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Concave reagents

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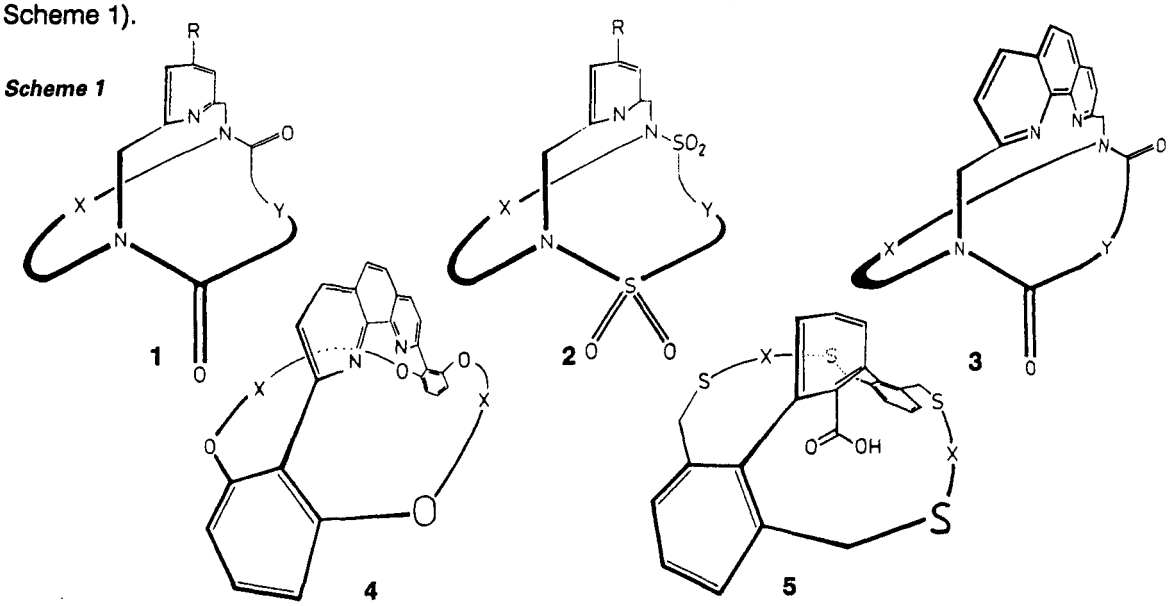
Abstract. Concave Reagents are molecules in which standard reagents of organic chemistry are incorporated into concave structures. Via combination of acidic or basic centers with bimacrocyclic systems, Concave Pyridines **1** and **2**, Concave 1,10-Phenanthrolines **3** and **4** and Concave Benzoic Acids **5** could be synthesized. The influence of the concave structure on the selectivities of these new reagents could be shown in protonations of nitronate ions and in base-catalyzed additions of alcohols to diphenylketene. Improvements towards enantioselectivity and towards easier recovery (polymer-bound Concave Pyridines) are presented, too.

The high stereoselectivity of enzymes is mainly caused by the concave shielding of the reactive centre. In order to increase selectivities of standard reagents of organic chemistry we have placed functional groups into a concave environment. Like a light bulb is placed in a lamp shade we have put 2,6-disubstituted pyridines, 2,9-disubstituted 1,10-phenanthrolines and 2,6-disubstituted benzoic acids into bimacrocyclic systems, generating Concave Acids and Bases (see Scheme 1).

