Concave reagents

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The concave geometry of enzymes is important for the high selectivity of their reactions. By analogy, the incorporation of standard reagents of organic chemistry into a concave environment gives concave reagents with a geometry resembling that of a light bulb in a lampshade. Selectivity enhancements have been realized in protonations, base catalysed reactions and metal ion catalysed reactions.

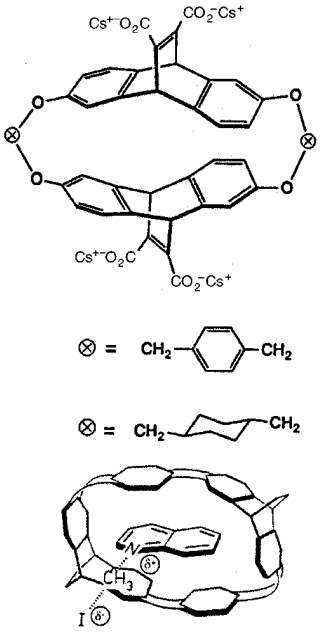
The geometry of enzymes is one factor which determines their high selectivity. The reactive centre is embedded in a concave pocket of the protein, and these geometrical factors are responsible for a large part of their extraordinary selectivity (lock and key principle[1]).

Therefore enzymes have been more and more often used as reagents in organic chemistry. However, they cannot be used in all cases for the following reasons: (i) many reactions exist for which no enzyme is known; (ii) enzymes are very specific, and are often unreactive when the substrate has been modified slightly, or the selectivity diminishes drastically when the substrate is varied; (iii) enzymes are labile, and often cannot be handled in organic solvents, at low and high pH values, in solution with high ionic strength or at high temperatures. Therefore, many approaches have been used to try to understand the action of enzymes and to mimic them with artificial systems.[2]

Enzymes accelerate reactions by binding the transition state and thus lowering its energy. For the methylation of quinoline, the stabilization of the transition state and thus an acceleration of the reaction has been achieved with a cyclophane which is able to bind positively charged guests.[3]

Other approaches to mimicking enzymatic activity have taken coenzyme moieties, especially the coenzymes of the vitamin B series, and incorporated them into macrocycles or attached them to binding sites.[2] Hydrolases have been mimicked by placing acidic and basic centres into geometrically defined host molecules.[2] A well defined orientation of an acidic and a basic centre is also responsible for an enolization and a hemiacetal cleavage catalysed by an artificial host system.[4] The accelerated oxidation of a diphenolic benzyl alcohol[5] is also caused by geometrically well defined binding regions and reactive sites.

Further mimicking activities have concentrated on the activation of a substrate by binding it to a host system. Also effective are systems that bind two components in close proximity to allow and accelerate a bimolecular reaction. Successes have been observed in hydrolyses,[6] regioselective 1,3-dipolar cycloadditions,[7] Diels–Alder reactions and acyl transfer



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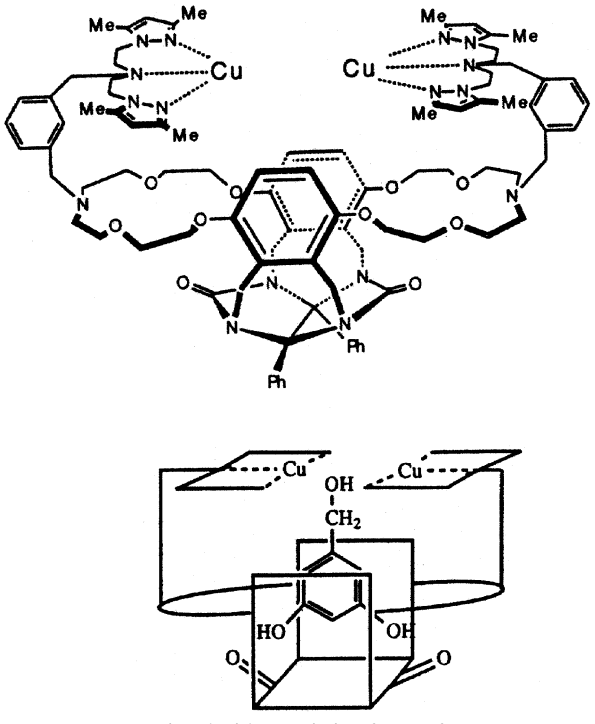

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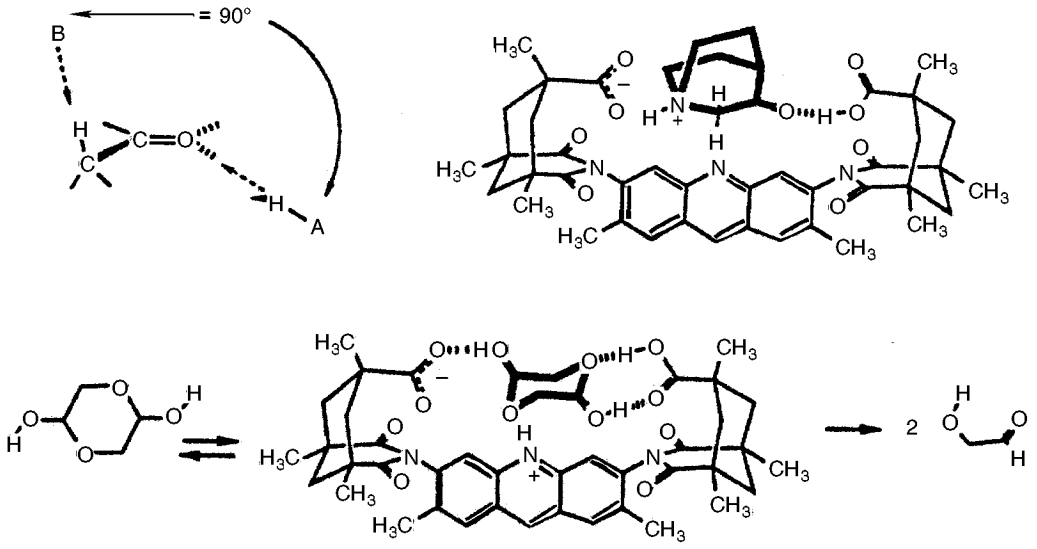

