Supporting Information for:

When Two Metal Centres are Needed instead of One: Exclusive Induction of Z-DNA by Dinuclear Metal Complexes

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Instrumentation and materials

All chemicals were purchased from Fluka (Buchs, CH) and used without further purification.

All the reactions were performed under a nitrogen atmosphere. The reactions were monitored by thin layer chromatography (TLC). TLCs were carried out on 0.25mm Merck aluminium oxide pre-coated plastic sheets (alox N/UV$_{254}$) using UV light or staining solutions as visualising agent:

Staining solutions

Schlittler's reagent[1]: Solution 1: 1g H_2PtCl_6 in 6ml H_2O + 20ml 1N HCl
Solution 2: 22.5g KI in 225ml H_2O

Solutions 1 and 2 were mixed and diluted with H_2O to a volume of 1000ml.

Ce-P-Mo reagent: 10g $Ce(SO_4)_2*4H_2O$ + 25g $H_3[P(Mo_3O_{10})_4]$ + 60ml conc. H_2SO_4 + 940ml H_2O.

Ion exchange chromatography was performed on AMBERLYST A26-OH, macromolecular ion-exchange resin (from ABCR).

Electrospray Ionisation (ESI) mass spectra were recorded on a Merck Hitachi M-8000 spectrometer or an Esquire HCT from Bruker (Bremen, Germany). Solvents used were aqueous TFA and formiate solutions containing methanol. The MS data are given for the most abundant isotope.

Elemental analyses were performed on a Leco CHNS-932 elemental analyser by Heinz Spring or Barbara Spring. NMR spectra were recorded on a Varian Mercury 200 MHz or Gemini 300 MHz, and on a Bruker DRX 400 or 500 MHz spectrometer. The chemical shifts are relative to residual solvent signals as reference; signals were assigned with the help of ^{1}H-NMR, ^{1}H-COSY, ^{13}C-NMR, C,H-correlation and

C,H-long range correlation. Circular dichroism measurements were performed using a Jasco J-810 spectropolarimeter equipped with a Jasco PFD-4255 Peltier temperature controller.

Crystallographic data were collected at 183(2) K on either a Stoe IPDS (Mo $K_{\alpha1}$ radiation, $\lambda = 0.71073$ Å) or a Stoe IPDS 2T (Cu $K_{\alpha1}$ radiation, $\lambda = 1.54186$ Å) diffractometer using a graphite-monochromated radiation. Suitable crystals were covered with Paratone N oil, mounted on top of a glass fibre and immediately transferred to the diffractometer. A maximum of eight thousand reflections distributed over the whole limiting sphere were selected by the program SELECT and used for unit cell parameter refinement with the program CELL[2]. For the IPDS 2T machine, data was processed with the X-Area software suite.[3] Data were collected for Lorentz and polarisation effects as well as for absorption (numerical). Structures were solved with direct methods using SHELXS-97[4] or SIR97[5] and were refined by full-matrix least-squares methods on F^2 with SHELXL-97[6]. CCDC entries 661093 – 661099 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The B- to Z-DNA transition at a DNA base concentration of about 0.1 mM was monitored by circular dichroism (CD) in 1 mM cacodylate buffer at a pH of 7.0 and 25°C, as previously described.[7]

1. Synthesis and characterization of 1,3-bis(1,5,9-triazacyclododecyl)-propane (L) [8] and its complexes 1 and 2

The hexaprotonated ligand **L**·$(CF_3SO_3H)_6$, 1,3-bis(1,5,9-triazacyclododecyl)-propane hexa-(hydrotrifluoromethanosulfonate), was synthesized according to the literature.[8,9,10]

MS (ES): m/z (%) = 532 $[M + F_3CSO_3H]^+$ (100)

EA: $C_{27}H_{52}F_{18}N_6O_{18}S_6$

Calculated: C (25.27%), H (4.08%) and N (6.55%)

Experimental: C (25.41%), H (4.08%) and N (6.61%)

L$(CF_3SO_3H)_4$: Crystals of partially neutralized **L** which were suitable for the X-ray analysis were grown by vapor diffusion of hexane into a methanol solution of the complex.

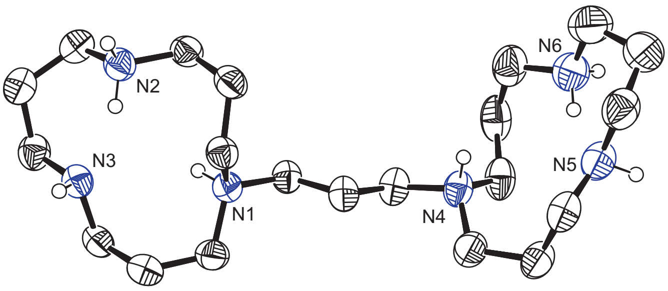
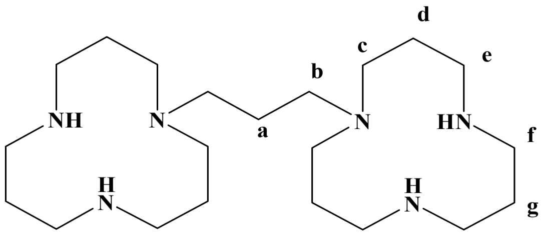


Figure S.1. ORTEP representation of ligand L. (Ellipsoids drawn at 50% probability; non-acidic

hydrogen atoms and four triflate anions were omitted for clarity).



