Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **24:** 43–60, 1996.

Review Article

Concave Reagents – Design and Application

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(Received: 19 February 1996)

Abstract. By incorporating standard organic reagents into a concave environment one can synthesize concave reagents. Their geometry resembles that of a light bulb in a lampshade. In protonations, base catalyses and metal ion catalyzed reactions the concave shielding leads to selectivity enhancements.

Key words: Pyridine, 1,10-phenanthroline, selectivity, macrocycle, concave reagents.

1. Introduction

In all chemical reactions transforming a starting material S into a product P, a transition state TS must be overcome. The activation enthalpy $\Delta G^{\#}_{TS}$ determines the rate of reaction. A catalyst can speed up the reaction by binding the transition state TS and thus lowering its enthalpy. This catalyst can be a chemical reagent or an enzyme. In all cases, the catalysts act as a host H for the transition state. The influence of binding the transition state TS to a host H (TS·H) is illustrated in Figure 1 showing the energetical stabilization of TS.

There are complications, however. Product inhibition is well known from enzyme chemistry. It occurs when the product P is extremely well bound to the host H. If this occurs only a small fraction of host H will be dissociated from the product and will be able to start a new catalytic cycle (Figure 2a). By analogy, one can expect a starting material inhibition if the starting material S is extremely well bound. Then the activation barrier $\Delta G^{\#}_{TS\cdot H}$ will be very large, as shown in Figure 2b. This will be a problem if the development of a host system concentrates on the binding of the starting material rather than the binding of the transition state. Therefore the approach in host–guest chemistry, via establishing good binding first and then introducing functional groups, is very risky.

Our approach is thus different. We choose systems where reactivity is well known but selectivity is insufficient. By incorporation of the functional (catalytic) group into a concave environment we try to alter the selectivity, just as the selectivity

Presented at the Sixth International Seminar on Inclusion Compounds, Istanbul, Turkey, 27–31 August 1995.

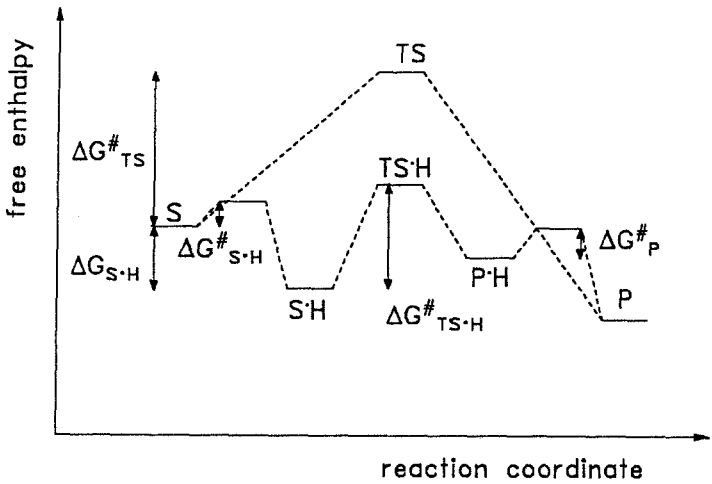


Figure 1. Reaction coordinate for the transformation of a starting material S to a product P via a transition state TS. By binding the transition state (TS·H), a host system catalyzes the reaction by lowering the enthalpy of activation $\Delta G^{\#}_{TS\cdot H}$.

of an enzyme is influenced by the concave environment of its active site. We call these systems *concave reagents* [1].

A lamp is a good model for such a concave reagent. While the light bulb represents the reactive center, the lampshade is the concave shielding. If this geometry is translated into molecular dimensions, two requirements have to be met: the rim of the lampshade must be a ring, and in order to let molecules or parts of molecules pass through this ring, it must be macrocyclic. Furthermore, 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* [2].

A Concave Reagent can in principle possess any functional group. Because very many reactions in organic chemistry are carried out with the help of acids and bases, the concave acids and bases, and their correspondent conjugate bases and acids, were synthesized first.

The functional group, the tool, of a concave reagent must be in a defined *in*-position (Figure 3a). If a concave base is to be synthesized, a 2,6-substituted pyridine is a suitable building block (Figure 3b). Next the three bridges of the bimacrocycle have to be connected, which can be achieved by using a trivalent atom like nitrogen (Figure 3c). But then a problem occurs. Nitrogen atoms are basic, and there would be a competition between the lone pair of the pyridine nitrogen atom in the concave position and the lone pairs of the bridgeheads, which are not in the concave environment. To solve this problem, the nitrogen atoms are incorporated into amide bridgeheads leaving the concave pyridine nitrogen atom as the only basic center in the molecule (Figure 3d).

