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Original article

Tetraphenylethene based zinc complexes as fluorescent chemosensors for pyrophosphate sensing

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ABSTRACT

We described a serious of zinc complexes that exhibit characteristic fluorescence responses toward pyrophosphate (PPi) and adenosine triphosphate (ATP) in aqueous media. These novel probes exploited tetraphenylethene (TPE) as fluorophore and macrocycle-polyamine (including 1,4,7,10-tetraazacyclododecane and 1,4,7-triazacyclononane) Zn(II) complexes as binding group. These "OFF–ON" type probes exhibited promising selectivity and sensitivity to PPi and ATP *via* a restriction of intramolecular rotation (RIR) mechanism. The detection limit for PPi was found within nmol/L range.

1. Introduction

Phosphate-based inorganic and organic molecules play important roles in biological processes such as energy storage, signal transduction and DNA sequencing [1–5]. Therefore, developing synthetic receptors for recognition and sensing of such anions have drawn much attention. Among the phosphates, adenosine triphosphate (ATP) and inorganic pyrophosphates (PPi) have been of particular interest [6,7], which are involved in energy transduction in organisms and control metabolic processes through participation in various enzymatic reactions [8,9]. In the past decades, a number of zinc-complex based fluorescent chemosensors for PPi sensing have been reported [10,11], including several classic ligands such as bis(2-pyridylmethyl) amine (DPA) [12,13], terpyridine (tpy) [14], and amide [15,16]. However, most of them exhibited low sensitivity (in the μmol/L range) [17]. It is necessary to develop novel chemosensors for phosphate sensing with high selectivity and sensitivity, especially those could respond in nmol/L range.

1,4,7,10-Tetraazacyclododecane (cyclen) and 1,4,7-triazacyclononane (TACN) are cyclic organic compounds. Both of them are versatile metal chelator with excellent water-solubility [18], and their Zn(II) complexes have been developed for biological polyphosphate anions detection [19]. Tetraphenylethene (TPE) is a kind of propeller-shaped fluorophore, which could affect the fluorescence intensity according to the restriction of intramolecular rotation (RIR) mechanism [20,21]. Because the energy is dissipated by the intramolecular rotation, non-emission is found when the probe is dissolved in solution; while in aggregation state or somehow else, the intramolecular rotation could be restricted that induced to emit efficiently. Previously, we reported a dicyclen–TPE Zn(II) complex as a fluorescent ensemble for PPi in water with a detection limit of 22.8 nmol/L [22]. To continue our work, herein, we synthesized a serious of cyclen- or TACN-TPE Zinc complexes, and investigated their performance for biologically important phosphate anions detection in aqueous solution.

2. Experimental

Mass spectrometer (ESI-MS) and high resolution mass spectrometer (HRMS) data were recorded on a Finnigan LCQDECA and a Bruker Daltonics Bio TOF mass spectrometer, respectively. The ^{1}H NMR and ^{13}C NMR spectra measured on a Bruker AM400 NMR spectrometer and the δ scale in ppm referenced to residual solvent peaks or internal tetramethylsilane (TMS). Absorption spectra recorded on Hitachi U1900 spectrophotometer at 298 K. Fluorescence emission spectra were obtained using FluoroMax-4 Spectrofluoro-photometer (HORIBA Jobin Yvon) at 298 K. Unless otherwise indicated, all syntheses and manipulations were carried out under N_2 atmosphere. All the solvents were dried according to the standard methods prior to use. All of the solvents were either HPLC or spectroscopic grade in the optical spectroscopic studies.

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Compounds **1**, **2**, **3**, **4**, **5** were prepared according to the literature procedures [23–25]. For dCT and dCT·Zn, they were prepared as discussed on our previous paper [22].