^{1}**H-NMR** (500 MHz, D_2O): $\delta = 2.15$ (m, 9H, **H**a + **H**d), 2.23 (broad t, 4H, **H**g), 3.19 (broad t, 4H, **H**b) and 3.28-3.38 ppm (m, 24H, **H**e, **H**f and **H**c).

^{13}**C-NMR** (125 MHz, D_2O): $\delta = 15.97$ (**C**d), 16.43 (**C**a), 18.28 (**C**g), 39.14 (**C**(f or e)), 40.25 (**C**(e or f)), 45.65 (**C**c) and 48.72 ppm (**C**b).

The hexaprotonated ligand was dissolved in ethanol and 6 equivalents of potassium hydroxide were then added. The precipitated KCF_3SO_3 was filtered off. To the filtered solution, 2 equivalents of nickel acetate or copper chloride were added to form the corresponding dinuclear metal complexes **1** and **2**.

Complex 1:

EA:	$C_{21}H_{46}N_6Ni_2(CH_3CO_2)_4(H_2O)_3(NaCF_3SO_3)$
Calculated:	C (37.44%), H (6.70%), and N (8.73%)
Experimental:	C (37.98%), H (6.65%), and N (8.42%)

[Ni_2**L**$(OAc)_2(H_2O)_2$]$(OTf)_2$: Crystals suitable for the X-ray analysis were grown by vapor diffusion of tetrahydrofuran into a methanol solution of the complex.[11]

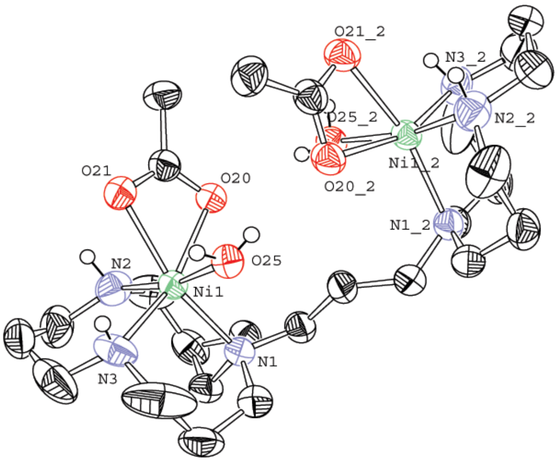


Figure S.2. ORTEP representation of the cationic complex 1. (Ellipsoids drawn at 50% probability; non-acidic hydrogen atoms, two water molecules and two triflate anions were omitted for clarity).

MS (ESI Bruker): m/z (%) = 765 [Ni_2**L**($CH_3COO)_2(CF_3SO_3)]^+$ (29), 675 [Ni_2**L**($CH_3COO)_3]^+$ (100), 661 [Ni_2**L**($CH_3COO)_2$(HCOO)]$^+$ (47), 649 [Ni_2**L**(H)($CH_3COO)_2$(MeOH)]$^+$ (7), 617 [Ni_2**L**(H)($CH_3COO)_2]^+$ (13), 499 [Ni**L**(CH_3COO)]$^+$ (10).