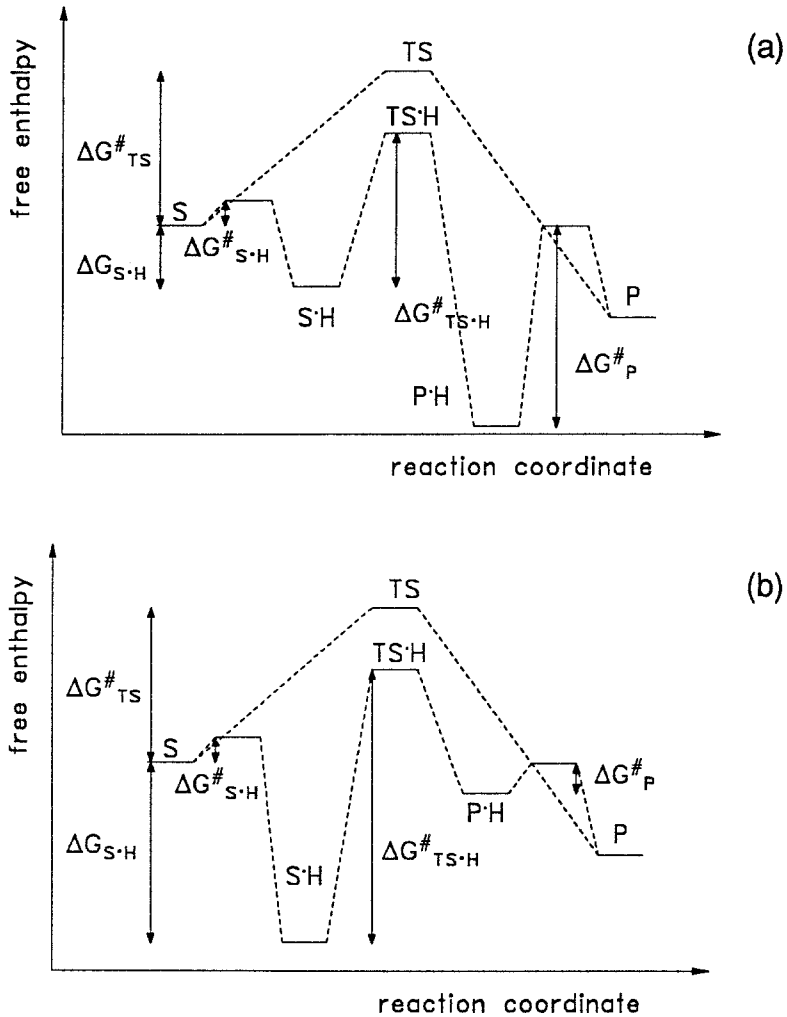


Figure 2. If the product P (a) or the starting material S (b) is extremely well bound to the catalyst H, only a small fraction of the host H exists unbound. Product and starting material inhibitions occur, respectively.

2. Syntheses

The task is therefore to synthesize bimacrocyclic 2,6-disubstituted pyridinebisamides. They are accessible by two subsequent macrocyclizations [3]: a metal ion template controlled biscondensation between a pyridinedicarbaldehyde and a diamine followed by reduction, and the bislactamization of the resulting macrocyclic diamine with a diacyl dichloride or with a bissulfonylchloride (Scheme 1). The yields of the metal template controlled cyclization are excellent (up to >90%) if the length of the chain X of the diamine is adjusted to the size of the metal ion

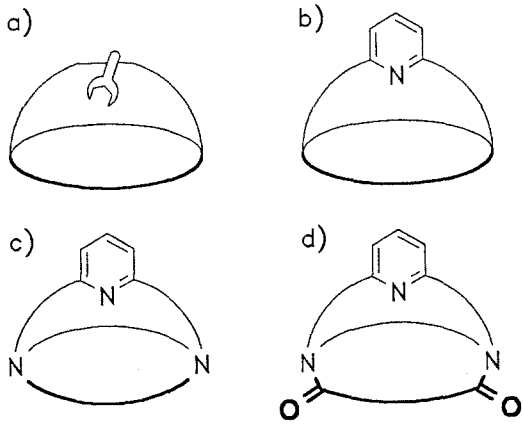
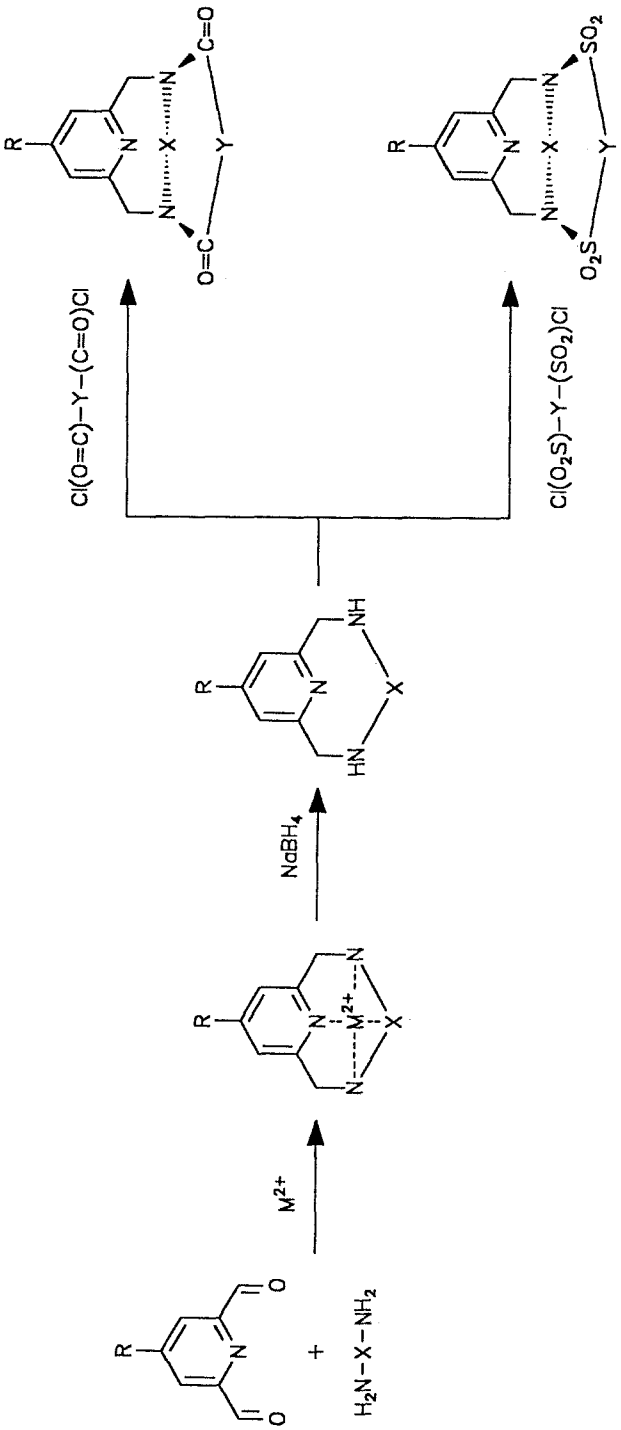


Figure 3. The minimal requirements for a concave pyridine are: *in*-position of the functional group which is realized by the use of 2,6-disubstituted pyridine bridges and non-basic bridgeheads for the connection of the three bridges of the macrocycle.