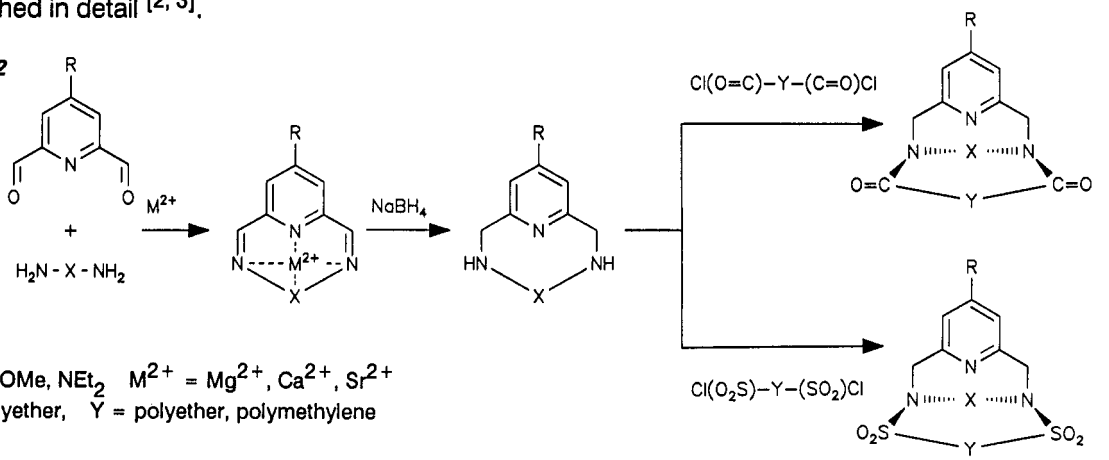
Scheme 1



All Concave Acids and Bases of Scheme 1 are bimacrocyclic systems but they differ in the nature of the bridgeheads. In the Concave Pyridines **1** and **2** and in the Concave 1,10-Phenanthroline **3**, the bridgehead is a nitrogen atom, and in order to avoid a competing basic centre, the bridgehead basicity was decreased by choosing carbonamides or sulfonamides. The synthetic strategy for the construction of these bimacrocyclic bisamides is depicted in Scheme 2 and published in detail [1]. By a metal ion template synthesis macrocyclic bisimines are built up, reduced to diamines, and then bridged by bis(acyl chloride)s or by bis(sulfonyl chloride)s.

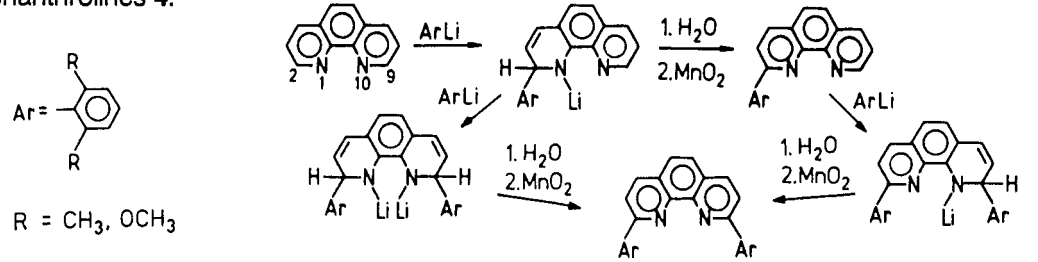
The bridgeheads of the Concave 1,10-Phenanthrolines **4** and the Concave Benzoic Acids **5** however are not trivalent atoms but trisubstituted arylrings. In the syntheses of these bimacrocycles, first the bridgeheads, the trisubstituted phenyl rings, are introduced into the 2,9- or 2,6-positions of 1,10-phenanthroline or of a benzoic acid precursor, respectively. Then the substituents of the aryl bridgeheads are functionalized. The last step of the synthesis of **4** and **5** is the bismacrocyclization of non-macrocyclic starting compounds i. e. no monomacrocyclic intermediates have to be isolated. Scheme 3 and 4 show the syntheses of **4** and **5** which are also published in detail [2, 3].

