binuclear Gd(III) complexes are expected to have a high MRI-enhancing capability and other functions such as a paramagnetic probe toward proteins [13,14]. Reactions of DTPA dianhydride with diamines yield azamacrocyles bearing carboxymethyl arms [2,3,15]. When butylenediamine (or BAN) is employed, 1:1- and 2:2-cyclizations proceed as shown in Scheme 1. The 2:2-cyclization product forms a binuclear Gd(III) complex whereas the 1:1-cyclization product gives a mononuclear complex; the X-ray structure of the binuclear complex is schematically illustrated in Scheme 1 [13]. Similar reactions have been extensively studied for ethylenediaminetetraacetic (EDTA) dianhydride, and it has been demonstrated that reactions with aromatic diamines predominantly yield 2:2-cyclization products because of the high rigidity and a consequent definite chain length of aromatic diamines [16–19]. The resulting cyclophanes form stable binuclear complexes with divalent metal ions [17,19–21]. In addition, the macrocyclic rings of these cyclophanes are well-defined and preorganized; such a structural character is one of crucial controlling factors for molecular recognition toward specific inorganic and organic ions [16,19,22]. Other advantages of the chelating cyclophanes are due to the conjugated systems: (1) absorption and emission spectra from aromatic group facilitate the characterizations of the compounds; (2) a sensitiveness of emission to environmental changes may allow the compounds to function as fluorescent probes toward inorganic and organic ions [20,22–25]. In this work, therefore, reactions between DTPA dianhydride and selected aromatic diamines have been studied, and chelating aza-cyclophane acids shown in Scheme 2 have been obtained; the cyclophanes are abbreviated as the general form, cy(dtpa-amine)H_3 or cy(*bis*dtpa-amine)H_6, that shows reactants as well as acidic protons related to CH_2CO_2H arms. These macrocycles exhibits well-defined fluorescence spectra, by which protonation and complexation with Gd(III) have been studied in relation to the rigidity of the macrocyclic ring.

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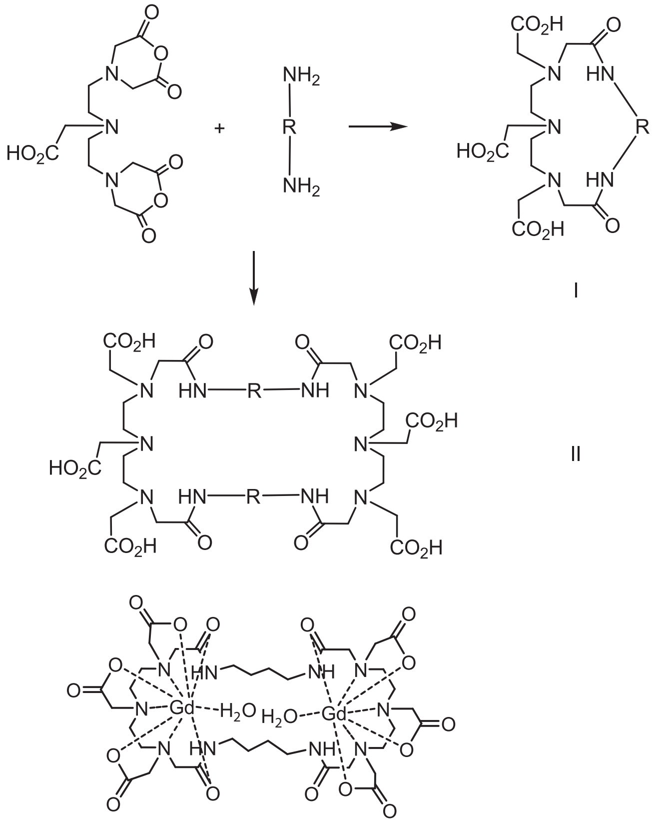


Scheme 1. (Top) Two types of reactions of DTPA dianhydride with diamines, and the products (**I**) cy(dtpa-aime)H_3 and (**II**) cy(*bis*dtpa-amine)H_6. (Bottom) Schematic illustration of the X-ray structure of a binuclear Gd(III) complex with cy(*bis*dtpaban)H_6 derived from butylenediamine [13].