M^{2+} (Mg^{2+}, Ca^{2+} or Sr^{2+}). In the second macrocyclization, yields of 60% can be obtained by high dilution for concave pyridinebislactams [3b], while concave pyridinebissulfonamides can be synthesized in 30% yield [3c]. Thus, multigram quantities of concave pyridines can be generated.

An alternative to atoms as bridgeheads are trisubstituted groups. To simplify the geometry of the concave reagent, flat and symmetrical structures were used: 1,2,3- and 1,3,5-trisubstituted benzenes. Cyclophanes are formed when these groups are incorporated into bimacrocyclic structures. Different strategies have been used to synthesize concave 1,10-phenanthroline cyclophanes [4], concave pyridine cyclophanes [5], concave benzoic acid cyclophanes [6] and concave sulfinic acid cyclophanes [7]. All methods have the common feature that the aryl bridgeheads were joined first with the functional group (1,10-phenanthroline, pyridine, or substituted benzene) before a double macrocyclization built up the final bimacrocycles. Figure 4 illustrates various classes of concave acids and bases synthesized to date.

After the synthesis of concave acids and bases, the question of whether these new molecules are indeed concave has to be answered. A number of X-ray analyses have been carried out, proving the lamp-like concave structure of the bimacrocyclic compounds. Figure 5 shows a side-on view and a view from below into a space filling model of a concave diaryl-1,10-phenanthroline with two octamethylene side chains X [4b]. Computer analyses (Connolly routine) [8] were used to study the accessibility of the functional groups of those concave acids and bases for which X-ray data were available. Spheres of varying sizes were rolled over the van der Waals surfaces generated from the X-ray data, and the resulting contact surface was monitored. The simulations clearly showed that small spheres are able to enter the cavity and can contact the functional group(s), whereas larger spheres were too


R
O
O
N
+
$H_2N-X-NH_2$
M^{2+}
R
N
N
M^{2+}
X
N
N
$NaBH_4$
R
N
NH
X
HN
NH
$Cl(O=C)-Y-(C=O)Cl$
$Cl(O_2S)-Y-(SO_2)Cl$
R
N
N
X
N
C=O
Y
O=C
R
N
N
X
N
SO_2
Y
O_2S

Scheme 1.

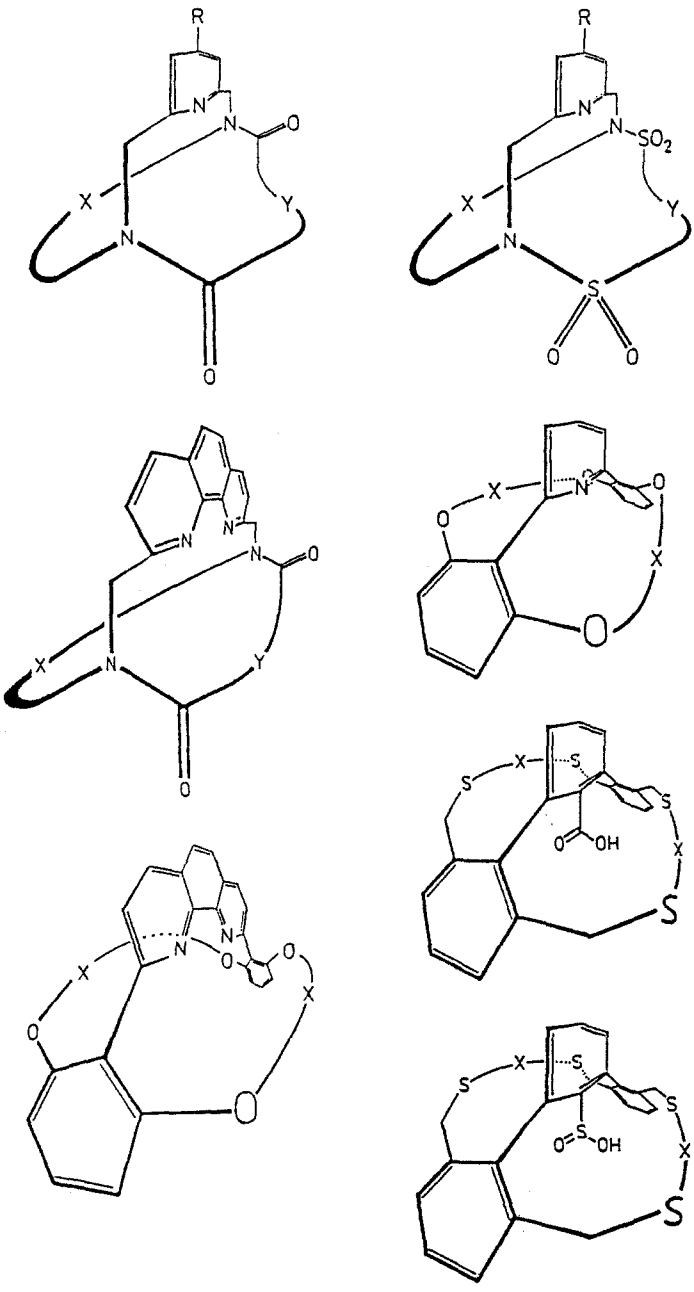


Figure 4. Examples of some concave acids and bases synthesized to date.

bulky. The cut-off radius for a sphere to contact the nitrogen atoms of the concave 1,10-phenanthroline of Figure 5 is 2.8 Å.

