1,2-Diphenyl-1,2-diaminoethane Derivatives as Scissors Shaped Allosteric Receptors

Hans-Jörg Schneider* and Frank Werner

FR Organische Chemie der Universität des Saarlandes, D-W 6600 Saarbrücken 11, Germany

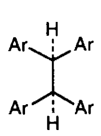
The binding of transition metal ions at one side of a simple molecular hinge induces geometric displacements of electrostatic binding sites at the other side and thus liberation of dianionic substrates.

Most of the synthetic allosteric host–guest systems described so far contain two conformationally coupled binding sites for metal ions,[1] with a few recent extensions.[2] We have already described a system with strongly positive heterotopic allosterism based on a combination of a lipophilic and an ionic binding centre on the *same* side of a molecular hinge; there the addition of transition metal ions leads to a 10 to 100 fold increase of binding constants of lipophilic substrates.[3] Sijbesma and Nolte recently reported a positively cooperative system with a two- to six-fold increase of corresponding binding constants.[4] We demonstrate here another principle of simple allosteric systems in which heterotopic binding centres are arranged on *opposite* sides of a molecular hinge or axle (Scheme 1).

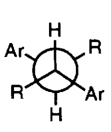
In this device vicinal diaminogroups provide for the strong complexation of transition metalions;[5] subsequent conformational changes on the opposite side can lead to either stronger or weaker binding of a second, *e.g.* ionic, substrate. The ditopic receptor **2** chosen was obtained as pure *meso* diastereoisomer starting from 4-(trimethylammonium)-benzaldehyde, [from 4-(dimethylamino)-benzaldehyde with methyliodide in acetonitrile] *via* a diaza-Cope rearrangement similar to literature procedures.[6] ^{1}H NMR spectroscopic titrations[7] with **2**, its cadmium complex **3** and the parent compound **1** with the geometrically different guest molecules **G1** to **G4** yielded satisfactory fitting curves for 1 : 1 complexes between host and guest (Table 1).

1,2-Diphenylethane derivatives such as **1** not only contain *trans* conformations but also *gauche* conformers,[8] for which models show a close to optimal distance *d* between the $^{+}NMe_3$ groups ($d \approx 8$ Å) for the corresponding COO^- groups in the guest molecule **G3** ($d \approx 7.5$ Å). The observed binding constants with **G3** (Table 1) indeed are close to those expected for a double salt bridge[9] ($K \approx 10^2$ dm^3 mol^{-1}); in contrast **G1**, **G2** and **G4** offer a less optimal distance *d* and, therefore, show smaller binding constants.

The hydrogen bonds in **2** lead here to a dominating *gauche* conformation *g*.[10] This is supported by ^{1}H NMR spectroscopic measurements of the vicinal H–C–C–H coupling constants obtained from the ^{13}C–^{1}H satellites, which yields ^{3}J 8.85 Hz at pH 10.0. This leads to an averaged torsional angle of $\theta_m = 47 \pm 5°$ on the basis of a modified Karplus equation.[11] At pH 1.0 we observe ^{3}J 11.45 Mz, or $\theta_m = 143 \pm 5°$ as expected in view of the double protonation and hence repulsion of the nitrogen substituents (the surprisingly small *K* values with **2** in comparison to **1** could originate in the smaller flexibility of the



1 R = H, Ar = p-$C_6H_4{}^{+}NMe_3$
2 R = NH_2, Ar = p-$C_6H_4{}^{+}NMe_3$
3 $^{1}/_{2}$ Cd•**2**



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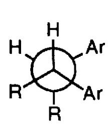
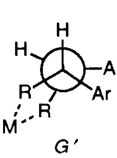
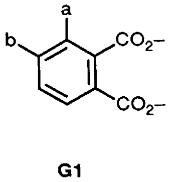


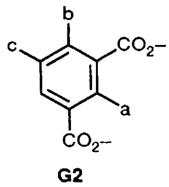
G



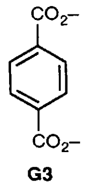
G′



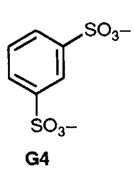
G1



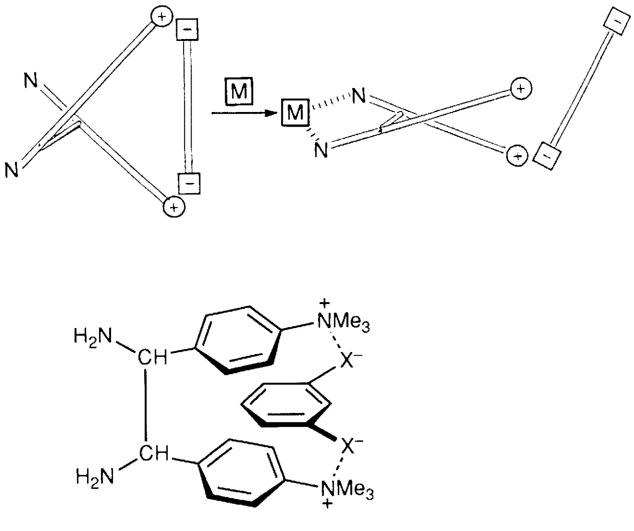
G2



G3



G4



Scheme 1

Table 1 Equilibrium constants K/dm^3 mol^{-1} and complexation induced ^{1}H NMR shifts (CIS)[a]

		G1		G2		G3		G4	
		K	CIS	K	CIS	K	CIS	K	CIS
1	H^a	35	0.104	51	0.107	80	0.154	74	0.075
	H^b		0.143		0.151		—		0.148
	H^c		—		0.186		—		0.188
2	H^a	18	0.060	12	0.159	10	0.190	27	0.054
	H^b		0.107		0.179		—		0.062
	H^c		—	12	0.161		—		0.044
3	H^a	7	[b]		0.166	5	0.260	16	0.094
	H^b		0.175		0.186		—		0.098
	H^c		—		0.162		—		0.083

[a] From NMR titrations in D_2O at pH = 10.0 and 298 K; with Me_4Si as external reference; CIS (shifts at 100% complexation) always *up*field/shielding; errors in K ± 5%, in CIS ± 0.005 ppm. [b] Signal not assigned because of overlapping with signals from **3**.

gauche conformer with **2**). The complexation induced shifts [CIS (complexation induced shifts) values for 100% complexation, Table 1], which were obtained together with the binding constants by non-linear least-square fitting procedures,[7] indicate by the invariably observed shielding effects arrangements of the substrates **G1** to **G4** between the anisotropy cones of the host phenyl ring as shown in Scheme 1.

Addition of cadmium ions lead, for **G1**, **G2** and **G4**, to a reduction in the binding constants by an approximate factor of 2 (Table 1): metallation obviously results in a rather rigid conformation g', which varies the $^+NMe_3\cdots{}^+NMe_3$ distance d and lowers the electrostatic binding of the guest in the sense of a negative heterotopic cooperatively (Scheme 1). The observed allosteric effect is decreased by the presence of the positively charged metal ion, which—in analogy with secondary coulombic interactions *e.g.* in lariat crown ethers[12]—should lead to *enhanced* instead of lowered K values for **3** in comparison with **2**. Such an *increase* of complexation constants is seen in preliminary studies with adenosine phosphates (AMP, ADP, ATP) for which model inspections suggest a simultaneous interaction of the adenine ring with the $^+NMe_3$ groups in **3** and the phosphate anions with the metal ion. Negatively cooperative heterotopic systems are in principle of interest with respect to numerous applications, such as liberation of drugs, of inhibitors, of catalysts, of dyes *etc.* by action of chemical effectors such as metal ions.

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