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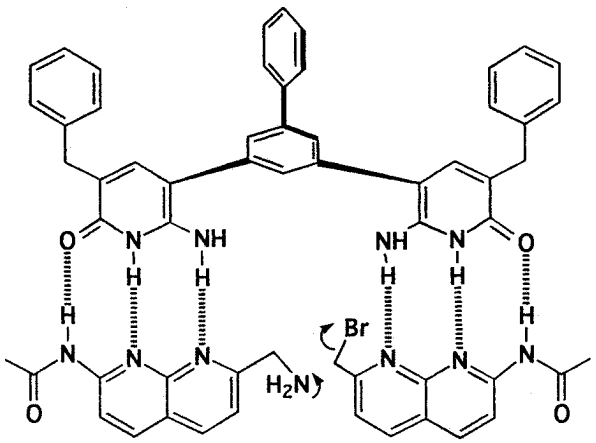
reactions.[8] Non-macrocyclic templates have also been synthesized for nucleophilic substitution reactions.[9]

If the product of such a reaction is the template itself, replication may be observed, an aspect of the well studied field of molecular self-organization.[10] The systems first used to investigate self-replication were nucleotides (as in nature),[11] but the formation of amides[12] and Schiff bases[13] can also be catalysed autocatalytically.

The interpretation of the data obtained from reactions involving catalysts, especially autocatalysts, is difficult. Catalysis by other molecules in the mixture and/or product inhibition[8] leads to complex kinetic behaviour.[14]

In summary, current efforts to mimic enzymes have met with limited success, and the catalytic efficiency of enzymes has yet to be reached for artificial systems.[2a] However, the insight gained into the mechanisms of enzymes gives guidelines for the development of non-enzyme catalysts and reagents which will be especially useful if the reaction cannot be carried out by enzymes.

It should be noted that three different types of interaction between a substrate and a concave host are possible: reaction, catalysis and host–guest complex formation. In a reaction as well as during catalysis, the concave molecule induces a change in the substrate. But during a reaction the host molecule itself is also altered, *e.g.* oxidized or reduced, protonated or deprotonated. During catalysis, however, the host molecule leaves the reaction unchanged and will be able to participate in the next catalytic cycle. But the third interaction, the formation of host–guest complexes, can prevent this (inhibition). For effective reactivity or catalytic activity this reaction must be minimized.



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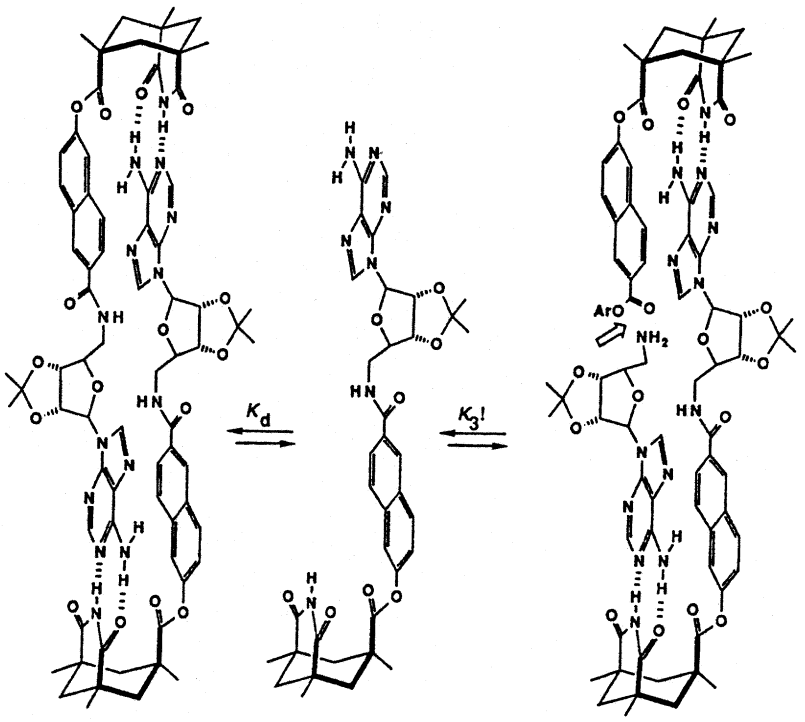
For the results presented here, the geometry of enzymes has been our inspiration. The work presented does not at all try to mimic enzymes, but instead tries to use the concept of concavity to increase the selectivity of organic reactions. This article will demonstrate that improved selectivities can be achieved when the standard reagents of organic chemistry are combined with a concave geometry such as is found in enzymes. The approach is therefore to take a reagent and to incorporate it into a concave environment in the same way as a light bulb sits in a lamp shade (Fig. 1). We call these compounds concave reagents.[15,16]

In comparison to enzymes this approach has the following advantages: (i) the nature of the lampshade is not restricted to amino acids—the building blocks are very variable; (ii) therefore substitution and tailoring of the geometry of the active site is easier; (iii) lower molecular weights will be possible because the task of most amino acids in an enzyme is to stabilize the reactive conformation by building up a large backbone; (iv) due to the large variability of the building blocks, concave reagents can be made solvent, pH and temperature resistent.