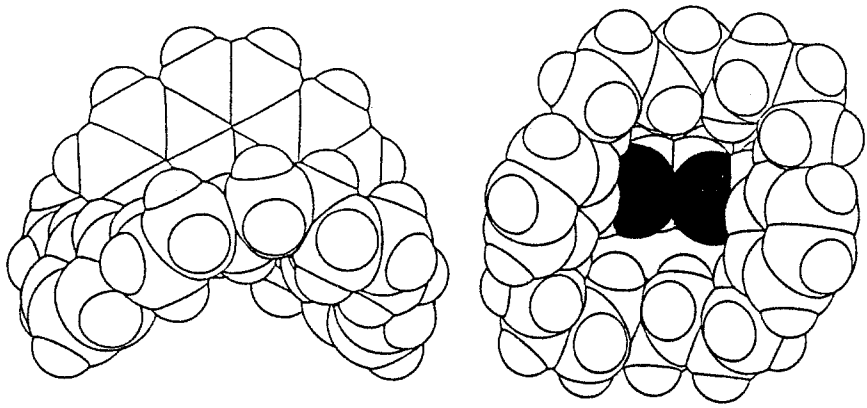


Figure 5. Space filling drawings of the structure of a concave 1,10-phenanthroline cyclophane with octamethylene side chains based on X-ray data. In the side view (left), the nitrogen atoms of the 1,10-phenanthroline are hidden behind the octamethylene chains. They are accessible from below through the 'rim' of the 'lamp shade'.

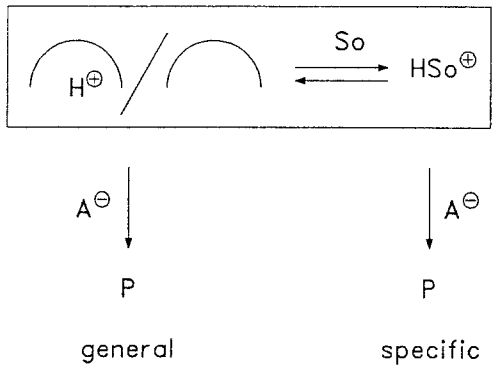


Figure 6. In a general protonation all acids including protonated concave buffer molecules may protonate an anion A^- to give the protonated products P. The protonated solvent molecule HSo^+ is the only protonating species in a specific protonation.

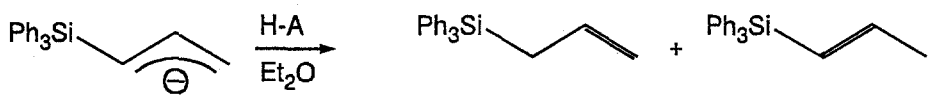
Analogously, the proton of a protonated concave pyridinebislactam is only approachable by small spheres [3b], suggesting a size selectivity in protonation reactions.

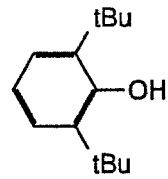
3. Model Reactions

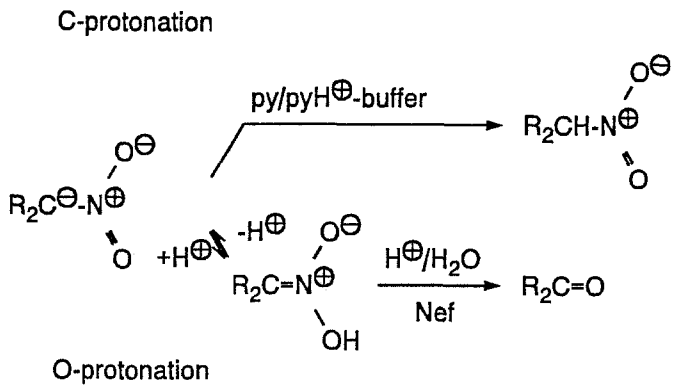
3.1. PROTONATIONS

If protonation reactions are looked at carefully two pathways for protonation must be discussed: the specific protonation via protonated solvent molecules (HSo^+), and the general protonation in which each acid in solution is able to transfer a proton [9]. For buffers of concave bases this competition is illustrated in Figure

Table I. Regioselective protonation (% α : % γ) of a triphenylsilyl substituted allyl anion by various acids H-A.



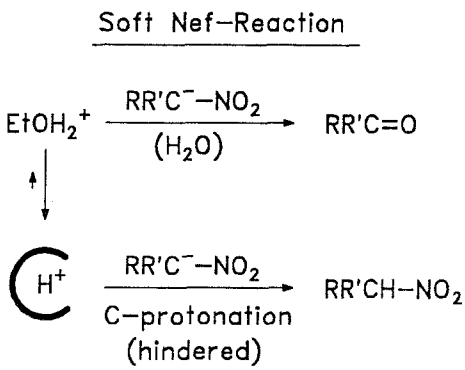
$RCH(COOEt)_2$	84 - 90	10 - 16
H_2O	60	40
C_6H_5OH	50	50
	10	90