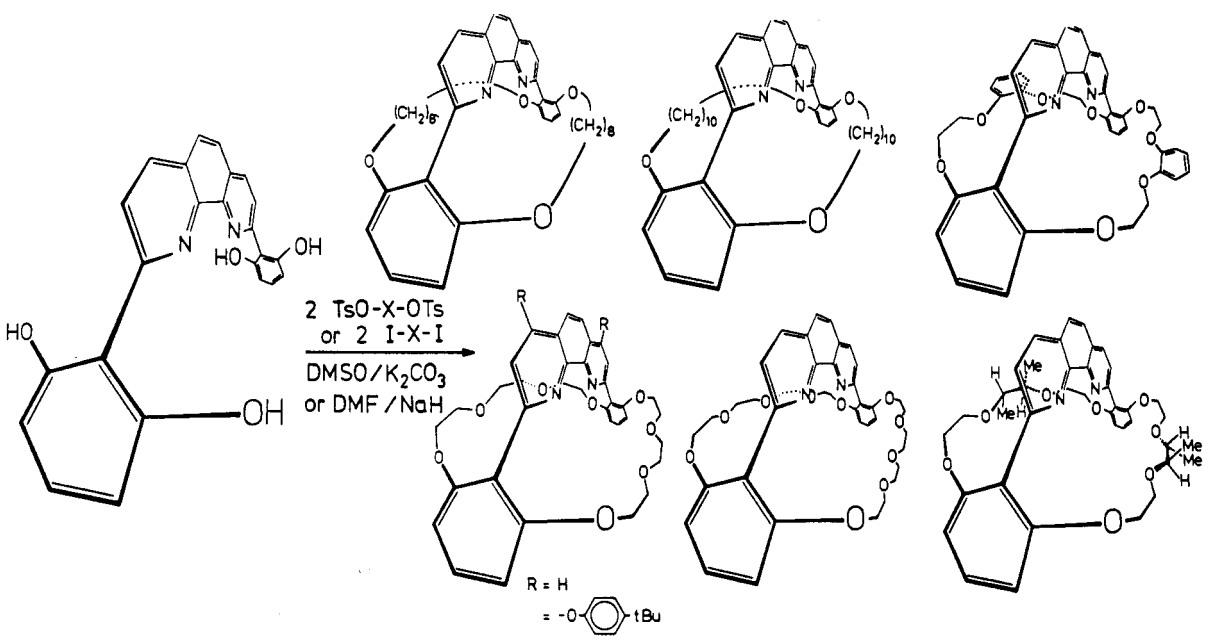
Scheme 2



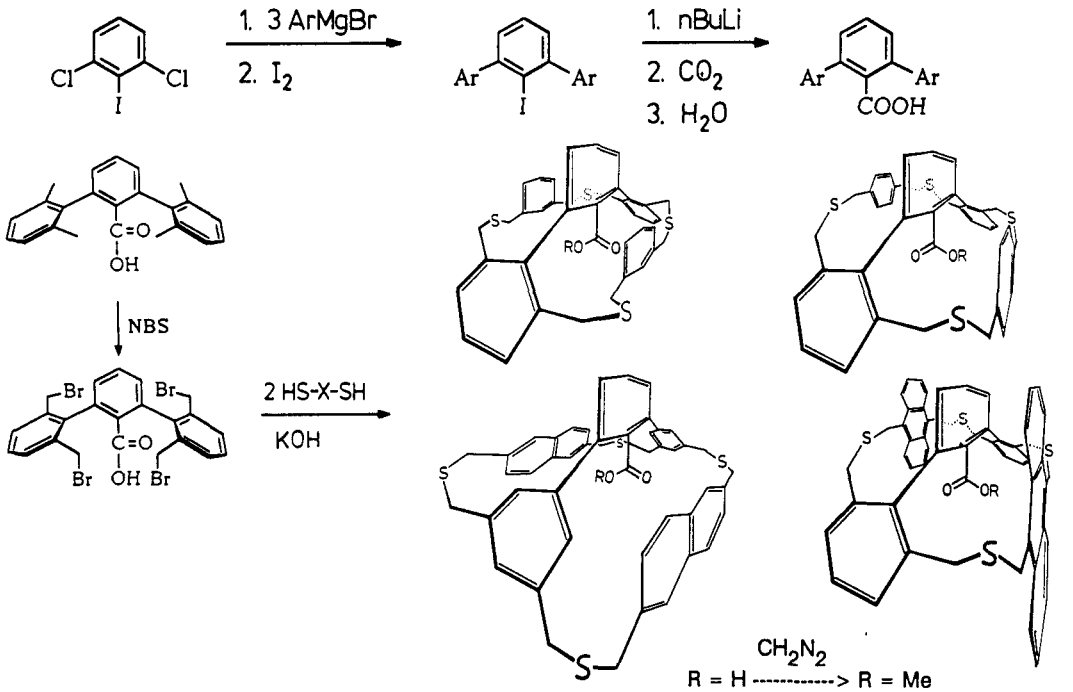
R = H, OMe, NEt_2 M^{2+} = Mg^{2+}, Ca^{2+}, Sr^{2+}
X = polyether, Y = polyether, polymethylene

Scheme 3 2,9-Diarylsubstituted 1,10-phenanthrolines can be synthesized by addition of substituted aryl lithium compounds to 1,10-phenanthroline. When R was methoxy, ether cleavage was possible with BBr_3 yielding a tetraphenol which then could be bridged to give Concave 1,10-Phenanthrolines **4**.