Let us now examine the model of the concave reagent: a light bulb in a lampshade.[17] The light bulb stands for the reactive centre, the lampshade is the concave shielding. If this geometry is translated into molecular dimensions, some requirements have to be met: (i) the rim of the lampshade must be a ring; (ii) in order to let molecules or parts of molecules pass through this ring to reach the active site, it must be macrocyclic; (iii) this macrocycle must be spanned by a bridge which carries the functional group. The minimal requirement for a molecular lamp is therefore that it must be at least bimacrocyclic.[18]

A concave reagent can in principle possess any functional group. So far we have incorporated acids, bases and catalytically active metal ions. These functional groups have to be fixed into the spanning bridge in such a defined way that they are inside. This can be achieved by using stiff aromatics substituted in the *ortho*- or α-positions, *e.g.* 2,6-disubstituted benzene derivatives, 2,6-disubstituted pyridines or 2,9-disubstituted 1,10-phenanthrolines.

As stated above, concave reagents are at least bimacrocyclic. Three bridges have therefore to be connected by bridgeheads. This task can be mastered by using nitrogen atoms or trisubstituted aryl rings.



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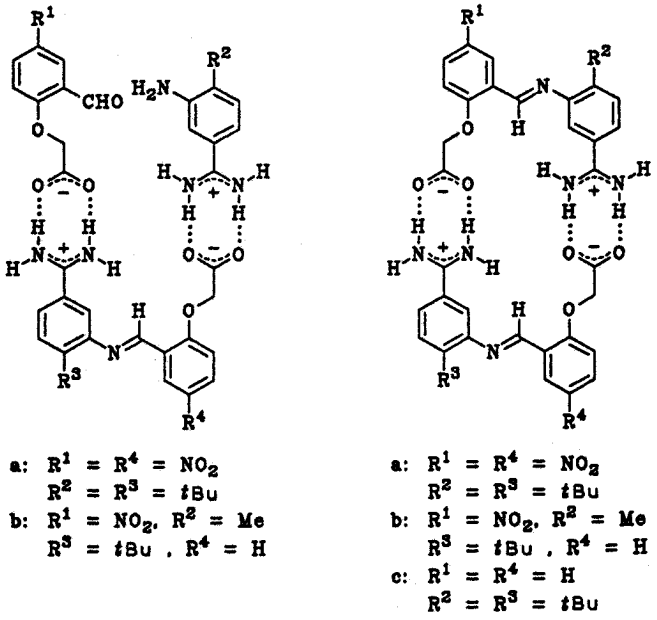

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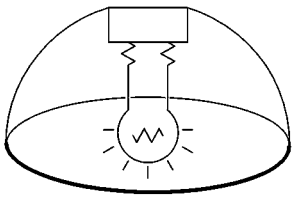


Fig. 1 Light bulb and lampshade model of concave reagents

The task was therefore to synthesize bimacrocyclic 2,6-substituted acids, bases or ligands for metal ions. In general, three possibilities exist for the synthesis of such a bimacrocyclic reagent: stepwise macrocyclizations or simultaneous construction of both macrocycles in one reaction step. In the former

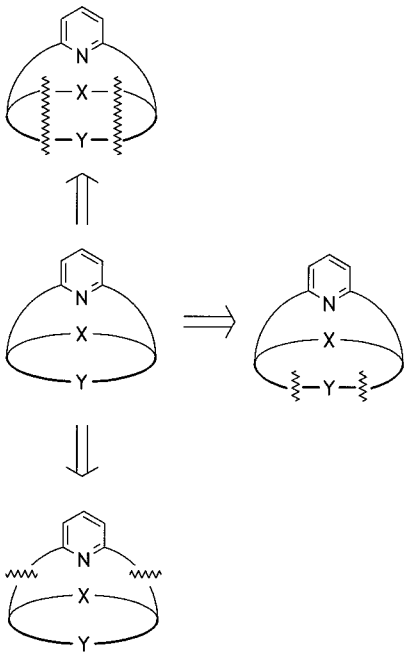


Fig. 2 Strategies for the synthesis of bimacrocyclic compounds containing a functional group in one chain (here pyridine)

case, two strategies can be used: the construction of a macrocycle containing the functional group followed by a second macrocyclization, and the use of presynthesized macrocycles which are bridged in a second reaction step with a building block containing the functional group. All three methods have been realized (see Fig. 2 and 3): (i) bislactams and sulfonamides have been synthesized by a stepwise reaction starting from a precursor containing a pyridine or a 1,10-phenanthroline unit;[19] (ii) in the pyridine-bridged calixarenes a pyridine-containing unit has been used to bridge the calixarene macrocycle;[20] (iii) bimacrocyclic diaryl pyridines,[21] diaryl 1,10-phenanthrolines[22] and diaryl benzoic[23] and benzenesulfinic acids,[24] as well as a diaryl-*m*-terphenylthiol[25] and its acetate,[26] have

