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Neutral Diamide Ionophores — Phenylenedioxydiacetamides[1]

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The preparation of a series of neutral ligands containing ether and amide groups is described. These ligands as well as related ones bearing other diamide groups are shown to selectively chelate Group II A cations by picrate extraction from water to methylene dichloride. This result was also confirmed by atomic absorption measurement. The changes in UV absorption of aromatic rings and amide groups in the ligands upon titration with metal salts in methanol allow the estimation of the ordering of cation binding.

(Keywords: Acyclic ionophores; Neutral ionophores; Phenylenedioxydiacetamide, complexation studies)

Neutrale Diamid-Ionophore — Phenylendioxyacetamide

Die Darstellung einer Reihe von neutralen Liganden mit Ether- und Amidgruppen wird beschrieben. Sowohl diese Liganden — als auch verwandte mit anderen Diamidgruppen — bilden mit Kationen der Gruppe II A selektiv Chelate, wie durch Pikratextraktion aus wäßriger Lösung gezeigt wurde. Dieses Ergebnis wurde auch durch Messungen der Atomabsorption bestätigt. Die Änderungen in der UV-Absorption der aromatischen Ringe und der Amidgruppen in Methanol erlauben eine Abschätzung der Größenordnung der Kationenbindung.

Introduction

Naturally occuring macrocyclic and acyclic ionophores are involved in the selective transport of essential metal cations across biological membranes[2a,b]. Synthetic ionophores are of interest in that they provide model systems which can be varied greatly in structure. They can solubilize metal cations in lipid-like solvents and are useful in applications such as cation analysis, catalysis, organic synthesis and the study of the mechanisms of ion transport across membranes.

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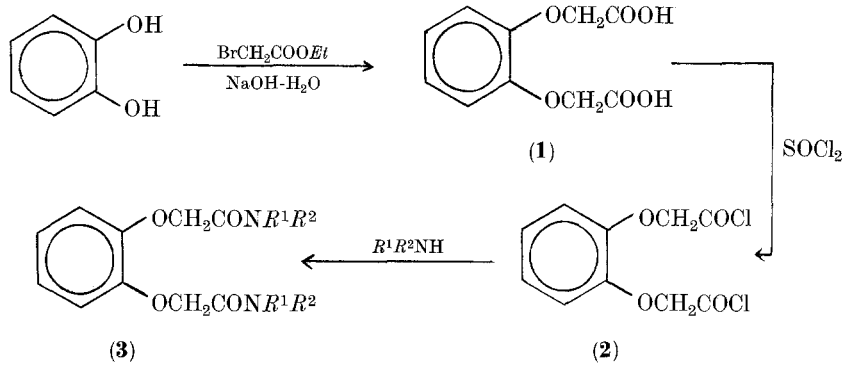
Previously, an acyclic 1,2-ethylenedioxydiacetamide system was found to show selective Group II A cation complexation[2c]. It was also reported that aromatic and acyclic analogues of this system display a wider range of selective binding properties in ion seneitive electrods[3a]. We would like to report the synthesis of a series of phenylenedioxydiacetamides together with the studies of their complexation properties using picrate extraction, atomic absorption and UV spectroscopy.

Results and Discussion

Phenylene dioxydiacetic acid (**1**) is known[3a,c]. Improved yields were obtained by reaction of catechol with ethyl bromoacetate in the presence of excess base (10% excess) in water. The reaction of acid chloride (**2**) with the amines in question gives the amides (**3**).



