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Isomeric DTPA-amide macrocycles of *p*-xylenediamine and their complexation with Gd^{3+}

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ABSTRACT

Three DTPA-amide cyclophanes – including conformational isomers – have been isolated by optimizing the conditions of a reaction between diethylenetriaminepentaacetic (DTPA) dianhydride and *p*-xylenediamine: a 2 + 2-cyclization product, abbreviated as $(cy2)H_6$, that integrates two phenylene groups in the macrocyclic frame and bears six pendant $-CH_2CO_2H$ arms, and two isomeric 1 + 1-macrocyles, $(cy1)H_3$, carrying three arms. A crucial factor for controlling the ring size is the concentration in the reaction. For $(cy2)H_6$, whose binuclear Gd^{3+} complex is a potential paramagnetic protein sensor, the synthetic method has been established in 70% yield. The isomerism of $(cy1)H_3$ is due to the conformation of the rigid macrocyclic frame; the ^1H NMR and geometry optimization show that the conformation is of quasi-C_2 symmetry in one $(cy1)H_3$ isomer, and of quasi-mirror symmetry in the other. Their distinct conformations define the chemical properties and coordination capability toward Gd^{3+}: in the C_2-symmetric isomer, the amino nitrogen is less basic and the N–H bond is more covalent than in the mirror-symmetric isomer; the former forms a mononuclear Gd^{3+} complex whereas the latter does not show sign of complexation with Gd^{3+}.

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1. Introduction

A variety of chelating macrocycles are prepared by cyclization reactions between reagents bearing functional groups on their chain ends [1,2]. Reactions of DTPA (or diethylenetriaminepentaacetic) dianhydride with diamines yield chelating macrocycles, cy(DTPA-Amine)H_n, that incorporate diamines with amide linkages in the macrocyclic frames and carry pendant carboxymethyl arms [3–6]. When aromatic diamines are employed, the resulting cyclophane-type macrocycles have highly rigid frameworks that define the coordination properties toward metal ions [7]. The gadolinium(III) complexes of these DTPA-amide macrocycles have attracted attention [5,6,8,9], because $[Gd{\cdot}DTPA]^{2-}$ and some Gd^{3+} complexes are used for MRI-enhancers in diagnostic practices [10–13]. In addition, a new type of diagnostic function as a paramagnetic probe toward proteins has been reported for the binuclear Gd^{3+} complex of a DTPA-amide cyclophane, $(cy2)H_6$ in Scheme 1, which is composed of two DTPA units and two *p*-xylenediamine (PX) units [14]. Despite this novel, important function of the Gd^{3+} complex, the ligand remains equivocal as to its synthesis and characterization: for example, the observation of four aromatic signals in the ^1H NMR has been reported in conflict with the chemical formula in which all aromatic protons should be chemically equivalent. This NMR observation suggests that $(cy2)H_6$ may be accompanied by byproducts having different ring sizes, as reported for macrocycles derived from acid dianhydrides [6,15,16]; a probable byproduct is a 1 + 1-cyclization macrocycle, $(cy1)H_3$ in Scheme 1. In view of the novelty of the binuclear Gd^{3+} complex as a biological sensor, we have established, in the present study, the method for preparing the macrocyclic ligand in its pure form in a high yield. In addition, two isomers of $(cy1)H_3$ have been isolated, which take different conformations of the macrocyclic rings and have consequent distinction in complexation capability toward Gd^{3+}.

2. Experimental

2.1. Synthesis of 2 + 2-cyclophane, $(cy2)H_6$

A dimethylformamide (DMF) solution of *p*-xylene-α,α′-diamine (0.27 g, 2.0 mmol in 10 mL) was added dropwise into DTPA dianhydride suspended in DMF (0.8 g, 2.2 mmol in 80 mL) with a vigorous

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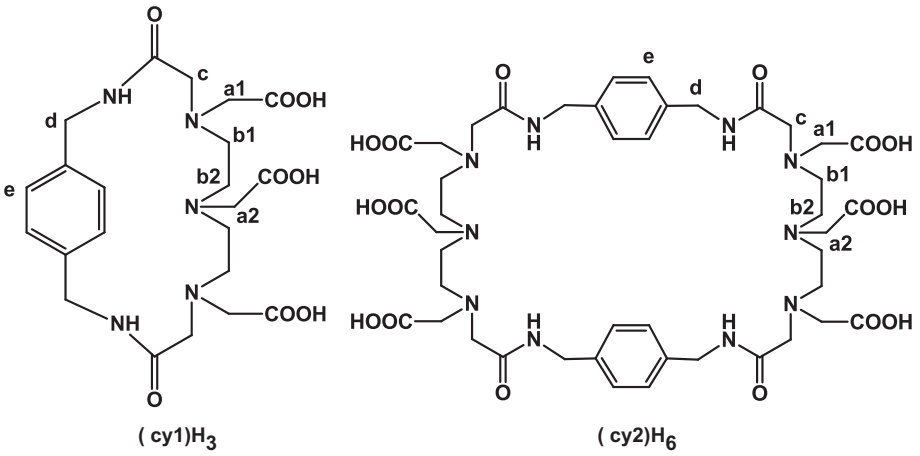

Scheme 1. DTPA-amide cyclophanes derived from *p*-xylenediamine in the 1 + 1- and 2 + 2-cyclization reactions, and their abbreviations. The labels of atoms in the cyclophanes are shown for NMR assignments.