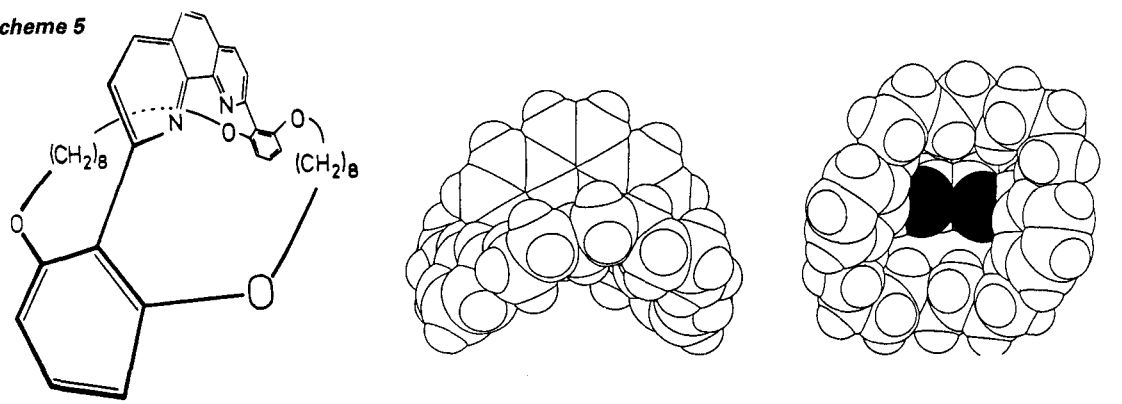


Scheme 4 Concave Benzoic Acids are synthesized by bridging a m-terphenyl precursor. In the case of the naphthalene bridged Concave Acid the starting *m*-terphenyl carried the methyl groups in 3- and 5-position of the outer benzene rings.



While titrations proved that the acidic or basic properties of the Concave Reagents **1** - **5** were conserved in a bimacrocyclic concave environment [1, 2, 3], X-ray analyses [1b, 3a, 4] showed the concave geometry and that the functionality is located on the inside. Scheme 5 shows two views of a Concave 1,10-Phenanthroline **4** [with X = $(CH_2)_8$]. Using a computer program (Connolly routine [5]), the accessibility of the nitrogen atoms of the 1,10-phenanthroline unit was monitored by rolling spheres of varying sizes over the van der Waals surface of this Concave Base: up to a radius of 2.8 Å the sphere may get into contact with the nitrogen atoms through the macrocyclic ring. In other words, molecules or parts of molecules with a diameter larger than 5.5 Å should not be able to react with the basic nitrogen atoms [4].

Scheme 5

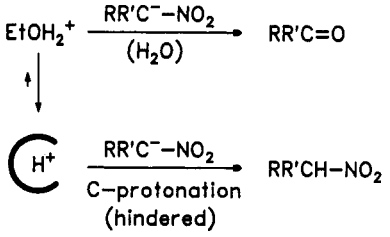


In two model reactions the size selectivity suggested by the Connolly investigation was checked. First the protonation of nitronate anions by buffers containing Concave Acids and Bases was investigated. In strong acidic milieu, nitronate ions are O-protonated and the resulting *aci*-nitro compound may be hydrolyzed to carbonyl compounds (Nef-reaction). In buffers, e.g. pyridine/pyridinium buffers, the nitronate ions are C-protonated to yield nitro compounds. If now

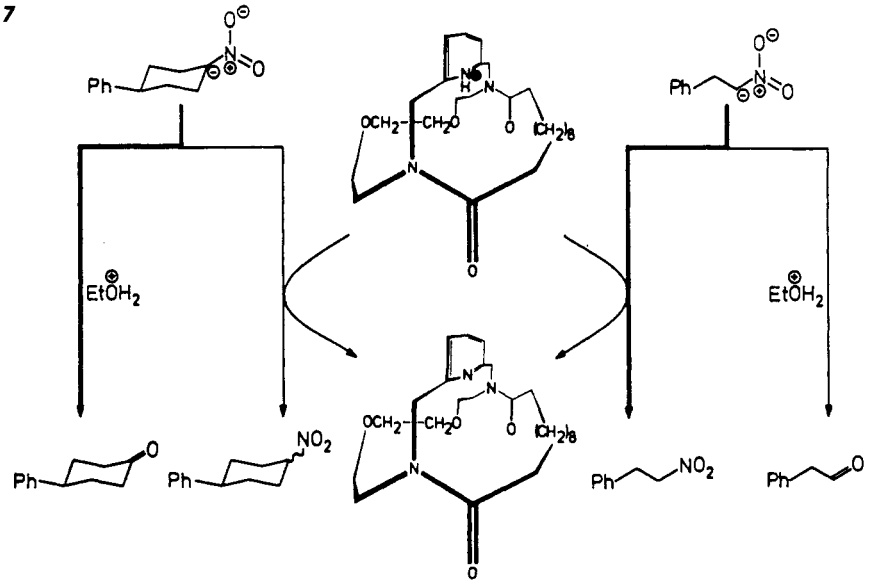
buffers of Concave Pyridines with the same basicity and the same concentrations (i.e. identical *p*H) are used for the protonation, again the products of the Nef reaction are found [6]. In other words, the Nef reaction which usually takes place in acidic milieu can now be carried out under softer conditions due to a hindered C-protonation. We call it the "**soft Nef-reaction**" (see Scheme 6).