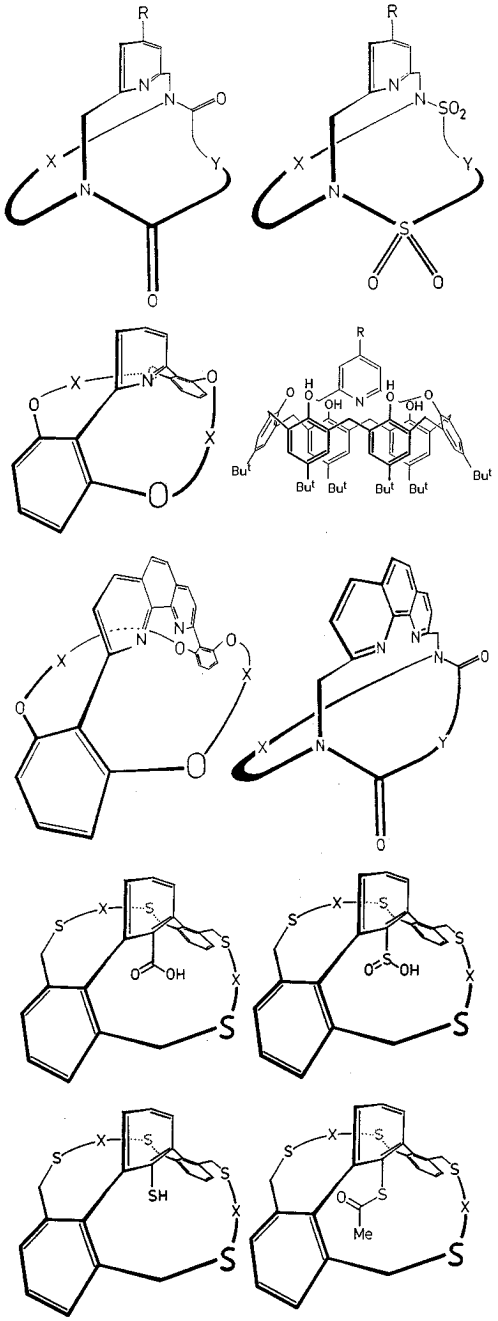


Fig. 3 Examples of concave pyridines (refs. 19,20,21), 1,10-phenanthrolines (ref. 19, 22), benzoic acids (ref. 23), sulfinic acids (ref. 24), thiols (ref. 25) and thiol acetates (ref. 26)

been synthesized in one reaction step starting from appropriate tetrafunctionalized precursors.

To achieve high yields in these cyclizations either high dilution principle conditions or template effects have been exploited. The yields vary but in many cases yields of 30–50% for the bismacrocyclizations have been achieved in both the one step and the two step reactions. Therefore concave reagents are relatively easy to obtain, and many of them have been synthesized in multigram quantities. Some of the concave reagents synthesized in past years are compiled in Fig. 3.

After the synthesis of the concave reagents, the question of whether these new molecules are indeed concave had to be answered. A number of X-ray analyses have been carried out, proving the lamp-like concave structure of the bimacrocyclic compounds. Fig. 4 shows the X-ray structure of a concave diaryl-1,10-phenanthroline with two octamethylene side chains X[22b] as an example.

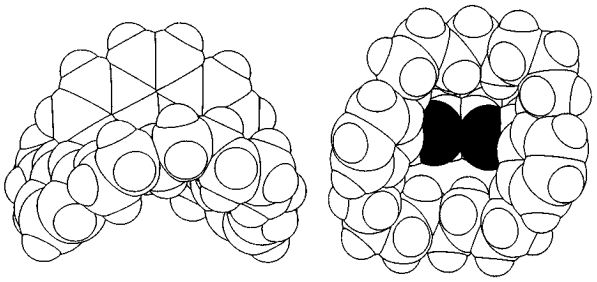


Fig. 4 Space-filling drawings of a concave 1,10-phenanthroline cyclophane with octamethylene side chains based on X-ray data [ref. 22(*b*)]. In the side view, the nitrogen atoms of the 1,10-phenanthroline are hidden behind the octamethylene chains. They are accessible from below through the 'rim of the lampshade'.

The accessibility of the functional groups of those concave acids and bases for which X-ray data are available has been studied by computer analysis (Connolly routine).[27] Spheres of varying sizes have been rolled over the van der Waals surfaces generated from the X-ray data, and the resulting contact surface has been monitored. The simulations show clearly that small spheres are able to enter the cavity and can contact the functional group(s), whereas larger spheres are too bulky. The cut-off radius for a sphere to contact the nitrogen atoms of the concave 1,10-phenanthroline of Fig. 4 is 2.8 Å.

Model reactions

Many concave reagents have been synthesized and are now accessible in useful quantities. They have been tested in a number of model reactions to learn which geometries lead to an increase in selectivity. In all model reactions an organic transformation has been chosen which can be carried out with a non-concave standard reagent (acid, base, metal ion complex). The changes in reactivity and selectivity caused by the incorporation of the functional group into the concave environment have been investigated. These results have then been compared to those obtained with non-concave molecules and other sterically shielded, related molecules.