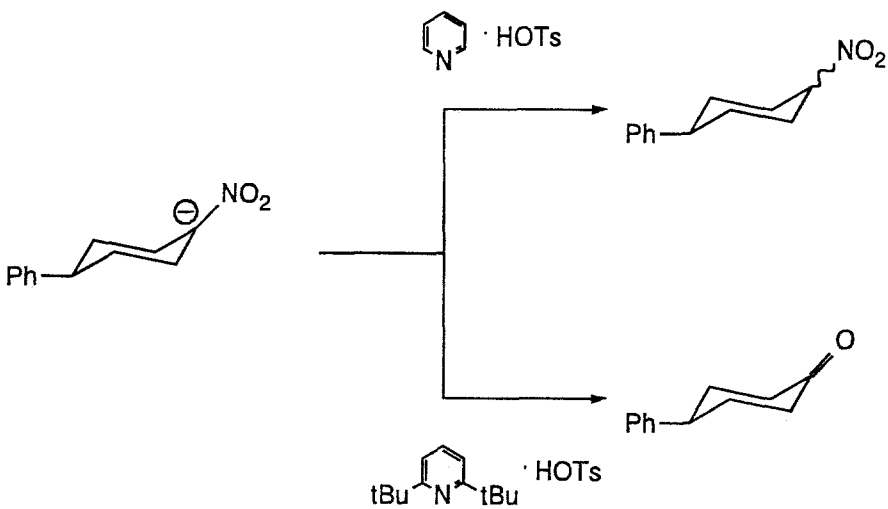
Scheme 2.

6. Only if the specific protonation is slow can reagent-controlled protonations be expected. The concave shielding of the acid/base center can then influence the course of the reaction.

As a first test, the regioselective protonation of ambidentate allyl anions was investigated [10]. A general protonation could indeed be observed (Table I). The regioselectivity depended on the nature of the acid. The sterically shielded 2,6-di-*tert*-butylphenol protonated the triphenylsilyl stabilized allyl anion in the γ-position



Scheme 3.

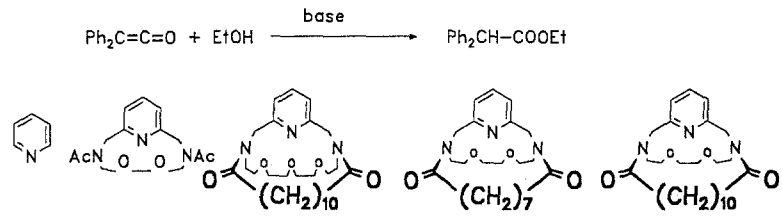


Scheme 4.

giving predominantly the vinyl product, while the use of malonic esters resulted in the allyl product via α-protonation.

This reaction is unfortunately restricted to diethyl ether as solvent in which buffers of concave proton donors are not soluble.

General protonation by concave proton transfer reagents was therefore checked with another class of ambidentate anions, the nitronate ions. Here C-protonation competes intramolecularly with O-protonation (Scheme 2). While C-protonation yields nitro compounds, O-protonation forms the *aci*-nitro compounds which, in the presence of water, react to form carbonyl compounds, the product of the Nef reaction [11]. While the Nef reaction (i.e. O-protonation) needs strong acidic conditions, the formation of nitro compounds (C-protonation) is achieved in buffers, e.g. in pyridinium/pyridine buffers.



k_{obs} (10^{-3} l/mol·s)	285	18.5	9.8	0.86	0.84
log K	0	−0.3	−0.3	−0.3	0.6

Figure 7. Comparison of the observed rate constants for the base catalyzed addition of ethanol to diphenylketene (k_{obs}) with the relative basicity of the catalyzing pyridines, log K [15].

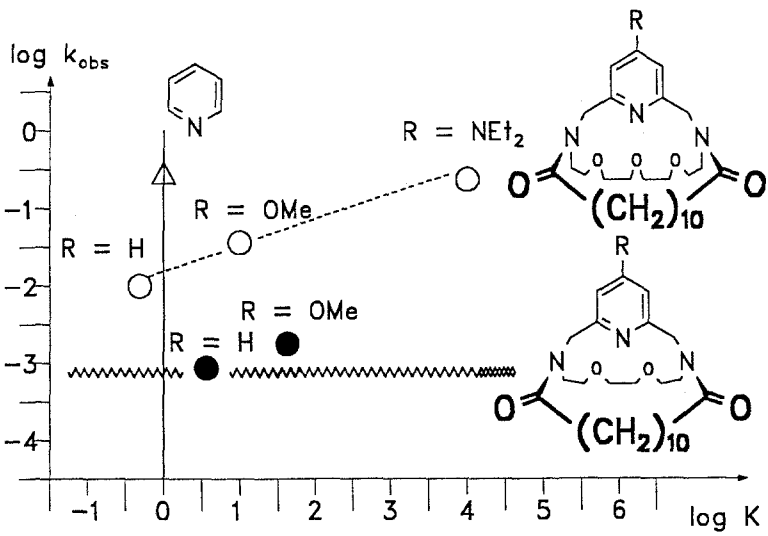
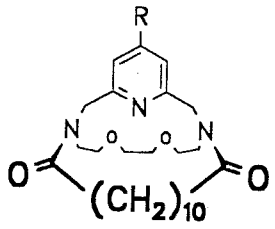
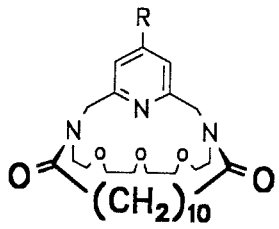
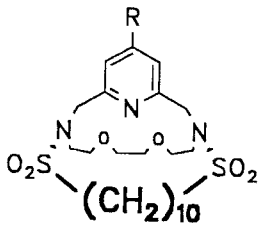
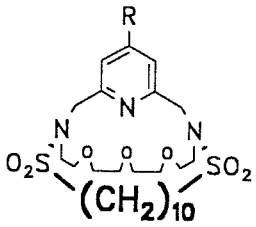


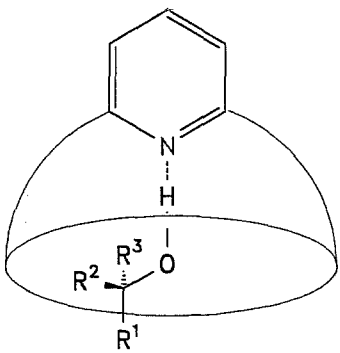
Figure 8. Brønsted plot of the logarithms of the observed rate constants k_{obs} for the base catalyzed addition of ethanol to diphenylketene under standardized conditions vs. the relative basicities log K [15].