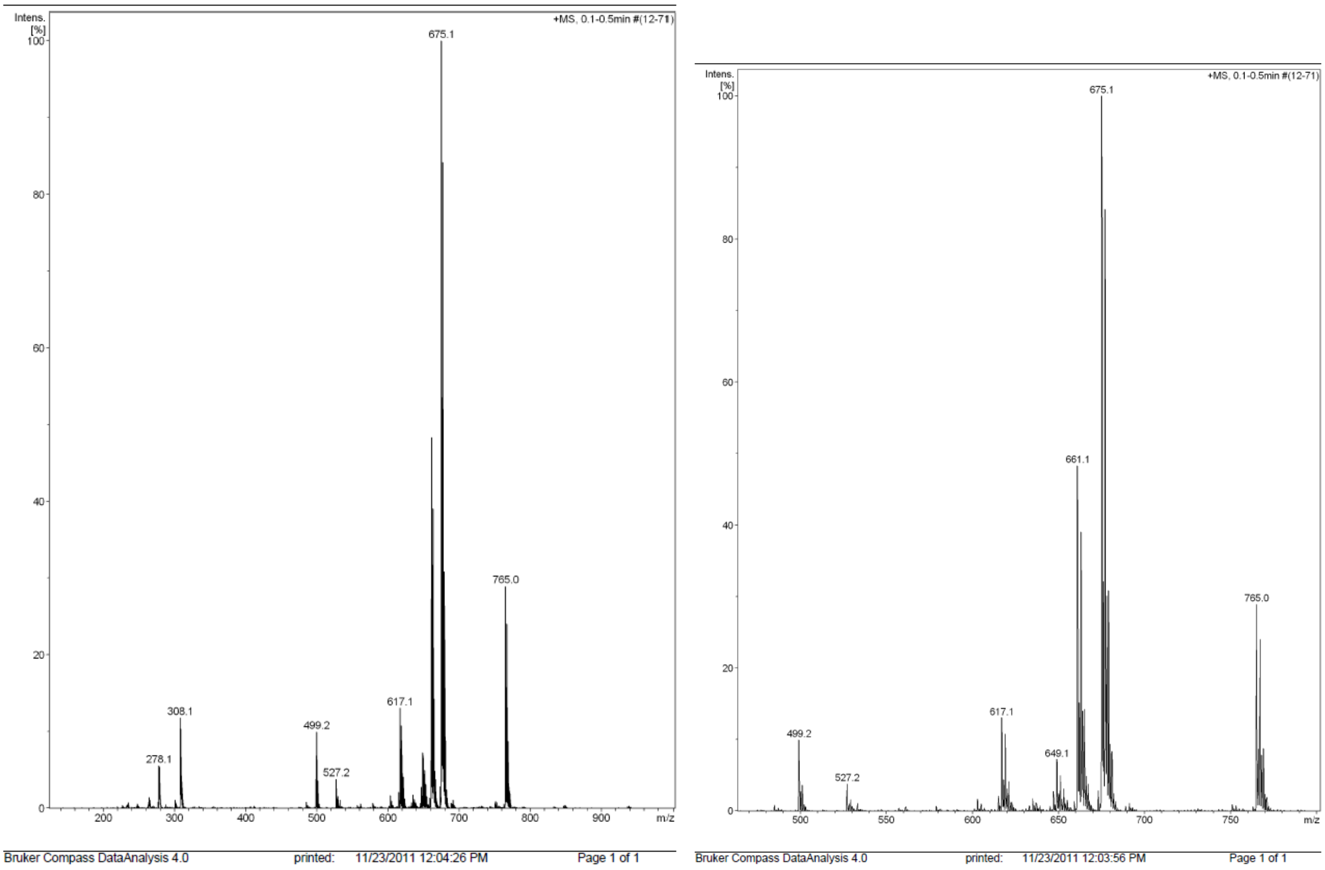
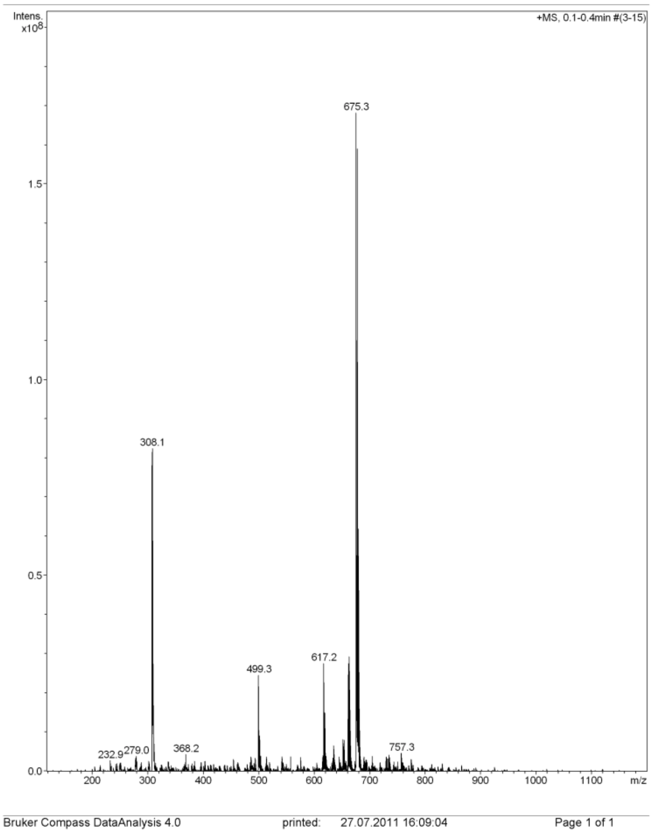
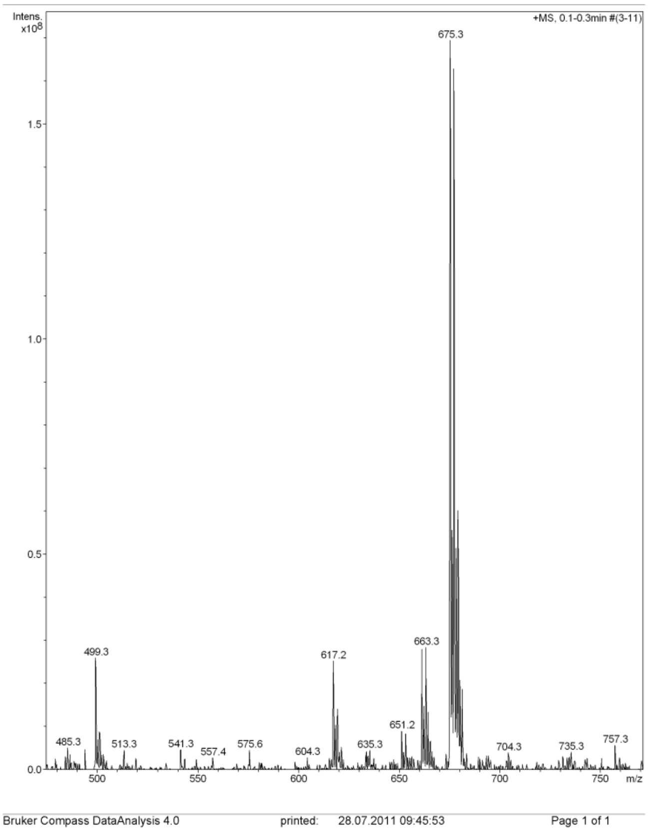