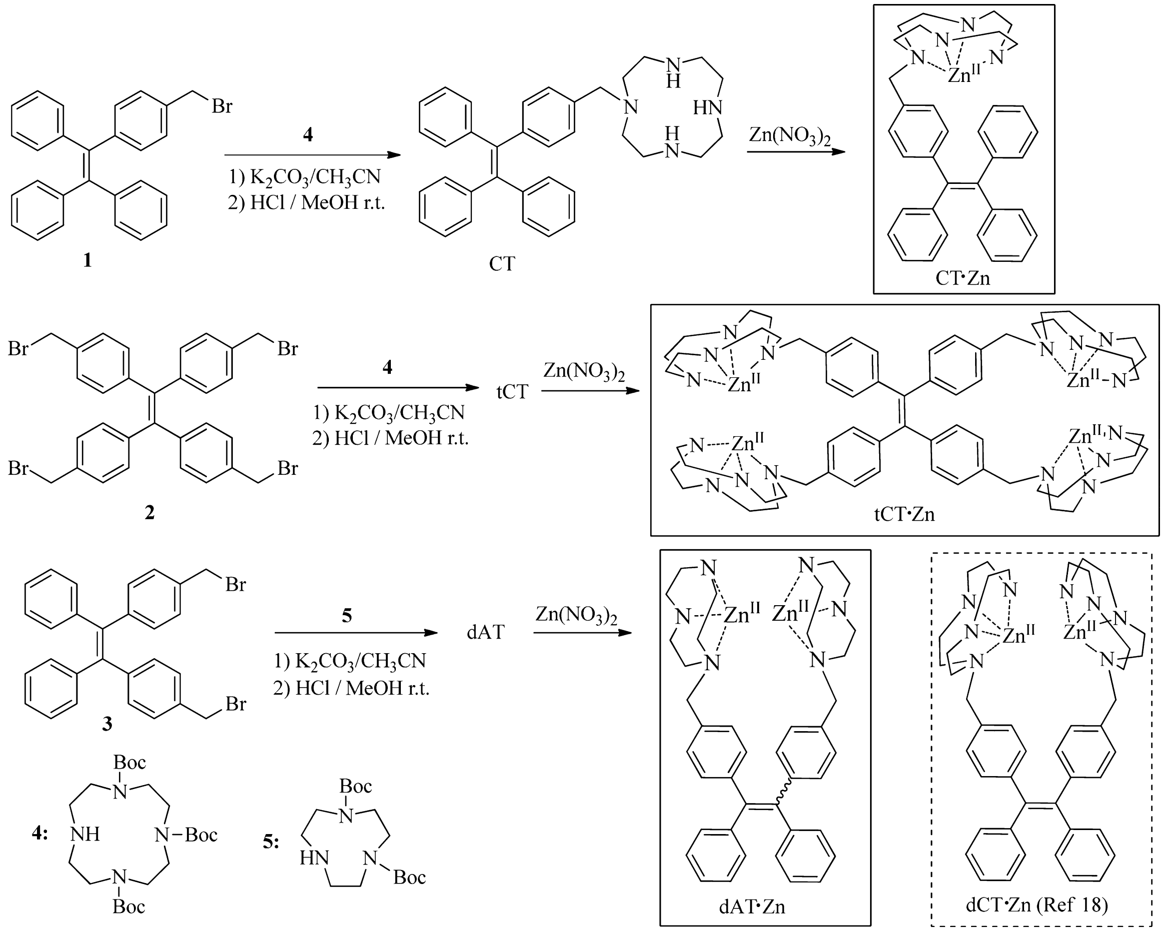
Synthesis and characterization of 1-(4-(1,2,2-triphenylvinyl)-benzyl)-1,4,7,10-tetraazacyclododecane (CT): A mixture of **1** (300 mg, 0.708 mmol), **4** (500 mg, 1.06 mmol) and K_2CO_3 (500 mg, 3.62 mmol) in acetonitrile was refluxed overnight. After the solution was concentrated, the residue was added to dichloromethane (100 mL), and the organic phase was washed with water and brine followed by drying over Na_2SO_4. The solvent was removed under reduced pressure; the crude product was purified by silica gel column eluting with EtOAc/PE (2:1, *v*/*v*) to give the product as a pale yellow solid (500 mg), yield 57.9%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13–6.98 (m, 19H), 3.64 (s, 2H), 3.57 (s, 4H), 3.34–3.15 (m, 8H), 2.65 (s, 4H), 1.50–1.46 (br, 27H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 143.6, 143.5, 143.0, 141.1, 140.6, 131.3, 129.6, 127.7, 126.5, 126.4, 79.3, 60.4, 57.9, 57.0, 53.4, 49.9, 48.6, 47.4, 47.0, 28.5.