stirring under nitrogen atmosphere during *ca.* 1 h. After the reaction mixture was stirred for *ca.* 23 h, a solid formed was removed by filtration. The filtrate was mixed with 20 mL of water, and was concentrated by a rotary evaporator to viscous oil. Addition of absolute ethanol to the oil yielded a voluminous solid mass; ethanol used was HPLC grade (>99.8%) or better, because its quality is crucial for the yield as well as the purity of the product. The obtained solid was washed repeatedly with water until colorless fine powder was obtained. Yield: 70%. Decomposition temp.: 224 °C. ^{1}H NMR (H_2O-d_2/Na_2CO_3, pD 12.4): δ = 2.72 (s, 16 H, assigned to *b1* and *b2* in Fig. 1 – separable at other pD values, *e.g.*, 2.99 (t, 8H, *b1*) and 3.25 (t, 8H, *b2*) at pD 6.4), 3.11(s, 4H, *a2*), 3.18 (s, 8H, *a1*), 3.30 (s, 8H, *c*), 4.40 (s, 8H, *d*), 7.28 (s, 8H, ar). ^{13}C NMR (101 MHz, Na_2CO_3/D_2O, DSS): 42.3 (C_d), 50.3 (C_{b1}), 52.4 (C_{b2}), 54.4 (C_{a2}), 57.2 (Ca_1), 58.3 (Cc), 127.6 (Ce), 136.9 (italicized C in Ar *C*–C_d), 170.9 (C_{amide}), 172.9 (Ca_1–CO_2–), 178.0 (C_{a2}–CO_2–). IR (KBr): ν/cm^{-1} = 3286 ($\nu_{NHamide}$), 1631 (ν_{CO2H}), 1624 (amide I), 1540 (amide II), 681 (δ_{CH}). MS (ESI$^-$) *m*/*z* (%): 985.4 (100) [(M–H)$^-$]. *Anal.* Calc. for $C_{44}H_{62}N_{10}O_{16}\cdot 3H_2O$: C, 50.76; H, 6.58; N, 13.45. Found: C, 50.78; H, 6.56; N, 13.48%.

2.2. Synthesis of 1 + 1-cyclophane isomer a, $(cy1a)H_3$

A DMF solution of *p*-xylenediamine (0.69 g, 5.0 m mole) in 150 mL) was added dropwise into DTPA dianhydride suspended in DMF (2.0 g, 5.6 mmol in 240 mL) for 3 h with a vigorous stirring under nitrogen atmosphere. After continuous stirring for *ca.* 20 h, the reaction mixture was left to stand. In a night, solid and liquid layers were separated; the former yielded an isomer denoted by $(cy1a)H_3$, while the liquid layer gave another isomer $(cy1b)H_3$.

The solid collected by filtration was soaked in THF (30 mL) for two days. The resulting solid was suspended in an acetone–water (1:1) mixture (30 mL). When the suspension was stirred with a spatula, the product separated out as colorless powder in a few minutes, while gummy impurity adhered to the spatula so as to be eliminated easily. The powder was collected by filtration, washed quickly on the glass filter with hot water, and dried in vacuum. The product was reprecipitated from water by addition of acetone until no gummy solid was appreciable in the treatment with an acetone–water mixture. Yield: 10%. Decomposition temp.: 275 °C. ^{1}H NMR (H_2O-d_2/Na_2CO_3, pD 12.4, DSS): δ = 2.15 (dd,

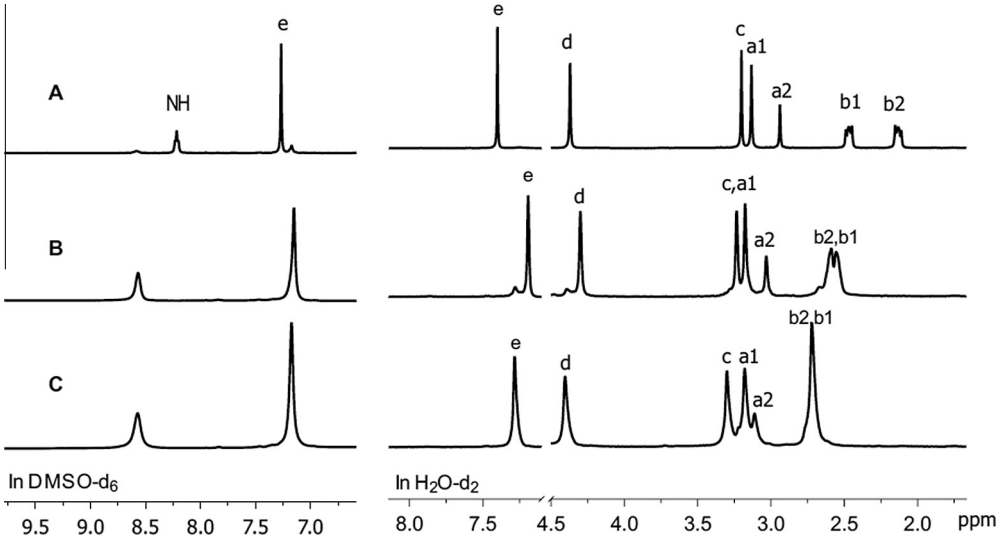

Fig. 1. ^{1}H NMR spectra of three DTPA–xylenediamine cyclophanes: (A) $(cy1a)H_3$; (B) $(cy1b)H_3$; (C) $(cy2)H_6$. The spectra on the right are those observed in H_2O-d_2 at pD 12.4; the left spectra show the aromatic and amide regions observed in DMSO-d_6. For the labels of the protons, see Scheme 1. The weak peaks accompanying peaks *d* and *e* of $(cy1b)^{3-}$ in D_2O are not observable in DMSO; the weak extra signals of $(cy1a)H_3$ in DMSO are undetectable in D_2O.

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