However, when the pyridine of the buffer was exchanged by a concave pyridine-bislactam of the same basicity while keeping the concentrations constant, the course of the reaction changed completely: no C-protonation was found, the only products being carbonyl compounds, although the reaction was carried out in a buffer [12]. This reaction is therefore called the *soft Nef reaction* (Scheme 3)

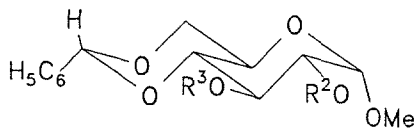
In the equilibrium of a buffer, the protons are either located in the concave reagent or they have protonated the solvent (ethanol in this reaction). Due to the basicity of the buffer molecules, the fraction of protonated ethanol is small.

Table II. Comparison of the ratio of the rate constants k_{EtOH}/k_{iPrOH} for the addition of ethanol and isopropanol to diphenylketene for various catalysts.

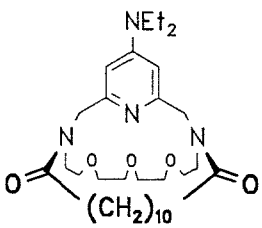
	uncatalyzed	$Me_2N-COMe$	Et_2N-SO_2Me	
selectivity k_{EtOH} / k_{IPrOH}	1.5	1.9	1.5	3.8
				
R = H	1.8	5.3	–	–
OMe	1.9	5.9	–	–
NEt_2	1.9	5.7	1.9	1.8



Formula 1.



R^2 =	H	Ph_2CH-CO	Ph_2CH-CO
R^3 =	Ph_2CH-CO	H	Ph_2CH-CO
uncatalyzed	36 %	42 %	3 %
pyridine	12.5 %	50 %	12.5 %



7 %	67 %	n.d.

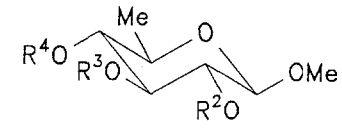
Figure 9. When a glucose derivative which contains only secondary and equatorial hydroxyl groups is acylated with diphenylketene in the presence of bases, the use of a concave reagent leads to high yields of only one acylation product.

Therefore C-protonation is found with pyridinium/pyridine buffers. But when the pyridine is sterically well shielded, the C-protonation becomes slower, giving the O-protonation a chance to compete, although the concentration of $EtOH_2^+$ is small.

Other sterically hindered pyridines as well as concave pyridines may also be used for the soft Nef reaction, e.g. 2,6-di-*tert*-butylpyridines (Scheme 4) [13].

3.2. Base Catalyses

In the above protonation reactions, the concave reagents were used in buffers to transfer a proton. Therefore the reacting species were the conjugate acids, the



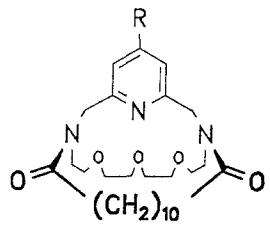
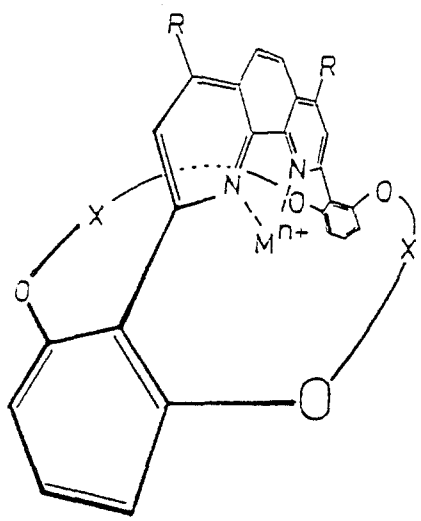
	R^2, R^4 =	H
	R^3 =	Ph_2CH-CO
pyridine		29 %
	R = OMe	60 %
	$R = NEt_2$	48 %

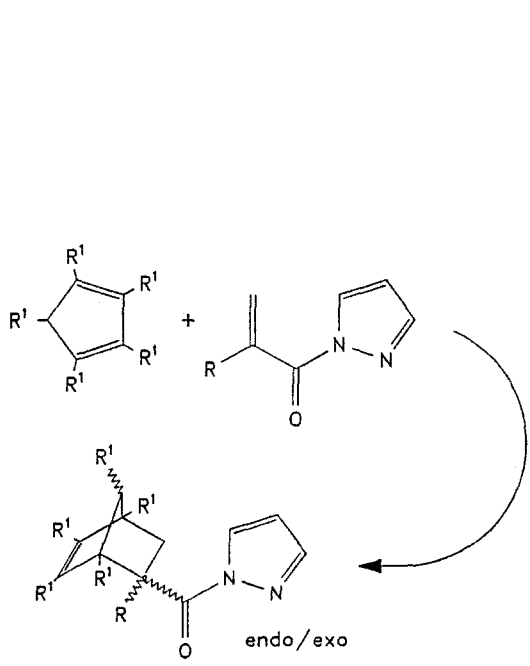
Figure 10. When a chinovose derivative which contains only secondary and equatorial hydroxyl groups is acylated with diphenylketene in the presence of bases, the use of a concave reagent leads to high yields of only one acylation product.

