DESIGN AND SYNTHESIS OF IMIDAZOLIUM CYCLOPHANE

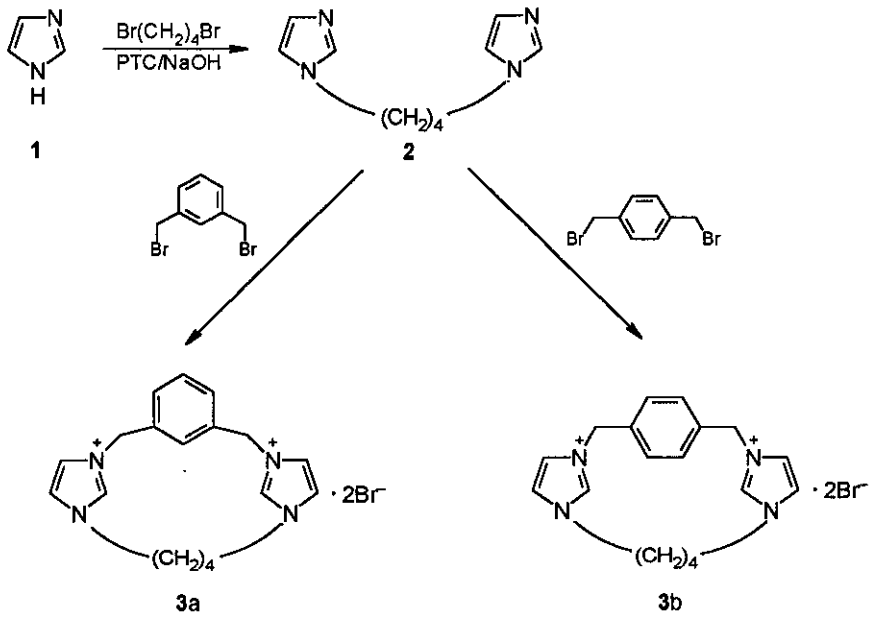
Meiming Luo, Shengjin Guo, Chenghe Zhou, and Rugang Xie*

Department of Chemistry, Sichuan University, Chengdu 610064, P. R. China

Abstract — 1, 4-Diimidazol-1-ylbutane (**2**) was prepared by PTC technique. Treatment of **2** with α, α'-dibromoxylene afforded novel imidazolium cyclophanes (**3a**, **b**) in good yields.

Host-guest complexation is a fundamental phenomenon in biological processes such as enzyme substrate interaction.[1] In these biochemical host/guest processes, onium compounds are of an importance in the electrostatic binding of substrate to enzyme. The large rate constant and catalytic specificity of enzymatic reaction are in part developed from the electrostatic stabilization of charged transition states by onium residues.[2]

Due to their cyclic structure and relatively hydrophobic enviroment in the interior cavity, cyclophanes exhibit enzyme-like behavior.[3-5] Among various types of cyclophanes, onium cyclophanes have attracted increasing attention for their effective inclusion-electrostatic catalysis.[5-7] Although a lot of onium cyclophanes have been documented in the literature, imidazolium cyclophane, to our knowledge, is hitherto unknown. To further develop and generalize the cyclophane chemistry, it is important for the imidazolium cyclophane to be studied, and it is to this goal that we are investigating imidazolium cyclophane and herein wish to report the design and synthesis of imidazolium cyclophane (**3**). The two imidazolium residues (catalytic site) are fixed at the definite position of the macrocycle (binding site), constituting a unique active site for an enzyme model. When **3** is employed to catalyze a reaction, in which a negatively charged transition-state complex is developed, the reaction would be facilitated not just by its discriminating binding of substrate, but also by its electrostatic stabilization of the anionic transition state.



Scheme 1 Route for synthesis of **3**

The synthetic route of **3** is depicted in Scheme 1. It was reported[8] that 1,4-diimidazol-1-ylbutane (**2**) was produced by treatment of imidazole (Im.) with 1,4-dichlorobutane in DMSO. In view of the phase transfer catalysis (PTC) has not been employed previously for the synthesis of compound (**2**) and its analogs, using tetra-n-butylammonium iodide as phase transfer catalyst, we prepared the intermediate (**2**) in 75% yield by reaction of imidazole with 1,4-dibromobutane in benzene/water in the presence of sodium hydroxide.

The imidazolium cyclophane (**3a**) and (**3b**) were prepared by treating **2** with α,α′-dibromo-*m*-xylene and α,α′-dibromo-*p*-xylene in acetonitrile respectively. We have found that important factor affecting this reaction is the variety of solvent. Experimental results showed that acetonitrile was preferable to DMF. In acetonitrile, the yields of **3a** and **3b** were 84% and 79%, while in DMF, relatively low yields, 33% for **3a**, 29% for **3b** were obtained.