The yellow solid achieved above (450 mg, 0.551 mmol) was dissolved in a saturated of HCl–methanol solution (100 mL) and stirred overnight at room temperature. The solvent and excess HCl were removed under reduced pressure, giving a yellow solid. The solid was dissolved in water and added pretreated anion-exchange resin until the solution is alkaline. Freeze-dried the solution to remove water and obtained the product as a pale yellow cotton-like solid (260 mg), yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12–7.09 (m, 9H), 7.07–7.03 (m, 8H), 7.00–6.98 (m, 2H), 3.56 (s, 2H), 2.80 (t, 4H, J = 8.0 Hz), 2.66 (t, 4H, J = 8.0 Hz), 2.57 (t, 8H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 143.8, 142.3, 140.8, 137.1, 131.4, 131.3, 128.2, 127.7, 127.6, 126.4, 126.3, 59.0, 51.3, 47.2, 46.4, 45.1; ESI-HRMS: *m/z* calcd. for $C_{35}H_{41}N_4$ $[M+H]^+$: 517.3326, found: 517.3326.

Synthesis and characterization of zinc 1-(4-(1,2,2-triphenylvinyl)benzyl)-1,4,7,10-tetraazacyclododecane (CT·Zn): To the methanol solution (15 mL) of CT (110 mg, 0.213 mmol) was added $Zn(NO_3)_2{\cdot}6H_2O$ (89 mg, 0.300 mmol) and stirred the solution overnight at room temperature. The solvent was evaporated under reduced pressure to give the yellow solid. The solid was washed with ethanol (5× 5 mL) and the mixture was centrifuged to afford the pure product as white solid (65 mg), yield 43%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.13–7.11 (m, 11H), 7.02–6.95 (m, 8H), 4.59 (s, 2H), 4.49 (s, 1H), 3.76 (s, 2H), 2.99 (br, 2H), 2.77–2.57 (br, 11H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 143.7, 143.5, 143.4, 143.3, 141.5, 140.5, 131.1, 130.3, 128.4, 128.3, 128.2, 127.1; ESI–HRMS: *m/z* calcd. for $C_{35}H_{40}N_5O_3Zn$ $[M+NO_3+Zn]^+$: 642.2417, found: 642.2372.

Synthesis and characterization of 1,1,2,2-tetrakis(4-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)phenyl)ethane (tCT): The preparation followed the similar procedure of CT with compounds **3** and **5**. Yellow solid, yield (110 mg, 12.1%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.09 (d, 8H, J = 8 Hz), 6.92 (d, 8H, J = 8 Hz), 3.64 (s, 8H), 2.81 (br, 16H), 2.68–2.61 (br, 48H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 142.6, 131.1, 129.1, 51.3, 47.9, 46.3, 45.1, 44.5; ESI-HRMS: *m/z* calcd. for $C_{62}H_{101}N_{16}$ $[M + H]^+$: 1069.8390, found: 1069.8390.

Synthesis and characterization of (*Z*)-1,2-bis(4-((1,4,7-triazonan-1-yl)methyl)phenyl)-1,2-diphenylethene (dAT): The preparation followed the similar procedure of CT with compounds **2** and **4**. Pale yellow cotton-like solid, yield (480 mg, 44.8%.) ^{1}H NMR (400 MHz, D_2O): δ 6.81–6.61 (m, 18H), 3.49–3.37 (br, 4H), 3.09 (s, 8H), 2.72–2.52 (m, 16H); ^{13}C NMR (100 MHz, D_2O): δ 143.2, 142.8,



Scheme 1. The structures and preparation routes of cyclen- and TACN–TPE based probes.