—NR^1R^2

a —NH_2
b —NH*Et*
c —NH*Bu-n*
d —NH*Bu-t*
e —NH- 
f —NH-
g —NEt_2
h —N*Et*C_6H_5
i —N
j —NO
k —$NHCH_2CH(OMe)_2$
l —N*Me*CONH*Me*
m —NHC_6H_5
n —NH- 
o —NHC*Me*=CHCOO*Me*
p —NH- 
CO*Me*

Qualitative UV Studies

The complexation of various cations with ligands **3** was studied in methanol, a solvent for which there is much data on the complexation of crown ethers and other molecules[4,5]. The single broad absorption of **3** at around 270 nm changes to either a doublet or higher absorbance upon its complexation

with various cations, a situation reminiscent of the behaviour of dibenzo-18-crown-6 and other catechol derived crown ethers[5a]. A qualitative estimate of the extent of complexation of **3** with various salt is obtained by the method of *Pedersen*[5a]. The UV spectrum of **3** is taken in the presence of a large (usually fifty-fold) excess of the salt so as to maximize the possibility of complexation. Although different anions are used, both our data and crown ether work[5] suggest that anion difference are negligible as long as the salt is soluble in methanol and dose not itself absorb in 270 nm region.

Table 1 shows the cations which form complexes. Changing the substituent on nitrogen atom of ligand **3** from ethyl group in **3b** to phenyl group in **3m** or naphthyl group in **3n** or —C(*Me*)=CHCOO*Et* in **3o** or *o*-acetylphenyl group in **3p** the potent of its ability to complex metal cations disappears. It is clear that the basicity of nitrogen in ligand **3** is decreased by introduction the unsaturated group therefore, reducing its ability to participate the complexation with metal cations.

Table 1. *Complexation studies by UV spectrometry*

Compound	Cations
3a	$Ca^{++} \approx Sr^{++} > Mn^{++}$
3b	$Ca^{++} \approx Sr^{++}$
3c	$Ca^{++} \approx Sr^{++}$
3d	$Ca^{++} \approx Sr^{++} > Mn^{++} \approx Al^{+++} \approx Li^{+}$
3e	$Ca^{++} \approx Sr^{++} > Mn^{++} \approx Ba^{++}$
3f	$Ca^{++} \approx Sr^{++} > Ba^{++} \approx Mn^{++}$
3g	$Ca^{++} \approx Sr^{++} > Al^{+++} > Mg^{++}$
3h	$Ca^{++} > Sr^{++}$
3i	$Ca^{++} \approx Sr^{++} \approx Mn^{++} \approx Ba^{++} > Mg^{++} \approx Al^{+++} \approx Na^{+}$
3j	$Ca^{++} \approx Sr^{++} > Al^{+++} > Mg^{++}$
3k	$Ca^{++} \approx Sr^{++} > Mn^{++}$
3l	$Ca^{++} \sim Sr^{++} > Mn^{++} \approx Ba^{++} \approx Na^{+}$

Extraction of Metal Cation Picrates by the Ligands

The extraction of metal cation picrates from water into an organic phase by a potential ligand provides a rapid screening of the selectivity of cation complexation of that ligand and a method for the comparison of the relative chelating abilities of different ligands[6].

Table 2 summarizes the relative extractability of cations by various ligands. Ligand **3k** as well as **3j** with more possible binding sites does not show extra selectivity or complexation power (—O*Me* of **3k** —$CH_2CH_2OCH_2CH_2$— of **3j**. The non-complexation of **3m–p** agrees with the result obtained from UV studies. Changing of mono-substituted amide to di-substituted amide **3f** to **3i**, **3b** to **3g**) the chelation capacity to different cations remains the same. Some of the picrate

extraction data were also confirmed by the same extraction in the absence of picric acid. The metal ion concentration before and after extraction was measured by atomic absorption, the result is shown in column B of Table 2.