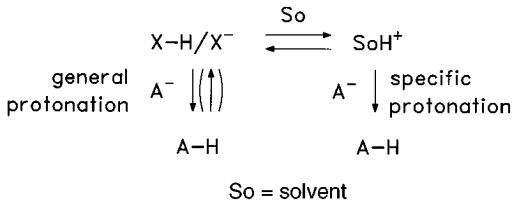
In the reactions chosen, the concave molecules have been applied as reagents and as catalysts. In contrast to a catalyst, a reagent is used up in a reaction. It is therefore necessary to find methods for 'recharging' the reagents because their synthesis is too tedious for them to be used only once. Such recharging is very easy for acids and bases. Therefore, the only reaction so far in which concave reagents have been employed in amounts equal to or exceeding the stoichiometry were proton transfer reactions. In all other reactions, the concave reagents were used as catalysts.

Protonations

Most asymmetrically substituted carbon atoms have a hydrogen atom as one of the four different substituents. If this hydrogen atom could be attached selectively to a prochiral carbon atom by a reagent controlled protonation, many enantio- and diastereo-selectivity problems would be solved.

However, there are always two mechanistical pathways possible for a kinetically controlled protonation: general and specific protonation (Scheme 1).[28,29] The proton can either be transferred directly from the acid to the substrate (reagent control, general protonation) or *via* the solvent or co-solvent (shuttle mechanism, specific protonation). Therefore for a reagent controlled protonation, reagents and reaction conditions have to be worked out to allow general protonation exclusively.

The protonation of three different groups of anions has been carried out: nitronate ions,[30] ester enolates[25a,31] and allyl

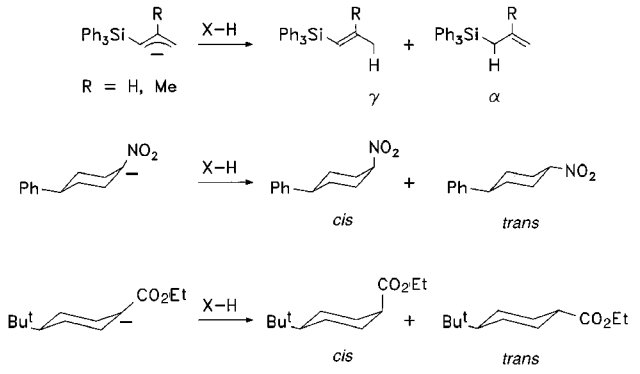


Scheme 1 General and specific protonation of an anion A^-. Direct proton transfer from the acid of the buffer (X–H) to the anion A^- leads to a reagent controlled general protonation, while dissociation of the acid and proton transfer *via* the protonated solvent $So \cdot H^+$ gives an uncontrollable specific protonation. To avoid thermodynamic control the deprotonation of A–H must not occur.

anions.[25a,32] Scheme 2 summarizes the investigated reactions and shows which stereo- and regio-isomers might be formed.

A variety of concave and other acids have been used for the reactions in Scheme 2. Not all of them led to a change in selectivity, but for each anion acids could be found with which a reagent controlled, general protonation was achieved and with which the regio- or stereo-selectivities could be altered. Steric shielding of the proton in the concave acid caused an increase in γ-protonation of the allyl anions, while the protonation of the cyclic anions by sterically shielded acids led to an increase of the *cis*-products.

In the latter case the thermodynamically less stable products have been formed. This can be rationalized by inspecting the transition state of such a protonation (Fig. 5). The proton is still partly bound to the concave acid, a *m*-terphenyl derivative[25a,31] or a protonated 2-aryl-1,10-phenanthroline.[30] The proton is therefore a large pseudo-substituent for which an equatorial orientation is favoured. In the product, however, the large pseudo-substituent becomes the smallest substituent,



Scheme 2 A general protonation of allyl anions by an acid X–H leads to γ- and α-regioisomers, while a general protonation of the cyclic anions gives *cis*- and *trans*-products

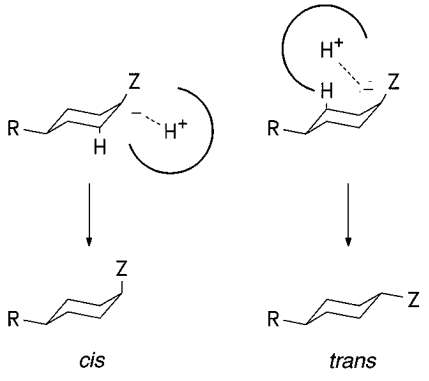
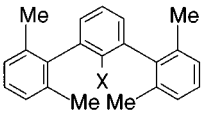


Fig. 5 Alternative transition states for protonation of cyclic anions by a concave acid

a hydrogen atom, which explains the contra-thermodynamic course of this protonation.

Surprisingly, acids successful in one of the reactions in Scheme 2 are often not suitable for the general protonation of another anion.

The γ/α-selectivity of the protonation of the allyl anions could be increased by a variety of acids. Tetra-*ortho*-methylsubstituted *m*-terphenyls carrying an acidic group in the 2′-position were successfully applied, leading to selectivities between 90 : 10 ($X = CH_2OH$) and 96 : 4 ($X = SH$). The results were almost independent of the nature of the group X.



$X = CO_2H$, SH, CH_2OH

However, when the same acids were tested for the stereoselective protonation of the cyclohexane ester enolate, only the acid with the smallest acidity, the alcohol ($X = CH_2OH$), gave a good *cis*-selectivity (94 : 6). *m*-Terphenyls carrying groups with a higher acidity showed no selectivity. Presumably the unselective specific protonation is faster than the general protonation if the acidity of the *m*-terphenyl is higher.