Figure S.3. ESI-MS of 1 and enlarged spectrum.

Complex [2 Cl(OH)($(CF_3SO_3)_2$)]:

MS (ESI Bruker): m/z (%) = 675 [Cu_2**L**(H)(OH)(CF_3SO_3)]$^+$ (100), 663 [(Cu_2**L**($CH_3COO)_2$Cl]$^+$ (17), 617 [Cu_2**L**(H)($HCOO)_2$(H_2O)]$^+$ (16), 308 [Cu_2**L**($HCOO)_2$(H_2O)]$^{2+}$ (49).





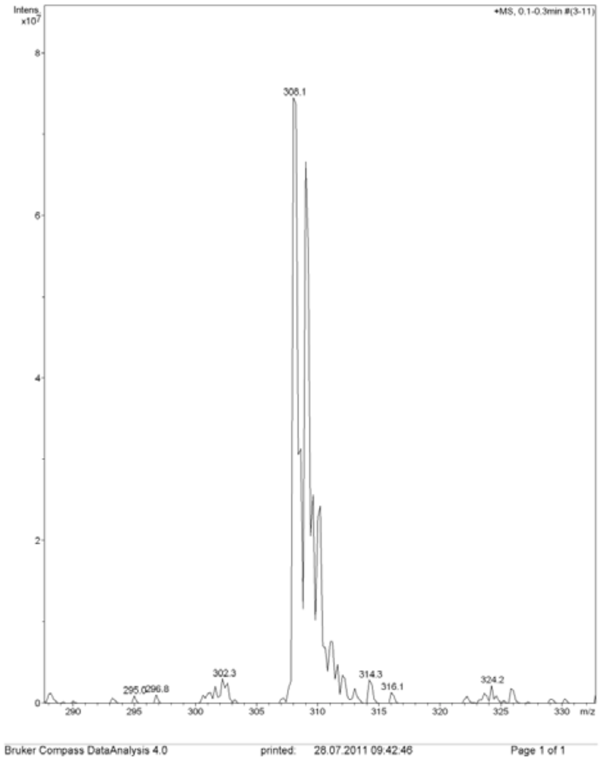


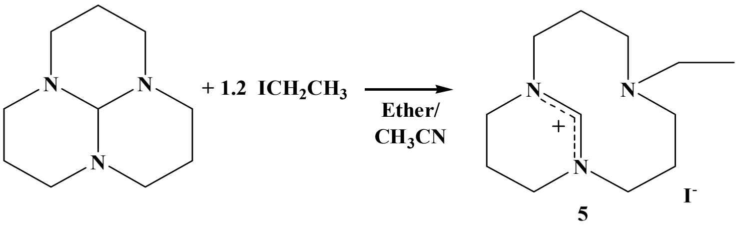
Figure S.4. ESI-MS of [2 Cl(OH)(CF_3SO_3)$_2$] and enlarged spectra.

EA: Cu$_2$**L**Cl(OH)(CF_3SO_3)$_2$:

Calculated:	C(32.16%), H(5.52%), and N(9.79%)
Experimental:	C(32.57%), H(5.02%), and N(9.53%)

Cu$_2$**L**(OH)(Cl)(OTf)$_2$: Crystals suitable for the X-ray analysis were obtained when the reaction mixture was concentrated and cooled down to 4ºC (Figure 3 in the main text).