2. Experimental

2.1. Synthesis of cy(bisdtpadab)H_6 in Scheme 2

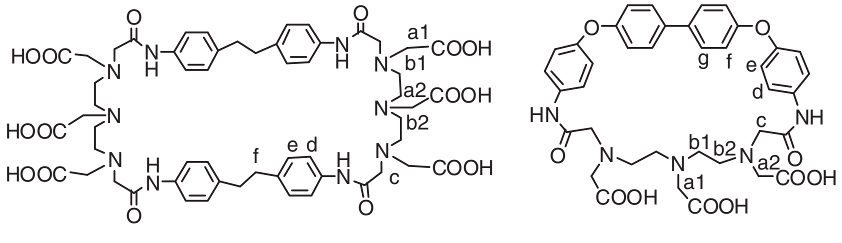
To suspension of 0.80 g (2.2 mmol) of DTPA dianhydride (supplied from Aldrich) in dry dimethylformamide (DMF) was added dropwise 10 mL of a DMF solution containing 0.43 g (2.0 mmol) of 4,4′-diaminobibenzyl (Aldrich); the addition was performed with vigorous stirring in 40 min under a nitrogen atmosphere at ambient temperature, and stirring was continued for 24 h. The reaction mixture was separated into two layers upon standing. The upper layer was collected by decantation, filtered, and concentrated by means of a rotary evaporator at 40 °C. The resulting viscous liquid was treated with 10 mL of water, and concentrated with a rotary evaporator. This process was repeated, normally four times, until a pearl-colored solid was precipitated upon treatment with water. The obtained solid was suspended in 15 mL of water, and dissolved by adding solid Li_2CO_3 little by little with stirring. The solution was concentrated to about one-third. Gentle heating of the concentrate on a water bath (*ca.* 40 °C) for several days yielded the lithium salt as colorless solid. The purified lithium salt was converted into the acidic form by acidifying an aqueous solution of the salt to pH 2 with 3 M HCl. After continuous stirring for 30 min, the solid formed was filtered off, washed with water and dried in vacuum. Yield: 15%. Decomposition temp.: 230 °C. ^1H NMR (400 MHz, Na_2CO_3/D_2O, pD = 8.5, DSS): $\delta = 2.67$ (s, 8H, H_f in Scheme 2), 3.16 (t, $J = 8$ Hz, 8H, H_{b1}), 3.32 (s, 8H, H_{a1}), 3.46 (t, $J = 8$ Hz, 8H, H_{b2}), 3.49 (s, 8H, H_c), 3.84 (s, 4H, H_{a2}), 7.07 (d, $J = 11$ Hz, 8H, H_e), 7.29 (d, $J = 11$ Hz, 8H, H_d). ^{13}C NMR (101 MHz, Na_2CO_3/D_2O, DSS): 35.7 (C_f), 39.5 (C_{b2}), 51.9 (C_{b1}), 54.8 (C_{a1}), 58.6 (C_c), 120.4 (C_d), 128.2 (C_e), 134.1 (Ar *C*–C_f), 138.2 (Ar *C*–N_{amide}), 171.3 (C_{amide}), 178.4 (C_{a1}–CO_2^-). IR (KBr): $\nu/cm^{-1} = 3275$ ($\nu_{NH\ amide}$), 1515 (amide II), 1620 (ν_{CO_2}), 831 (δ_{CH}). MS (ESI$^-$) *m/z* (%): 1137.5 (84) $[(M-H)^-]$, 1159.4 (100) $[(M-2H+Na)^-]$. *Anal.* Calc. for $C_{56}H_{70}N_{10}O_{16}\cdot 2.5H_2O$: C, 56.61 H, 6.39; N, 11.50. Found: C, 56.70; H, 6.54; N, 11.81%.

2.2. Synthesis of cy(dtpabpa)H_3 in Scheme 2

A DMF solution (10 mL) containing 0.75 g (2.04 mmol) of 4,4′-(1,1′-biphenyl-4,4′-diyldioxy)dianiline (Fluka) was added dropwise to 0.80 g (2.23 mmol) of DTPA dianhydride suspended in 80 mL of DMF over a period of 1 h with vigorous stirring at room temperature under a nitrogen atmosphere. The resulting reaction mixture was left to stand overnight. After removal of any precipitates by filtration, the solution was concentrated to a viscous liquid. Addition of acetone yielded a white solid, which was filtered off, washed successively with water and acetone, and dried in vacuum. Yield: 33%. Decomposition temp.: 230 °C. ^1H NMR (400 MHz, KOD/D_2O, pD 12, DSS): $\delta = 2.74$ (s, 8H, H_{b1} and H_{b2} in Scheme 2), 3.17 (s, 4H, H_{a2}), 3.29 (s, 4H, H_{a1}), 3.32 (s, 4H, H_c), 6.65 (br, 4H, H_e) 6.77 (br, 4H, H_f), 7.02 (br, 4H, H_d), 7.36 (br, 4H, H_g). ^{13}C NMR (101 MHz, DMSO-d_6, TMS): $\delta = 35.7$ (C_f), 39.5 (C_{b2}), 51.9 (C_{b1}), 54.8 (C_{a1}), 58.6 (C_c), 120.4 (C_d), 128.2 (C_e), 134.1 (Ar *C*–C_f), 138.2 (Ar *C*–N_{amide}), 171.3 (C_{amide}), 178.4 (C_{a1}–CO_2^-). IR (KBr): $\nu/cm^{-1} = 3288$ ($\nu_{NH\ amide}$), 1720 (ν_{CO_2H}), 1610 (amide I), 1492 (amide II), 829 (δ_{CH}). MS (ESI$^+$) *m/z* (%): 763.6 (57) $[(M+K)^+]$, 637.3 (100) $[(M-2CO_2)^+]$. *Anal.* Calc. for $C_{38}H_{39}N_5O_{10}\cdot 2H_2O$: C, 59.91; H, 5.69; N, 9.19. Found: C, 59.77; H, 5.57; N, 9.37%.

2.3. Spectroscopic and potentiometric experiments

The emission spectra were observed with a Perkin-Elmer model LS50B luminescence spectrometer at a temperature of 25 °C. For pH dependence experiments, a stock solution of a sample compound in 0.01 M NaCl was divided into a desired number of sample solutions, and the pH of each solution was adjusted to a desired value with 0.01 M (= mol dm^{-3}) HCl and 0.01 M NaOH so that all solutions had identical ionic strength and constant sample concentration.



cy(bisdtpadab)H_6 cy(dtpabpa)H_3

Scheme 2. Chelating cyclophanes studied in this work, their abbreviations, and labeling used for NMR assignments.