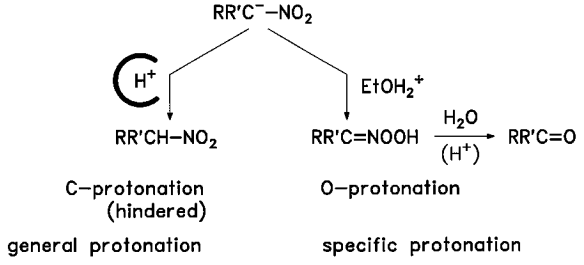
This competition between general and specific protonation can be exploited. If the proton in a concave acid is extremely shielded, a general protonation will be retarded, which should allow a specific protonation even if the concentration of protonated solvent is very low (high pH) (Scheme 3). This has been used to carry out the Nef reaction[33] which usually requires strongly acidic conditions in a buffered medium. Due to the mild reaction conditions this reaction has been called the soft Nef reaction.[30]

The Nef reaction is an important method for the conversion of nitro compounds into carbonyl compounds. The strong acidic conditions needed for this reaction have often prohibited its application to molecules with acid labile groups. However, the reaction conditions of the soft Nef reaction are mild enough that protective groups such as *tert*-butyldimethylsilyl (TBDMS), methoxymethyl (MOM) or acetals survive.[30d]

Base catalysis

In contrast to protonations, which have to be carried out with an at least equimolar amount of acid, in a base catalysed reaction less concave reagent is needed if the reaction occurs fast enough. In addition, the catalyst will remain unaltered during the reaction.

For example, the base catalysed addition of alcohols to ketenes has been investigated for concave and non-concave pyridines.[34] By formation of a hydrogen bond between the alcohol and the nitrogen atom of the pyridine, the nucleophilicity of the alcohol is increased and the rate of its addition to the ketene is increased. The net reaction is an acylation of the hydroxy group (the formation of an ester) which may serve as a protective group for the alcohol.



Scheme 3

The rates of the catalysed addition depend on the geometry and the basicity of the catalyst.[34] By plotting the logarithms of the rates of addition *versus* the basicities (Brønsted plot), geometrical and basicity influences on the reactivity of the pyridines could be separated.[34,35] For pyridines of the same geometry, linear correlations exist between the basicity and the rate. The more shielded a pyridine is, the smaller is the rate of addition.[34]

However, when a size variation in the concave pyridines gives rise to a change in rate, size variation of the alcohol should also have an influence on the reaction rate. In other words, the addition of primary, secondary or tertiary alcohols should be catalysed differently (Fig. 6). Therefore the base catalysed addition of different hydroxy species (EtOH, Pr^iOH, Bu^tOH or propane-1,2-diol) has been compared and indeed a selectivity increase in favour of the acylation of primary hydroxy groups has been found when concave pyridines have been used.[36]

Thus concave pyridines are able to discriminate between different alcohols, which would be very useful if it could be exploited in intramolecular competition reactions. For example, two carbohydrate derivatives were reacted with diphenylketene in the presence of concave catalysts. The results of the acylation of a glucose derivative, and those of the acylation of a chinovose derivative are listed in Tables 1 and 2, respectively. In both carbohydrates, the hydroxy groups are secondary and equatorial. The use of a concave pyridine leads to the predominant formation of only one product (>9:1 in the glucose case; one of seven possible acylation products in 60% yield in the chinovose case).[36]

Metal ion catalysis

The free electron pair(s) in concave pyridines, and especially in concave 1,10-phenanthrolines, are not only able to bind a proton, they may also complex a metal ion (Fig. 7). For concave 1,10-phenanthrolines, transition metal complexes have already been generated.[22b,37] They form readily in acetonitrile solution with binding constants of 10^4–10^7 and larger.

These complexes have been applied in two transition metal ion catalysed reactions: the Lewis acid catalysed Diels–Alder reaction[37] and the Cu^+-catalysed cyclopropanation of alkenes by diazo compounds.[38] Scheme 4 and Fig. 8 show the Ni^{2+} and Co^{2+}-catalysed cycloaddition of pyrazole-substituted acrylamides with cyclopentadiene and the increase in *exo*-selectivity when concave ligands are used.

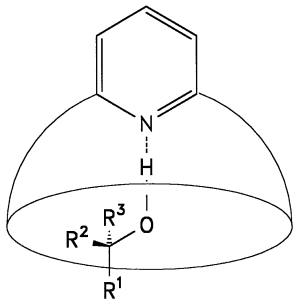
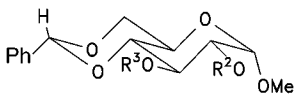


Fig. 6 Model of a concave pyridine–alcohol complex

Table 1 Acylation of a glucose derivative in the presence of a concave catalyst



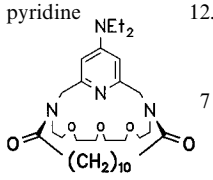
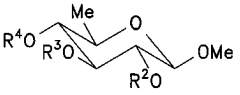
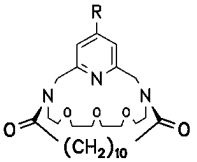
	product yield (%)		
catalyst	$R^2=H$ $R^3=Ph_2CHCO$	$R^2=Ph_2CHCO$ $R^3=H$	$R^2=Ph_2CHCO$ $R^3=Ph_2CHCO$
none	36	42	3
pyridine	12.5	50	12.5
	7	67	—