2. Synthesis and characterization of 1-ethyl-1,5,9-triazacyclododecane (L1) and its complexes 3 and 4



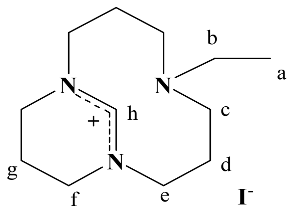
Scheme S.1. Synthesis of compound 5 from 1,5,9-triazatricyclo[7.3.1.0]-tridecane.

Ethyl iodide (1.4ml, 17.3mmol) was dissolved in a mixture of diethylether and acetonitrile (1:1, 35ml) and slowly added to a solution of 1,5,9-triazatricyclo[7.3.1.0]tridecane[9] (2.893g, 16.0mmol) in the same mixture (25ml) under Schlenk line techniques. The resulting reaction mixture was stirred for 18 hours, resulting in abundant precipitation. The white precipitate was filtered off and more ethyl iodide was added to the solution, obtaining more precipitate after few hours stirring. The total yield of **5** was 3.977g (85.5%). Crystals suitable for X-ray diffraction studies were obtained from a supersaturated mixture of water-ethanol (9:1).

MS (ES): m/z (%) = 210 $[M - I]^+$ (100).

EA: $C_{12}H_{24}IN_3$

Calculated:	C (42.74%), H (7.17%), and N (12.46%)
Experimental:	C (42.98%), H (7.19%), and N (12.82%)



^{1}H-NMR (400 MHz, CD$_3$OD): δ = 0.99 (t, J = 8Hz, 3H, **H**a), 1.35 (broad d, J = 16Hz, 2H, **H**d), 2.05-2.35 (m, 4H, **H**g + **H**d'), 2.65 (t, J = 16Hz, 2 H, **H**c), 2.85 (q, J = 8Hz, 2H, **H**b), 3.08 (double d, J = 16Hz, J' = 4Hz, 2H, **H**c'), 3.30- 3.42 (m, 4H, **H**c), 3.49 (d, J = 16Hz, 2H, **H**f), 3.85(double t, J = 12Hz, 2H, **H**f') and 8.34 ppm (s, 1H, **H**h).

^{13}C-NMR (125 MHz, CD$_3$OD): δ = 8.10 (**C**a), 20.76 (**C**g), 24.13 (**C**d), 43.68 (**C**c), 44.97 (**C**b), 55.13 (**C**e), 56.40 (**C**f) and 158.33 ppm (**C**h).

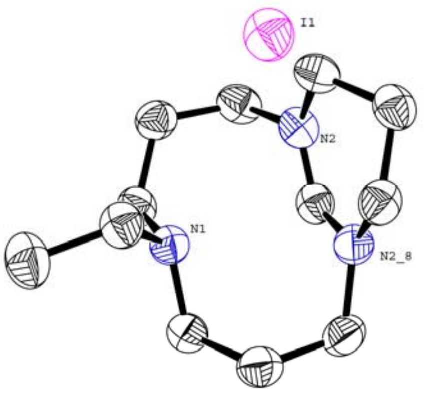
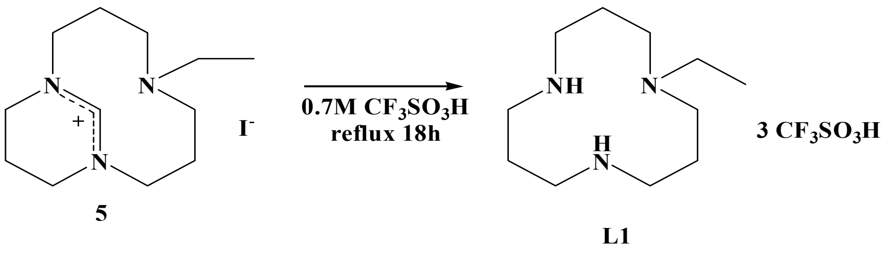


Figure S.5. ORTEP representation of 5. (Ellipsoids drawn at 50% probability; hydrogen atoms omitted for clarity).



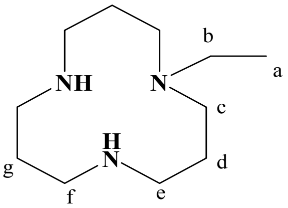
Scheme S.2. Synthesis of 1-ethy1,5,9-triazatricyclododecane tris-(hydrotrifluoro-methanesulfonate) (L1) from compound 5.

