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Synthesis and Association Behaviour of Pyridine Based 18-Membered Diamide - Diester - Thioether Macrocycles[†].

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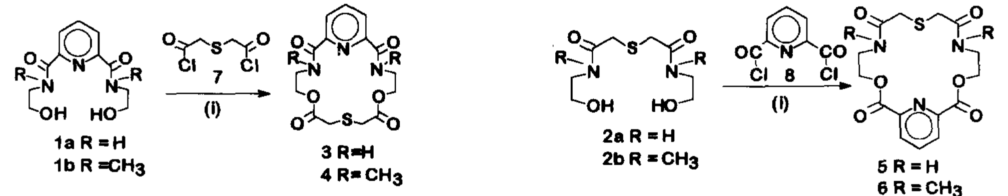
Abstract: Macrocycles; **5** lacking intramolecular hydrogen bonding and **4** and **6** with three dimensionally organised ligating sites bind Ag^+ with remarkable selectivity.

The in-built configurational rigidity around amide carbon nitrogen bond through steric control and hydrogen bonding, where possible, has shown paramount influence in the preorganisation of synthetic receptors and consequently their binding selectivity[1]. However, in pyridine - amide macrocycles, the N_{py}----HN_{amide} hydrogen bonding is deterimental to cation binding[1a]. Hence, we envisaged that in such macrocycles, the presence of -CH_2-S-CH_2 linkage in place of a pyridine unit, both due to its binding preference towards soft cations and lack of intramolecular hydrogen bonding would induce silver selectivity. Based on these features and the optimal requirement of 2-4 coordinating sites for Ag^+ receptors[2], we have designed 18-membered amide -ester receptors (**3-6**) and have found that amongst planar receptors **3** and **5**, the latter which lacks intramolecular hydrogen bonding and the receptors **4** and **6** with three dimensional cavity, show remarkable extraction selectivity towards Ag^+.



(i) = KF, TBA HSO_4 in CH_3CN or CH_2Cl_2

The diols **1** and **2** obtained by condensation of corresponding diesters with aminoalcohols, cyclise with acid chlorides (**7**/**8**) to give respective macrocycles **3** (23%), m.p. 200°C, M^+ m/z 367; **4** (13%), m.p. 135°C, M^+ m/z 395; **5** (18%), m.p. 155°C, M^+ m/z 367; **6** (13%), m.p. 185°C, M^+ m/z 395.The ^1H nmr ($CDCl_3$) spectra of compounds **3** and **5** show normal singlet for SCH2; triplet for OCH2 ; quartet for HNCH2 and 1H triplet and 2H doublet for PyH which support their planar configuration. In **3**, the appearance of NH signal (δ8.62) at lowerfield by Δδ +0.82 in comparison with NH in compound **5** (δ7.80), shows the presence of N_{py} ----HN_{amide} hydrogen bonding. The ^1H (^{13}C) nmr spectra of **4** and **6** show multitude of signals for each chemically equivalent proton (carbon) and point to their existence in more than one conformation and their three dimensional structures, also envisaged in their CPK models.

Extraction behaviour[3] of **3-6** have been determined towards picrates of cations. **4** extracts Ag^+ 34% and Pb^{2+} 1.39%, whereas other cations Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+} and Tl^+ are extracted by less than 0.1% amounts (fig. **1**). The multiple signals of each chemically equivalent CH_2 or CH_3 units in the ^1H and ^{13}C nmr spectra of **4** on addition of silver picrate spectacularly merge to one signal each for every chemically equivalent proton and carbon respectively. This phenomenon is not observed with other cations. Therefore **4** has such a high propensity of binding with Ag^+ that it undergoes conformational changes during complexation. This phenomena is quite similar to the one observed in a silver selective marine compound[4].

Macrocycle **6** in solution phase exists in more than one conformation (^1H and ^{13}C nmr) which on addition of Ag^+ or Pb^{2+} picrate do not converge to one. Its CPK model also elaborates its relatively rigid structural framework than **4**. However, **6** extracts Ag^+ 62% and Pb^{2+} 7.7%.

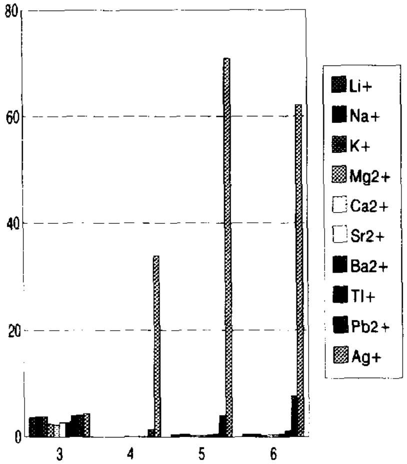


Fig. 1 Extraction (%) profile of macrocycles 3-6

Amongst the macrocycles **3** and **5** which possess planar configuration, the macrocycle **3** shows poor and nearly similar extraction of all the cations (fig **1**) but **5** shows quite selective extraction of Ag^+ over Pb^{2+} and other cations. Probably, the absence of intra-molecular hydrogen bonding in **5** allows out of plane placement of its -S- resulting in availability of both -S- and pyridine N for forming stable linear complex with Ag^+, which is not possible for other cations.

Evidently in these macrocycles, the replacement of pyridine diamide unit with $NHCOCH_2SCH_2CONH$ induces copious Ag^+ selectivity.

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[†]Dedicated to Prof. U.K. Pandit on his 65th birthday.

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3. Conditions: 2 ml Metal picrate(0.01M)/ 2ml, H_2O; Ionophore (0.01M), 2ml $CHCl_3$.The values are in terms of % extraction. Each value is the mean of three independent measurements which are consistent within ± 1% error. Moore, S.S.; Tarnowski, T.L.; Newcomb, M.; Cram, D.J. J.Am.Chem.Soc., **1977**, 99, 6398.
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