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Molecular recognition of amino acids with some fluorescent ditopic pyrylium- and pyridinium-based crown ether receptors

A. Moghimi[a,*], B. Maddah[b], A. Yari[b], M. Shamsipur[b,*], M. Boostani[a], M. Fall Rastegar[c], A.R. Ghaderi[a]

[a]Department of Chemistry, Imam Hossein University, P.O. Box 16575-347, Tehran, Iran
[b]Department of Chemistry, Razi University, Kermanshah, Iran
[c]Department of Chemistry, Carleton University, Ottawa, Ont., Canada

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Abstract

The molecular recognition of L-amino acids such as asparagine, glutamine, lysine and arginine with some crownpyryliums, CP's, and a crownpyridinium compound, as receptors, were examined in methanol. ^{1}H NMR spectroscopy was used to examine the structural stability of the receptors in the presence of the amino acids. The fluorimetric titration of the receptors by specified amino acids, other than arginine, was followed within a few minutes and the stoichiometry and stability of the resulting amino acid complexes were evaluated. The data analysis clearly demonstrated the critical role of the terminal amino group to carboxylic acid distance of amino acids for their proper fixation on the receptor molecules. Ion pairing for the two oppositely charged carboxylate anion and pyrylium (or pyridinium) cation, as well as the hydrogen bonding between crown ethers' oxygens and ammonium hydrogens are expected as the main interaction sources in the host–guest complexations.

Keywords: Crown ether; Amino acid; Molecular recognition; Pyrylium; Pyridinium; Spectrofluorimetry

1. Introduction

The assay of amino acids in different food, biological and chemical samples is of particular importance [1,2]. Due to the complex matrices often encountered, the analytical methods for amino acid determination rely heavily on the separation processes using liquid chromatography or capillary electrophoresis [3]. In addition, some extraction and derivatization steps are often required to achieve optimum selectivity and sensitivity [1,3]. Such methodologies do not lend themselves to rapid analysis, as might be required in industrial processes. Fluorescent sensing of amino acids is a very important task in biochemistry and molecular biology, with a special regard to determinations which require both temporal and spatial resolution [4]. However, only a few fluorescent chemosensors for amino acids have been described thus far. One includes a heteroditopic system, containing a NO_5 crown fragment and a guanidium subunit, suitable for linear recognition of analyses of formula NH_3^+–$(CH_2)_n$–COO^-, which displays selective behavior for $n=3$ [5] and signals the corresponding recognition process through a useful fluorescence off/on switching. The other one is a dizinc(II) cryptate, which recognizes histidine through the formation of an imidazolate bridge between the two Zn(II) centers [6], an event indicated by a less valuable on/off fluorescent response.

The design and molecular recognition of artificial receptors for amino acids have attracted extensive interest [7–15]. A receptor for zwitterionic amino acids has to be enantioselective, and can recognize the side chain, the positively charged ammonium group and the anionic carboxylate, simultaneously. Metalloporphyrins have been used as artificial receptors for amino acids because they can provide various multiple recognition sites via their central metal ions and various types of functional groups at the four meso positions and eight β-positions of pyrroles.

* Corresponding authors. Tel.: +98 217 313 930; fax: +98 217 313 938.
E-mail addresses: samoghimi@yahoo.com (A. Moghimi), shamsipur@razi.ac.ir (M. Shamsipur).

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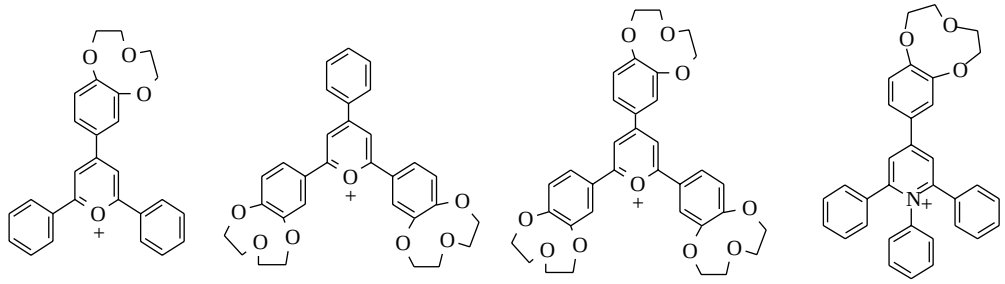

(I) (II) (III) (IV)

Fig. 1. Chemical structures of CP's **I–III** and crownpyridinium **IV**.