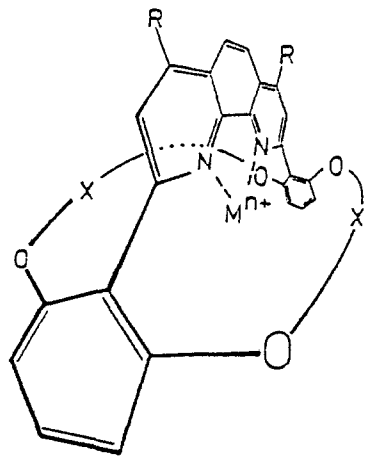


Formula 2.

protonated reagents. Furthermore, the buffers had at least to be equimolar. Concave reagents can also be applied in base catalyzed reactions.

As an example, the base catalyzed addition of alcohols to ketenes was investigated. Figure 7 compares the observed rate constants k_{obs} for the addition of ethanol to diphenylketene under standardized conditions [14] with the relative





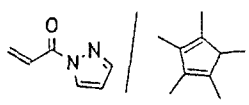
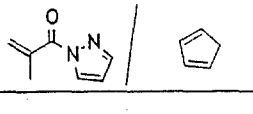
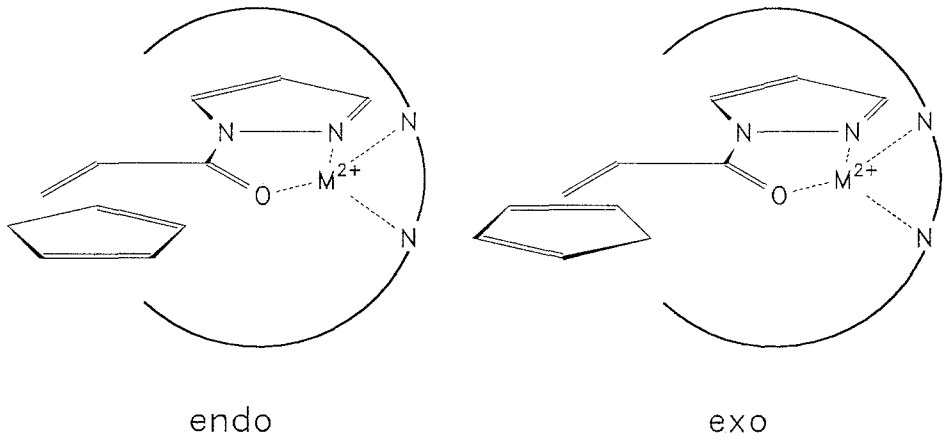
			X			
			Me Me	$(CH_2)_8$	n=2	n=3
	6.2	$CoNf_2$	1.4	1.2	1.0	1.5	0.15
		$NiNf_2$	1.0	0.6	0.8	0.9	0.2
	10.0	$CoNf_2$	10.0	3.7	7.1	12.5	3.0
		$NiNf_2$	11.0	4.0	10.0	12.5	2.7
	–	$CoNf_2$	1.5	0.7	1.1	0.6	0.5
		$NiNf_2$	1.3	0.5	0.9	0.6	0.5

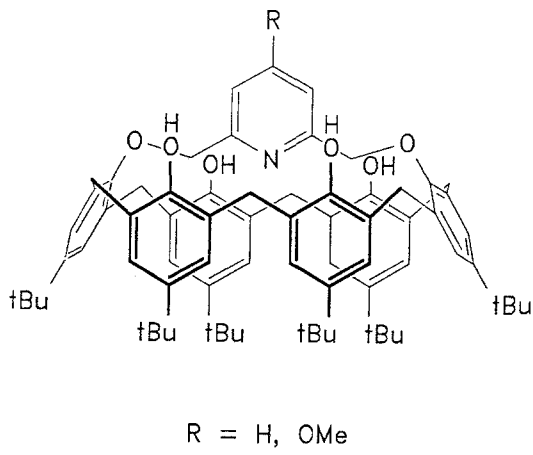
Figure 11. The reaction of pyrazole substituted acrylamides with cyclopentadienes can be catalyzed by transition metal salts. With increasing shielding of the metal ion by the use of concave 1,10-phenanthrolines, the *endo*/*exo*-selectivity can be shifted towards *exo*.

basicity log K [15] of the (concave) pyridines used. Although three pyridines have the same basicity, they show a different catalytic behavior, demonstrating that the geometry of the pyridines and not the basicity influences the catalysis.

Using a Brønsted plot (plotting the observed rate constants against the basicities), allows these two influences to be separated from one another. Figure 8 shows a Brønsted plot for some selected concave pyridines and pyridine itself. For pyridines of the same geometry, linear correlations exist between the basicity and the rate. The larger concave pyridines containing three oxygen atoms in the



Scheme 5.