The ^{1}H-nmr peaks of compound (**3**), δ 9.1-8.2 ppm for Im^+ H-2, 5.5-5.7 ppm for Im^+ CH_2Ph and 4.2-4.4 ppm for Im^+ CH_2alkyl strongly suggest the formation of imidazolium moieties[9] Despite no molecular ion appeared in the mass spectra, the fragement ion m/z 373(M^+-Br) and 293 (M^+-2Br) support the unique cyclic structure of **3**. The thermo-gravimetric analysis and elemental analysis show that compounds (**3a,b**) obtained

were monohydrates.

EXPERIMENTAL

Melting point was measured on micro-melting point apparatus and uncorrected. The ir, nmr and ms spectra were recorded on Nicolet FT-IR 170SX, JEOL FX 90 and Finigan MAT 450 respectively. Elemental analysis was carried out with Carlo-Erba 1106 instrument. Thermogravimetric analysis was performed with Du Pont 951 Thermogravimetric Analyzer.

Procedure for preparation of **2** A mixture of imidazole (1.76 g, 26 mmol), 1,4-dibromobutane (2.7 g, 13 mmol), NaOH(5 g, 125 mmol), $(n\text{-}Bu)_4N^+I^-$(0.3 g, 0.8 mmol), benzene (12 ml) and water (5 ml) was refluxed for 36 h under stirring. After cooling to room temperature, the mixture was filtered off. Recrystallization of the obtained solid from water afforded 1.7 g(68%) of white product. The aqueous phase was seperated and extracted with benzene. The combined extracts were dried with Na_2SO_4, filtered and evaperated to give a second crop (0.15 g, 7%) which was indistinguishable from the first in all respects. The combined crops gave 1.85 g(75%) of pure white product.

1,4-Diimidazol-1-ylbutane (**2**) Yield 75%, mp 61-63 ℃(83-86 ℃)[8]

General procedure for preparation of **3** To a solution of 1,4-diimidazol-1-ylbutane (**2**) (380 mg, 2 mmol) in acetonitrile (30 ml), α,α′-dibromoxylene (264 mg, 2 mmol) in acetonitrile (10 ml) was added dropwise in 40 min at 60 ℃ under stirring. The mixture was stirred at 60 ℃ for 20 h, followed by evaporating to remove acetonitrile. The resulting solid was dissolved in water and the insoluble precipitates were filtered off. The filtrate was evaporated to dryness in vacuo. The solid obtained was washed with acetone and ether, and dried in vacuo with a P_2O_5 trap.

[1]Metacyclo[1,4](1,3)imidazolophanium dibromide (**3a**) Yield: 84%, mp 287-290 ℃(methanol). Anal. Calcd for $C_{18}H_{22}N_4Br_2 \cdot H_2O$: C, 45.76; H, 5.12; N, 11.87; Br, 33.87; Found: C, 45.82; H, 4.95; N, 11.60; Br, 33.75. ^{1}H-Nmr (D_2O) δ 9.07-8.93 (2H, d, J=13.19 Hz, Im^+ H-2), 7.72-6.64(8H, m, Ar-H, Im^+ H-4, H-5), 5.60-5.57(4H, d, J=2.64 Hz, Im^+ CH_2Ph), 4.40(4H, br s, Im^+ CH_2alkyl), 2.05-1.90 (4H, d, J=13.77 Hz, Im^+ $CCH_2CH_2CIm^+$). Ms m/z: 373

(M^+-Br), 293 (M^+-2Br).

〔1〕Paracyclo〔1,4〕(1,3)imidazolophanium dibromide (**3b**) Yield: 79%, mp 284-287 ℃(methanol). Anal. Calcd for $C_{18}H_{22}N_4Br_2 \cdot H_2O$: C, 45.76; H, 5.12; N, 11.87; Br, 33.87; Found: C,45.61; H, 5.29; N, 11.67; Br, 33.52. ^{1}H-Nmr (D_2O) δ 8.98-8.19 (2H, d, J=8.42 Hz, Im^+ H-2), 7.78-7.46 (8H, m, Ar-H, Im. H-4, H-5), 5.50 (4H, s, Im^+ CH_2Ph), 4.33-4.21 (4H, br s, Im^+ CH_2alkyl), 2.04-1.90 (4H, br s, Im^+ $CCH_2CH_2CIm^+$). Ms m/z: 373 (M^+-Br), 293 (M^+-2Br).

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