Ogoshi et al. [16–22] have synthesized a series of metalloporphyrins and applied them to the molecular recognition studies of amino acid esters. Xiao et al. [23] constructed a new type of amino acid recognition system, in which the host molecule was an unsymmetrical tetraphenylporphyrinatozinc(II) derivative bearing a carboxylate group at one of the four phenyl groups in porphyrin ring, and found a new binding mode for the recognition of amino acid esters. Recently, Ballistreri et al. have reported that calix [5] arenes bearing an urea unit at the upper rim show a strong affinity for ω-amino acids and lysine derivatives [24]. Rensing et al. [25] have investigated the optimization of benzylic bisphosphonates host molecule as synthetic arginine receptors and found out that the binding strength can be improved by increasing the π-cation as well as the electrostatic interactions. Gas phase studies by electrospray ionization mass spectrometry have shown that the protonated alkyl-guanidinium side chain of arginine forms a stable non-covalently bonded complex with dibenzo-30-crown-10 [26].

Based on the existing knowledge of molecular recognition and the specifications required for an appropriate artificial amino acid receptor, we have recently reported the synthesis of novel ditopic crownpyryliums, Fig. 1, and studied the recognition properties of CP **I** toward amino acids [27]. The excitation and emission spectra of **I** revealed that it has an absorption band at about $\lambda_{ex}=450$ nm and a fluorescence emission band at about $\lambda_{em}=580$ nm and the fluorescence intensity is sensitive to the concentration of appropriate amino acids. A related study has also been reported on some of pyridinium-based benzocrown ethers and their applications as ionophores [28].

In this article, we wish to report the synthesis of crownpyridinium **IV** and the recognition properties of receptors **II–IV** toward L-amino acids and to compare their recognition properties with those reported for **I** [27].

2. Experimental

2.1. Instrumentatation

All fluorescence spectra were recorded on a Perkin–Elmer LS-30 spectrofluorometer equipped with a Xenon lamp, a peristaltic pump, and a 7-μl flow-cell. The temperature was kept constant within ± 0.1 °C by means of a Huber C3 thermostat having a cooling operation machine (Germany). In order to provide thermostated titrations, a thermostat assembly including a water bath circulating system and a glass double layer vessel connected to the bath were used. All measurements were carried out at 20.0 ± 0.1 °C using a magnetic stirrer (~300 rpm). The solution NMR spectra were recorded on a Bruker Avance 250 MHz spectrometer. Samples of compound **IV** for both ^{1}H and ^{13}C NMR were obtained in 5-mm tubes at a concentration of 0.1 M in DMSO-d_6 solution. For other NMR studies, either DMSO-d_6 or CD_3OD solutions were used. All chemical shifts are reported in ppm downfield from TMS. The mass spectra were recorded on a MS80RFA mass spectrometer by positive ion ES at McGill University. The IR spectra were obtained with a Nicolet FT-IR 800 spectrometer using KBr discs. The melting points were measured on a digital Electrothermal FP61 apparatus and were uncorrected.

2.2. Materials

B9C3, HCO-B9C3 and pyrylium-based crown ethers **I–III** were synthesized and purified following the procedures described before [27,29,30]. Methanol (pro. grade, Merck) used as solvent, amino acids were purchased from Merck and all solutions were kept in a cool and dark place for next applications. Doubly distilled water was used throughout the fluorescence measurements. Glacial acetic acid (>99.5%) and aniline (>99%) were purchased from Merck.

2.3. Synthesis of IV

Compound **I** (0.3 g, 0.6 mmol) was added to ethanol (40 ml) in a 50 ml flask. The reaction mixture was heated in a water bath (70 °C) and then aniline (0.06 ml, 0.6 mmol) in ethanol (5 ml) was added dropwise. The reaction mixture was refluxed for 4 h and then filtered while hot. Glacial acetic acid (30 ml) and ethanol (6 ml) were added to the hot filtrate and allowed to cool to room temperature. Upon standing the solution, the yellowish needle crystals were