The soft Nef-reaction can be applied to different nitronate ions, to primary and secondary ions and as well to open-chain and cyclic compounds. If the Concave Pyridine is chosen well, in a competition reaction the primary 2-phenylethylnitronate ion can be selectively C-protonated while secondary ions form the Nef products. Concave Pyridine buffers show **substrate selectivity** [7].

Scheme 6 The Soft Nef-Reaction. The C-protonation by protonated Concave Bases (proton in circle) is hindered leading to the Nef product via O-protonation by $EtOH_2^+$.



Scheme 7

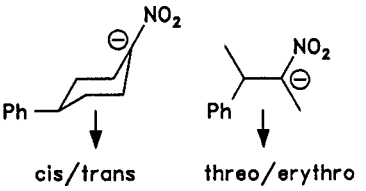


The C-protonation products of the cyclic nitronate ion in Scheme 7 may exist in form of two stereoisomers. For normal pyridine buffers the stereoselectivity of the protonation is in favor of the thermodynamic less stable *cis*-product. The larger the α-substituents in the pyridines are the more *cis*-product is formed. Therefore, the stereoselectivity of protonations by buffers of Concave Pyridines which are pyridines with enormously large α-substituents were checked. To avoid the soft Nef-reaction, the buffers had a high *p*H. But hardly any stereoselectivity was found when Concave Pyridines were used in this protonation. However when 2-[bis(*ortho*-substituted)-aryl]-1,10-phenanthroline buffers were used, the thermodynamic less stable *cis*- and *threo*-compounds were formed in large excess in the case of the C-protonation of the 4-phenylcyclohexylnitronate ion and the 3-phenyl-2-butylnitronate ion. Scheme 8 shows the data for this **contra-thermodynamic** and **stereoselective** protonation [8].

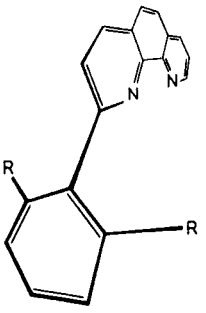
The reason for this selectivity is the concave wrapping of the protons by the Concave Bases. In the transition state the wrapped proton is a very large pseudo-substituent whereas in the product the hydrogen atom is the smallest substituent. For the cyclic nitro compound the transition states and the products are shown in Scheme 8, too.

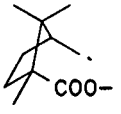
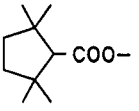
While in the nitronate protonation reaction the Concave Reagents were used at least stoichiometric and the reacting reagent was the conjugated acid, the second model reaction is a **base catalysis**. A variety of Concave Pyridines and Concave 1,10-Phenanthrolines was used to catalyze the addition of alcohols to diphenylketene. The Concave Bases do catalyze this reaction but the catalytic power is depending on the basicity of the base and also on the size of the bimacrocycles [9] (see Scheme 9).

Scheme 8

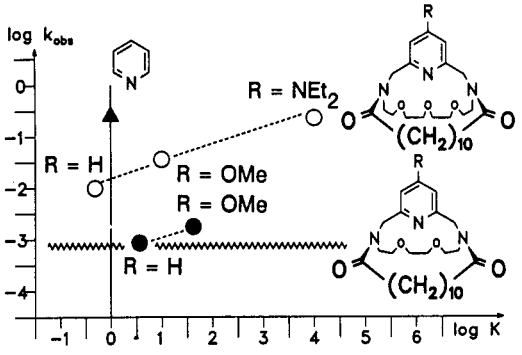


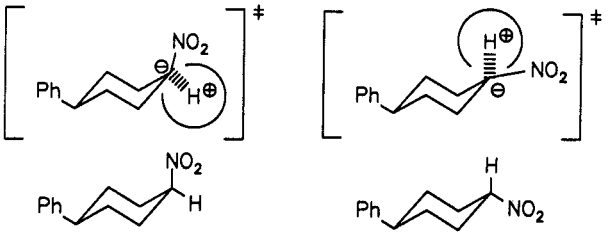
	cis/trans	threo/erythro
equilibrium	0.2 – 0.25	< 1
pyridines	0.7 – 3.4	0.9 – 1.2
Concave Pyridines	0.6 – 1.0	–
Concave 1,10-Phenanthrolines	0.7	–