Compound **5** (3.2g, 9.5mmol) was dissolved in 250ml of CF$_3$SO$_3$H (0.7M) and refluxed for 18h. The resulting brown solution was concentrated under reduced pressure, observing the formation of solid I$_2$ on the condenser at the same time as the solution became colourless. The reaction mixture was further stirred for 24 hours. The resulting solution was concentrated under reduced pressure and then dissolved again in few millilitres of ethanol. To the ethanol solution, ether-hexane (5:1, 30ml) was added observing the formation of white precipitate. 1-ethyl-1,5,9-triazatricyclododecane (**L1**) consisted in a white powder, which then was filtered off and the mother liquid was kept in the fridge. Some more crystalline material was obtained after few days in the fridge. The total yield for **L1** was 6.978 g (9.4 mmol, 99%). Ligand **L1** crystallised by vapour diffusion of chloroform into a solution of **L1** in acetone.[11]

MS (ES): m/z (%) = 200 $[MH]^+$ (100) and 349 $[M + CF_3SO_3H]^+$ (15)

EA: $C_{11}H_{25}N_3*(H_2O)(CF_3SO_3H)_{3.5}$

Calculated:	C (23.45%), H (4.14%), and N (5.66%)
Experimental:	C (23.86%), H (4.16%), and N (5.58%)



^{1}H-NMR (500 MHz, D_2O): δ = 1.40 (t, 3H, **H**a), 2.26-2.34 (m, 6H, **H**d + **H**g) and 3.33-3.52 ppm (m, 14H, **H**b + **H**c + **H**e + **H**f).

^{13}C-NMR (75 MHz, D_2O): δ = 9.57 (**C**a), 17.89 (**C**d), 20.89 (**C**g), 41.27 (**C**f), 42.39 (**C**e), 46.83 (**C**c) and 51.50 ppm (**C**b).

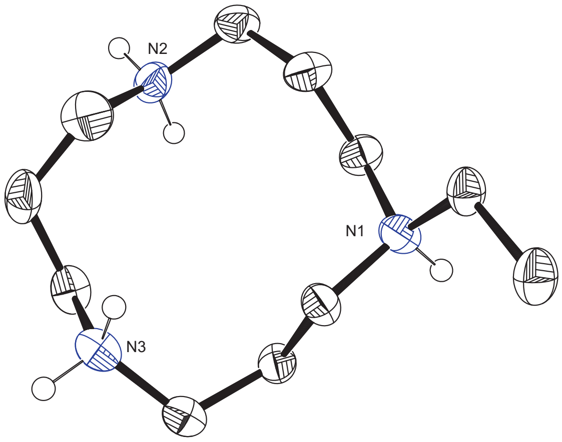


Figure S.6. ORTEP representation of ligand L1. (Ellipsoids drawn at 50% probability; non-acidic hydrogen atoms and three triflate anions were omitted for clarity).

The protonated ligand **L1** was neutralized in an aqueous solution with NaOH and extracted with dichloromethane. The organic phase was concentrated under reduced pressure. The resulting oil was run through an ion exchange column (amberlyst A-26, macromolecular ion-exchange resin) to yield the free base. The free ligand was dissolved in acetonitrile and reacted either with nickel or copper acetate to yield the final metal complexes **3** and **4**. The complexes were precipitated with the help of diethylether.

Complex 3:
MS (ES): m/z (%) = 316 $[M - CH_3CO_2]^+$ (100)
EA: Ni**L1**$(CH_3CO_2)_2(CH_3CH_2OCH_2CH_3)(CH_3CN)$
Calculated: C(51.33%), H(9.03%), and N(11.40%)
Experimental: C(51.42%), H(8.26%), and N(11.43%)
Ni**L1**$(CH_3CO_2)_2(H_2O)$: Crystals suitable for the X-ray analysis were grown by vapor diffusion of pentane into a dichloromethane solution of the complex (Figure 4 in main text).

Complex 4:
MS (ES): m/z (%) = 262 $[M - 2CH_3CO_2]^+$ (100)
EA: Cu**L1**$(CH_3CO_2)_2(CH_3CH_2OCH_2CH_3)(CH_3CN)$
Calculated: C(50.84%), H(8.94%), and N(11.29%)
Experimental: C(51.07%), H(8.95%), and N(11.21%)
Cu**L1**$(CH_3CO_2)_2$: Crystals suitable for the X-ray analysis were grown by vapor diffusion of cyclopentane into a dichloromethane solution of the complex (Figure 4 in main text).[11]