Table 2 Acylation of a chinovose derivative in the presence of a concave catalyst



catalyst	product yield (%) (R^2,$R^4=H$,$R^3=Ph_2CHCO$)
pyridine	29
	
R = OMe	60
$R=NEt_2$	48

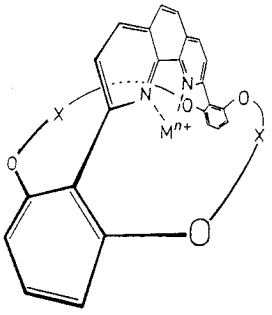
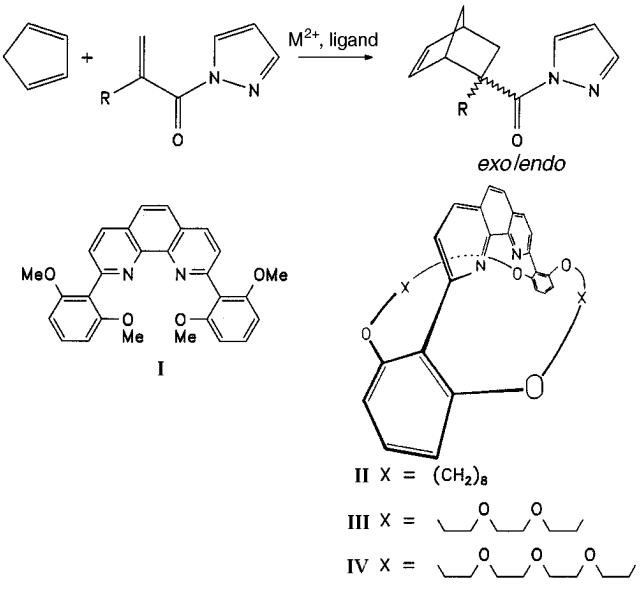


Fig. 7 A metal ion bound to a concave 1,10-phenanthroline



Scheme 4 The reaction of pyrazole-substituted acrylamides with cyclopentadiene can be catalysed by transition metal salts. With increasing shielding of the metal ion by the use of concave 1,10-phenanthrolines, the *exo*/*endo*-selectivity can be shifted towards *exo*.

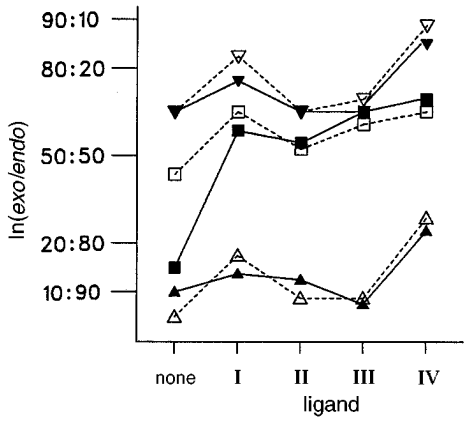


Fig. 8 Plot of ln(*exo*/*endo*) for the reaction of pyrazole-substituted acrylamides with cyclopentadiene catalysed by transition metal salts and various concave ligands (Scheme 4): (▽) M = Ni, R = Cl; (▼) M = Co, R = Cl; (□) M = Ni, R = Me; (■) M = Co, R = Me; (△) M = Ni, R = H; (▲) M = Co, R = H

Without the presence of a ligand, *endo*-norbornenes are usually the main products. But when the metal ion is sterically shielded an *exo*-preference is found, which can be rationalised as shown in Fig. 9. In the transition state leading to the *endo*-norbornene, the cyclopentadiene has to approach with the atoms C-2 and C-3 foremost, which is sterically disfavoured compared to the orientation leading to the *exo*-compound (C-5 foremost).

The second transition metal ion catalysed model reaction is shown in Table 3, the Cu^+-catalysed cyclopropanation of alkenes by ethyl diazoacetate. With Cu^I salts alone a mixture of *cis*- and *trans*-cyclopropanes or *endo*- and *exo*-cyclopropanes is formed. The use of concave ligands leads to the preferred formation of the *trans*-product, *e.g.* 73 : 1 for indene when a diaryl-1,10-phenanthroline was used as ligand for the catalyst instead of 2.1 : 1 without concave ligand.[38]

The increase in the formation of the *trans*-products of the cyclopropanation of a *cis*-alkene is explained in Fig. 10. First Cu^+ reacts with a diazoacetate molecule and forms a carbenoid, which is then transferred to the alkene. Due to the concave shielding, the sterically most favoured orientation is unproductive because the C=C and Cu=C bonds are orthogonal. Therefore the alkene must rotate with respect to the carbenoid, leading to two twisted transition states in which two orientations of the substituents of the alkene are possible: *anti* to the ester leading to a *trans*-product or *syn* leading to the *cis*-product. The greater steric repulsion in the *syn*-orientation explains the large *trans*-selectivity.

Outlook

As outlined in this article, various classes of concave reagents may be synthesized in multigram quantities. However, the syntheses are multistep sequences and the yields are often limited by the macrocyclization steps. Therefore for practical use these reagents are quite 'expensive' and recovery and recycling is necessary.

