

A Simple Quantitative Structure-Property Relationship (QSPR) Approach to Stability Constants of Metal-Crown Ether Complexes in Methanol

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The discovery of crown ethers in late 60's as effective metal cation carriers (ionophores) opened a new area in metal chemistry. Ionophores are used today for complexation (in homogeneous solutions) or solvent extraction of alkali, earth alkaline, transition and other metals. The search for desired metal selectivity of crown ethers and other ionophores in one- or two-phase liquid systems is interesting from the point of view of analytical chemistry, because related analytical techniques are employed in vital, agricultural, biological and industrial processes. These search efforts are still predominantly empirical. This work is a theoretical approach (QSPR: Quantitative Structure-Property Relationships) to model stability constants of complexes formed by cations Ag^+ , Na^+ , K^+ , Mg^{2+} , Ca^{2+} , Sr^{2+} and Ba^{2+} and four crown ethers in methanol: 18-crown-6 (18C6), dibenzo-18-crown-6 (DB18C6), dicyclohexyl-18-crown-6 (DCY18C6), and dibenzopyridino-18-crown-6 (DBPY18C6).

Measured stability constants for the 28 complexes were from literature¹. Various atomic descriptors for metals and ligand descriptors for the crown ethers were collected from literature or were calculated from the crystal structures of crown ether and metal complexes retrieved from the Cambridge Structural Database (CSD). Five descriptors were manually selected for the final QSPR model: cation radius, metal electron affinity, mean metal-O,N bond length (from CSD median values), and two more steric descriptors. These two descriptors included the metal radii and metal-O,N bond lengths, macrocycle size (average O-O,N diametral distances from the CSD median values), and O,N van der Waals radii. Autoscaled data were then used in the Partial Least Squares (PLS) regression to predict metal-macrocycle binding constants in log form. The dataset was also used in exploratory analysis (Principal Component Analysis - PCA and Hierarchical Cluster Analysis - HCA).

The descriptors are moderately correlated with the stability constants (absolute correlation coefficients are 0.44-0.75). Three principal components (PCs) were used for the PLS model (99.2% of the total variance), resulting in acceptable QSPR statistics: $Q = 0.730$, $R = 0.830$, $SEV = 0.46$, $SEC = 0.40$, 7 samples with relative error greater than 10% (10-16%). The regression vector and correlograms show relationships that can be well interpreted chemically. Higher complex stability is related to larger ions that are tightly bound to the macrocycle and probably to the solvent, ions that are displaced from the O,N macrocycle plane due to their size and higher coordination number (more than 6), and ions with higher electron affinity (good electron acceptors in coordinative bonds). Small variations in the stability constants originate from the differences in crown ether structures. More rigid DB18C6 and DCY18C6 are basket-shaped and somewhat poorer binders. More flexible 18C6 and DCY18C6 (with cyclohexyl units acting as additional arcs) are better metal binders. Ag-DBY18C6 is an exception due to electronic effects accounting for pyridine-Ag bond. Crystal structures for the CSD and simple molecular modeling were used to visualize stereoelectronic relationships in the complexes and other related structures.

Clustering of the samples is almost identical in PCA (3 PCs: 99.6% of the total variance) and HCA, and agrees with previously noted trends. There are seven metal clusters at similarity index 0.85 (complete linkage was used), among which that for Mg is isolated, and Ba-K and Ca-Na clusters form a group at similarity index around 0.75. PC1 is mainly related to the cation size, whilst PC2 distinguishes well metal groups *i.e.* discriminates alkali (Na, K) from alkaline earth (Mg, Ca, Sr, Ba) and other (Ag) metals.

The presented approach to model metal-crown ether stability constants was based on available structural data from literature and structural databases and not on descriptors from molecular modeling. This methodology can be expanded to other metal-macrocycle systems and used in practice as the first-aid QSPR that provides reasonable interpretation of the obtained results.

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References

¹Zolgharnein J.; Tahmasebi H.; Habibi M.; Amani S. J. *Inclus. Phenom. Macrocyc. Chem.* **2004**, *49*, 231-234.