3. Titration of poly d(GC) with complexes 1-4

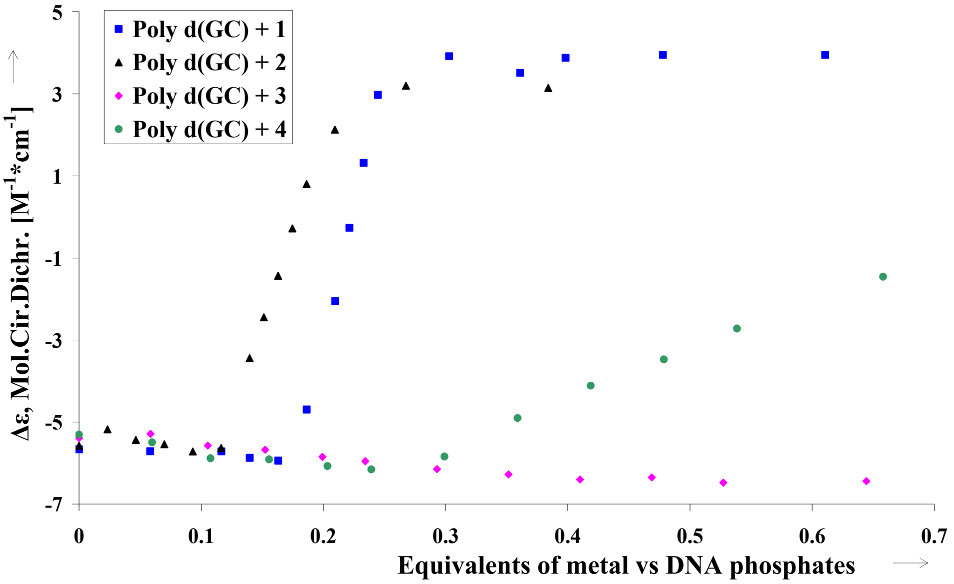


Figure S.7. Molar ellipticity at 255 nm as a function of metal equivalents versus DNA phosphates. Using metal equivalents as units instead of complex equivalents allows to directly compare the efficiency of the mono- and dinuclear complexes.

References:

1. E. Schlittler and J. Hohl, *Helv. Chim. Acta*, 1952, **35**, 29.
2. *STOE-IPDS Software package*, (1998) STOE & Cie, GmbH, Darmstadt, Germany.
3. *X-Area*, (2006) STOE & Cie, GmbH, Darmstadt, Germany.
4. G. M. Sheldrick, *Acta Cryst.*, 1990, **A46**, 467.
5. A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, *J. Appl. Cryst.*, 1999, **32**, 115.
6. G. M. Sheldrick, *Acta Cryst.*, 2008, **A64**, 112.
7. B. Spingler and C. Da Pieve, *Dalton Trans.*, 2005, 1637.
8. M. D. Snodin, P. D. Beer and M. G. B. Drew, *J. Chem. Soc., Dalton Trans.*, 1997, 3407.
9. R. W. Alder, R. W. Mowlam, D. J. Vachon and G. R. Weisman, *J. Chem. Soc., Chem. Commun.*, 1992, 507.
10. A. Medina-Molner, O. Blacque and B. Spingler, *Org. Lett.*, 2007, **9**, 4829.
11. B. Spingler, S. Schnidrig, T. Todorova and F. Wild, *CrystEngComm*, accepted.

Table S1:Crystallographic Data

	$[1(OAc)_2(OH_2)_2](OTf)_2$	**$[2(Cl)(OH)(OTf)_2]$**
Empirical formula	$C_{27}H_{60}F_6N_6Ni_2O_{14}S_2$	$C_{23}H_{49}ClCu_2F_9N_6O_8S_2$
Colour	Blue	Green
Formula weight [g mol^{-1}]	988.35	878.33
Crystal system	Monoclinic	Triclinic
Space group	I2/a	P-1
Crystal dimensions [mm]	0.43 x 0.14 x 0.12	0.22 x 0.18 x 0.08
a [Å]	16.1025(10)	11.6587(9)
b [Å]	15.5813(8)	11.9119(10)
c [Å]	17.0644(11)	13.8305(11)
α [°]	90	97.909(10)
β [°]	98.454(8)	96.699(9)
γ [°]	90	114.467(9)
Volume [Å^3]	4234.9(4)	1819.2(3)
Z	4	2
Absorption coefficient [μ, mm^{-1}]	1.080	1.438
Temperature [K]	183(2)	183(2)
Wavelength	Mo K_α ($\lambda = 0.71073$Å)	Mo K_α ($\lambda = 0.71073$Å)
Theta range for data collection [°]	2.87 to 30.47	2.89 to 30.51
Reflections collected	24077	33110
Independent reflections	6269 [$R_{(int)}$ = 0.0474]	10097 [$R_{(int)}$ = 0.0960]
Data/restraints/parameters	6269 / 95 / 305	10097 / 1 / 435
Goodness-of-fit on F^2	1.078	0.971
Final R indices [I>2sigma(I)]	R1 = 0.0658 wR2 = 0.1939	R1 = 0.0489 wR2 = 0.1311
R indices (all data)	R1 = 0.0821 wR2 = 0.2106	R1 = 0.0830 wR2 = 0.1516
Largest diff. peak and hole [e/Å^3]	1.001 and -0.595	0.944 and -0.564