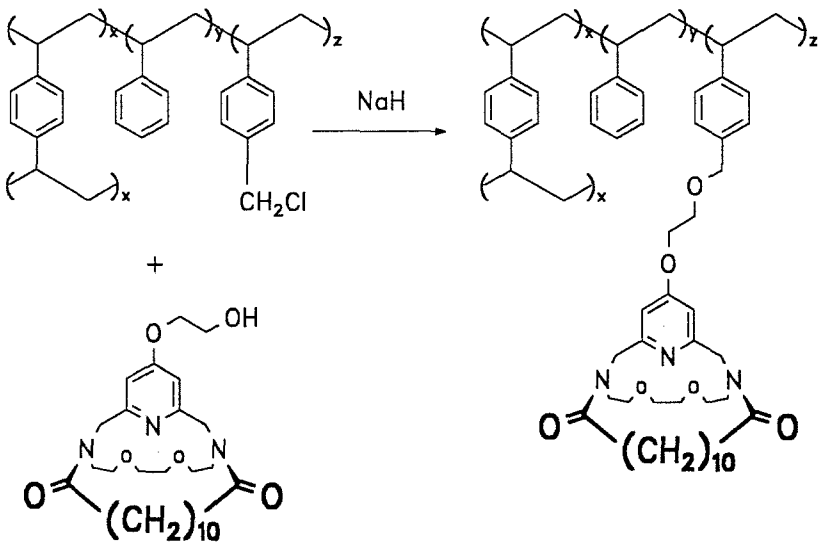
R = H, OMe

Formula 3.

polyether chain catalyze better than the smaller analogs, with pyridine itself being the most reactive catalyst.

The findings of Figure 8 can be explained by general base catalysis via the formation of a hydrogen bond between the concave pyridine and the alcohol (Formula 1).

However, when a size variation in the concave pyridines gives rise to a change in rate, a 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 catalyzed differently. The base catalyzed addition of ethanol and isopropanol was therefore measured. The ratio of these rate constants are listed for a variety of different catalysts in Table II. A comparison of the k_{EtOH}/k_{iPrOH} values reveals that the largest selectivities (>5) have been determined for the concave pyridines with three oxygen atoms in the polyether chain.



Scheme 6.

Concave pyridines are thus able to discriminate between different alcohols. This ability would be very useful if it could be exploited in intramolecular competitions.

Carbohydrate derivatives have therefore been treated with diphenylketene in the presence of concave catalysts. The results of the acylation of a glucose derivative and of a chinovose are given in Figures 9 and 10, respectively. The hydroxyl groups are secondary and equatorial in both carbohydrates. 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 case of chinovose).

3.3. METAL ION CATALYZED REACTIONS

The free electron pair(s) in the concave pyridines, and especially in the concave 1,10-phenanthrolines, are not only able to bind a proton, they may also be used to coordinate a metal ion (Formula 2). Transition metal complexes of concave 1,10-phenanthrolines have already been generated [4b,15]. They form readily in acetonitrile solution with binding constants of 10^4–10^7 and greater.

These complexes have been applied in transition metal catalyzed Diels–Alder reactions [16]. Pyrazole substituted acrylamides were used as dienophiles and were allowed to react with cyclopentadienes in the presence of nickel-(II)- and cobalt-(II)-nonafluorobutanesulfonates ($NiNf_2$, $CoNf_2$) with and without different 1,10-phenanthrolines as ligands as shown in Figure 11.

The incorporation of the catalytical metal ions into the concave 1,10-phenanthroline leads to a shift in the diastereoselectivities. Without ligand, the *endo*-norbornenes are the main products. But when the metal ion is sterically shielded, an *exo*-preference is found. A rationalization is given in Scheme 5. In the transition

state leading to the *endo*-norbornene, the cyclopentadiene would have to go in with the atoms C-2 and C-3 first, which is sterically disfavored compared to the orientation leading to the *exo*-compound (C-5 in first).

4. Outlook

As outlined in this article, various classes of concave reagents may be synthesized in gram quantities. But 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 or a high yield synthesis are necessary. Scheme 6 and Formula 3 show two approaches to solving this problem.

Concave reagents can very easily be synthesized from the readily available calix[6]arenes in good overall yields (42–48% in two steps starting from *tert*-butylphenol) (Formula 3) [17]. The second method is the attachment of 4-substituted concave pyridinebislactams to a polymer (Merryfield resin) (Scheme 6) [13, 18].

Acknowledgements

This work was carried out by my talented co-workers. I would very much like to thank: Dr. H. Baumgartner, Dr. R. Baumstark, Dr. M. Gelbert, Dr. M. Gerst, W. Hacker, M. Hagen, J. Krüger, C. Kühl, M. Kümmerlin, C. Manthey, B. Meynhardt, Dr. M. Müller, S. Petersen, D. Rapp, H. Ross, Dr. W. Schyja, Dr. C. Wangnick. The 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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2. The term *bimacrocycle* will be used instead of macrobicycle because bimacrocycles often also contain smaller rings (e.g. aryl rings). They are thus macro*poly*cyclic although only two *macro*cycles exist. (In addition, no bicycle company has offered sponsorship yet.)
3. (a) Concave Reagents 1: U. Lüning: *Liebigs Ann. Chem.* 949 (1987). (b) Concave Reagents 3: U. Lüning, R. Baumstark, K. Peters, and H. G. v. Schnering: *Liebigs Ann. Chem.* 129 (1990). (c) Concave Reagents 8: U. Lüning, R. Baumstark, and M. Müller: *Liebigs Ann. Chem.* 987 (1991).
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6. (a) Concave Reagents 7: U. Lüning, C. Wangnick, K. Peters, and H. G. v. Schnering: *Chem. Ber.* **124**, 397 (1991). (b) Concave Reagents 11: U. Lüning and C. Wangnick: *Liebigs Ann. Chem.* 481 (1992).
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8. QCPE program No. 429 by M. L. Connolly, used with Chem-X, developed and distributed by Chemical Design Ltd, Oxford, England.
9. The term *general* and *specific protonation* is used in the same sense as the terms *general* and *specific acid catalyses* are used: *specific* means a specific protonated solvent molecule is the

reacting species while *general* means that in general all acids in solution contribute to the reaction.
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15. log K parallels the pK_a scale. For the definition of log K see: Concave Reagents 2: U. Lüning and M. Müller: *Liebigs Ann. Chem.* 367 (1989).
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