R = H	1.5	–
R = Me	8.0	–
R = OMe	8.7	1.0
R = OAc	2.7	10.4
R = OOCtBu	16.1	1.1
R = 	13.3	27.4
R = 	12.6	0.9

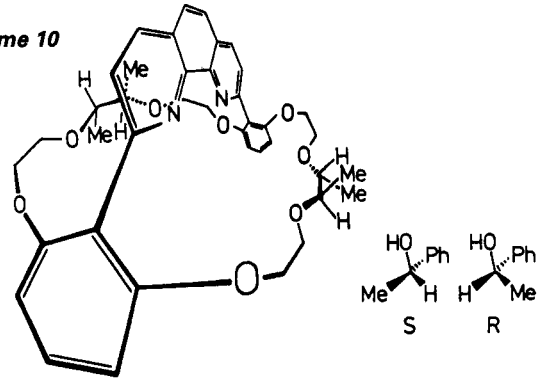
Scheme 9 The logarithms of observed rate constants, log k_{obs}, for the base catalyzed addition of ethanol to diphenylketene are plotted against the relative basicity log K [10] of the Concave Bases (Brønsted-plot). The horizontal line indicates the rate of catalysis by an amide group.





But also when the base was kept constant and the alcohol was varied, differences in the rate of addition (i.e. selectivity) could be found. Even **enantioselectivity** was found when a chiral Concave Base was used as catalyst. The chiral Concave 1,10-Phenanthroline shown in Scheme 10 catalyzes the addition of *R*-1-phenylethanol 20 % faster than the addition of the *S*-enantiomer [4].

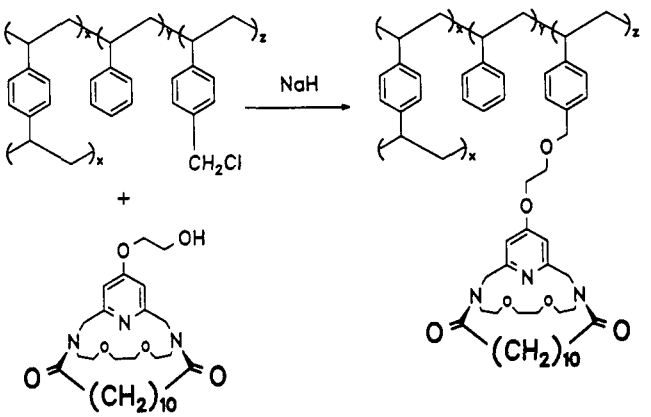
Scheme 10



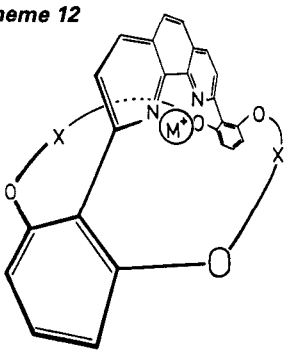
In the model reactions one draw-back of the Concave Bases became apparent; the reagents had to be recycled after each model reaction. In order to facilitate this recovery, a strategy was worked out to attach a Concave Pyridine to a polymer. In Scheme 11, a Concave Pyridinebislactame was substituted in 4-position by a spacer and then bound to a Merryfield resin by nucleophilic substitution [11].

The model reactions have shown that Concave Acids and Bases may be used to increase selectivities. For the future, (i) the effects found in the model reactions have to be transferred to application and (ii) the general strategy of embedding a functionality in a concave environment shall be extended to other reactions, e.g. to redox-reactions. There the Concave 1,10-Phenanthrolines may play an important role as ligands for redox-active transition metals as shown in Scheme 12.

Scheme 11



Scheme 12



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[5] Based on the X-ray data, in the Connolly routine, spheres of varying sizes are rolled over the van der Waals surface of the molecule, and the resulting contact surface is monitored. QCPE program No. 429 by M. L. Connolly, used with Chem-X, developed and distributed by Chemical Design Ltd., Oxford, England.

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[10] Log K parallels the pK_a scale. For a definition see [1c].

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