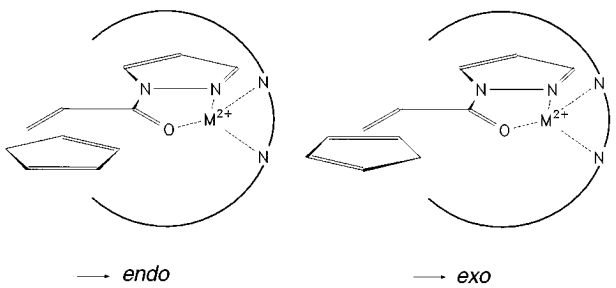
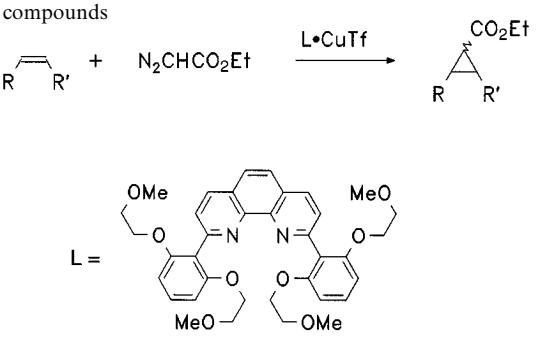


Fig. 9 The approach of cyclopentadiene towards the complexed acrylamide determines the *exo*/*endo*-selectivity

Table 3 The Cu^+-catalysed cyclopropanation of alkenes by diazo compounds



alkene	*trans*/*cis* ratio without ligand	*trans*/*cis* ratio with ligand
	1.1	3.0
	1.4	4.7
	3.3	56
	5.2	66
	2.1	73
	1.3	12

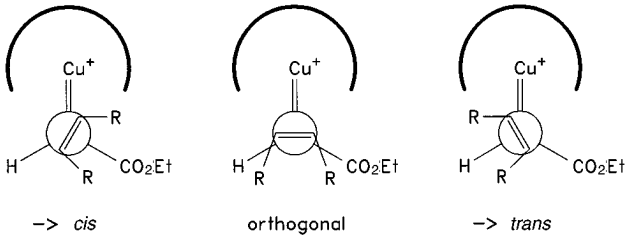
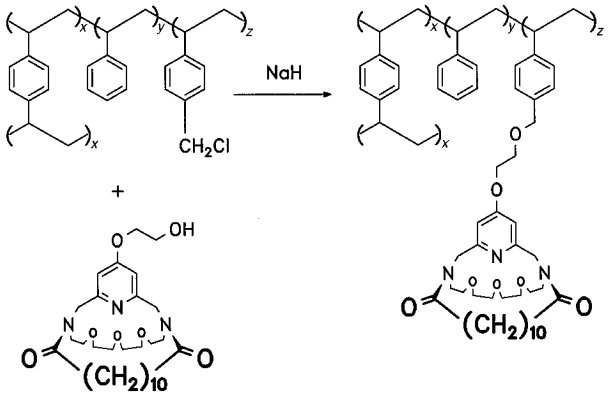


Fig. 10 Due to the concave shielding of the copper ion the least hindered approach of the alkene to the carbenoid formed by the reaction of Cu^+ with ethyl diazoacetate is the unproductive orthogonal approach. A clockwise rotation of the alkene diminishes the steric interactions between the substituents R of the alkene and the ester group, favouring the formation of the *trans*-products.

In order to be able to reisolate the concave reagents by filtration we have attached 4-substituted concave pyridines to a polymer (Merryfield resin) (Scheme 5).[30d,39]

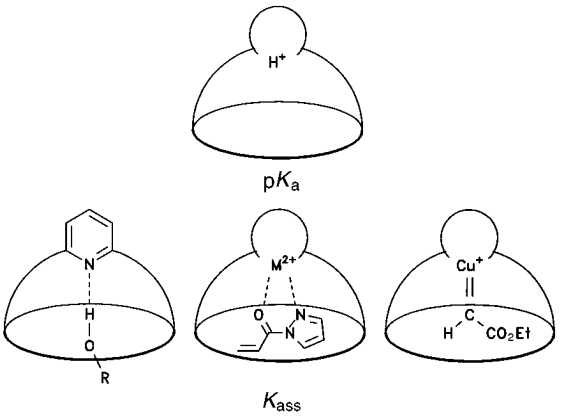
The amount of concave pyridine bound to the polymer has been determined to be *ca.* 20% (w/w). The polymer-bound concave pyridines are catalytically active and the selectivity in the base-catalysed addition of hydroxy groups to ketenes is comparable to that of non-bound concave pyridines. The concave pyridine-loaded polymer resin has been placed in an HPLC column and the selective acylation of the hydroxy groups in the glucose derivative used in Table 1 with diphenylketene has been successfully carried out.

For further application of the concave acids, bases or complexes presented in this article, these compounds need to be investigated more thoroughly. As seen in the protonation



Scheme 5 Attaching a concave pyridine to a polymer

reactions, equilibria between bound and free protons exist and can alter the course of the reaction. Therefore the association of the reagents inside the lamp shade must be guaranteed. In other words, large pK_a or K_{ass} binding constants are required.



This work was carried out by my talented co-workers whose names appear in the references. Financial support came from the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the Schwerpunkt des Landes Baden-Württemberg: Sensoren and the Wissenschaftliche Gesellschaft Freiburg.

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