	[3$(CH_3CO_2)_2(H_2O)$]	**[4$(CH_3CO_2)_2$]·CH_2Cl_2**
Empirical formula	$C_{15}H_{33}N_3NiO_5$	$C_{16}H_{33}Cl_2CuN_3O_4$
Colour	Blue	Green
Formula weight [g mol^{-1}]	394.15	465.89
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12$	$P2_1/c$
Crystal dimensions [mm]	0.41 x 0.22 x 0.15	0.15 x 0.11 x 0.10
a [Å]	15.612(2)	11.898(5)
b [Å]	15.6754(18)	14.067(5)
c [Å]	7.9380(9)	13.146(5)
α [º]	90	90
β [º]	90	90.368(5)
γ [º]	90	90
Volume [Å^3]	1942.6(4)	2200.2(15)
Z	4	4
Absorption coefficient [μ, mm^{-1}]	1.348	1.260
Temperature [K]	183(2)	183(2)
Wavelength	Mo K_α (λ = 0.71073Å)	Mo K_α (λ = 0.71073Å)
Theta range for data collection [º]	2.60 to 30.48	2.72 to 29.13
Reflections collected	42415	33708
Independent reflections	5891 [$R_{(int)}$ = 0.0587]	5844 [$R_{(int)}$ = 0.1201]
Data/restraints/parameters	5891 / 0 / 224	5844 / 0 / 238
Goodness-of-fit on F^2	1.103	0.923
Final R indices [I>2sigma(I)]	R1 = 0.0556 wR2 = 0.1462	R1 = 0.0672 wR2 = 0.1358
R indices (all data)	R1 = 0.0581 wR2 = 0.1513	R1 = 0.0897 wR2 = 0.1472
Largest diff. peak and hole [e/Å^3]	1.261 and -0.440	0.728 and -0.684

	5
Empirical formula	$C_{12}H_{24}IN_3$
Colour	Colourless
Formula weight [g mol^{-1}]	337.24
Crystal system	Orthorhombic
Space group	Pnma
Crystal dimensions [mm]	0.23 x 0.19 x 0.15
a [Å]	16.6238(5)
b [Å]	9.1011(5)
c [Å]	9.5117(10)
α [º]	90
β [º]	90
γ [º]	90
Volume [Å^3]	1439.07(18)
Z	4
Absorption coefficient [μ, mm^{-1}]	2.207
Temperature [K]	183(2)
Wavelength	Mo K_α (λ = 0.71073Å)
Theta range for data collection [º]	3.10 to 30.51
Reflections collected	26656
Independent reflections	2295 [$R_{(int)}$ = 0.0653]
Data/restraints/parameters	2295 / 0 / 83
Goodness-of-fit on F^2	1.159
Final R indices [I>2sigma(I)]	R1 = 0.0463 wR2 = 0.1262
R indices (all data)	R1 = 0.0495 wR2 = 0.1340
Largest diff. peak and hole [e/Å^3]	1.355 and -0.868

	L·(TfOH)$_4$	**L1·(TfOH)$_3$**
Empirical formula	$C_{25}H_{50}F_{12}N_6O_{12}S_4$	$C_{14}H_{28}F_9N_3O_9S_3$
Colour	Colourless	Colourless
Formula weight [g mol^{-1}]	982.95	649.57
Crystal system	Triclinic	Orthorhombic
Space group	P-1	Pna2$_1$
Crystal dimensions [mm]	0.33 x 0.25 x 0.15	0.28 x 0.24 x 0.19
a [Å]	14.5787(11)	8.6228(2)
b [Å]	10.7388(8)	20.3707(4)
c [Å]	15.1058(12)	15.0841(3)
α [º]	91.857(9)	90
β [º]	117.268(8)	90
γ [º]	87.518(9)	90
Volume [Å^3]	2099.9(3)	2649.6(1)
Z	2	4
Absorption coefficient [μ, mm^{-1}]	1.555	3.612
Temperature [K]	183(2)	183(2)
Wavelength	Mo K$_\alpha$ (λ = 0.71073Å)	Cu K$_\alpha$ (λ = 1.54186Å)
Theta range for data collection [º]	2.64 to 28.28	3.65 to 66.46
Reflections collected	36077	25107
Independent reflections	9617 [R$_{(int)}$ = 0.1039]	4361 [R$_{(int)}$ = 0.0902]
Data/restraints/parameters	9617 / 135 / 604	4361 / 1 / 344
Goodness-of-fit on F^2	1.085	1.143
Final R indices [I>2sigma(I)]	R1 = 0.0814 wR2 = 0.2480	R1 = 0.0550 wR2 = 0.1376
R indices (all data)	R1 = 0.0992 wR2 = 0.2676	R1 = 0.0637 wR2 = 0.1468
Largest diff. peak and hole [e/Å^3]	1.220 and -0.916	0.466 and -0.402