Table 2. *Extraction of metal cations by the ligands*[a]

Compound	Ca^{++}		Sr^{++}		Ba^{++}		Mn^{++}	
	A[b]	B[c]	A	B	A	B	A	B
3b	0.06	—	0.08	—	0.06	—	0.12	—
3c	0.06	0.22	0.12	0.15	0.06	0.07	0.10	0.05
3d	0.06	—	0.09	—	0.06	—	0.09	—
3e	0.06	—	0.09	—	0.06	—	0.10	—
3f	0.06	0.22	0.15	0.12	0.06	0.05	0.12	0.07
3g	0.06	—	0.08	—	0.06	—	0.08	—
3h	0.06	—	0.06	—	0.06	—	0.06	—
3i	0.06	0.12	0.16	0.31	0.13	0.16	0.07	0.05
3j	0.06	—	0.07	—	0.06	—	0.06	—
3k	0.06	0.18	0.15	0.12	0.06	0.05	0.10	0.05

[a] Experimental procedures as described. [Ligand] = $1.4 \times 10^{-3}\,M$; [Picric Acid] = $7.0 \times 10^{-5}\,M$; [Cation] = $1.0\,M$. The error limit is estimated to be less than 0.01 for extraction performed in triplicate. Fraction extracted = 0.02 without ligand.

[b] Data from picrate extraction.

[c] Data from atomic absorption spectroscopy.

In picrate extraction measurements, the assumption is made that only picrate anions are transferred and not Cl^- which is used in the situ preparation of the metal cation picrates. This was shown to be valid for the extraction of monovalent cation picrates with actins[7]. Data for divalent cation have not been available. The result from atomic absorption showed that in the case of divalent cation not only the picrate anion but also the other anion, for example Cl^- has been transferred from water to organic phase. The amount of Ca^{2+} transferred by **3c** with calcium picrate alone or with calcium picrate—$CaCl_2$ containing varying amounts of excess Cl^- varied by only 3%. Since organic anion-picrate is known to be better solvated by organic solvent than the inorganic anion, the small difference in the above two extractions together with the result from atomic absorption suggest that in the mixture of picrate-excess $CaCl_2$ the picrate was extracted predominately and only when this extraction reachs maxima the $CaCl_2$ starts to be transferred. Thus the use of picrate transfer could only estimate the relative amount of divalent cation transferred by different ligands.

The original idea to change the ligand's selectivity toward the different cations by increasing the number of the coordination sites of the system, from **3i** to **3j** or **3k** or **3o** or **3p**, was not observed. This suggests that the participation of the terminal oxygen containing group is minimum. The only crystalline complex isolated is **3l**. $Ca(SCN)_2$ in 1:1 stoichiometry.

3l $C_{16}H_{22}N_4O_6$, calc. C 52.45%, H 6.05%, N 15.29%; found C 52.19%, H 6.05%, N 15.29%, for **3l** $Ca(SCN)_2$, calc. C 41.38%, H 4.21%, N 16.16%, found C 41.35%, H 4.25%, N 16.20%.

Probably an intramolecular hydrogen bonding forms a rigid structure which increases the complexation capacity and thus suggests the possible participation of the terminal carbonyl group.

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Experimental

Infrared spectra were taken on a Perkin-Elmer model 180 spectrophotometer and ultraviolet spectra were recorded on Perkin-Elmer model 356 spectrophotometer in methanol. The nuclear magnetic resonance spectra were measured in $CDCl_3$ solution with Hitachi Perkin-Elmer R 20 B spectrometer and *TMS* was used as internal reference. Mass spectra were taken on a Varian Mat. 111 mass spectrometer.

All solvents used were dried by distillation and if necessary they were purified by following the procedure mentioned in Ref.[8]. All inorganic salts were reagent grade.

Phenylenedioxydiacetic acid (**1**)

Catechol (3 g, 0.027 mol) was dissolved in 10 ml water and a base solution (NaOH 5.2 g, 0.13 mol in 20 ml water) added slowly to maintain the temperature at 80°. After ten minutes 8 ml of ethyl bromoacetate (0.065 mol) was added. The mixture was maintained at this temperature for additional 2 h. Some precipitate formed at the end of the reaction. The reaction mixture was acidified by conc. HCl to $pH = 1$ to give the solid diacid **1**. Rescrystallization from dilute HCl solution gave pure product m.p. 175-178° (60% yield)[3c].

Phenylenedioxydiacetyl chloride (**2**)

A mixture of diacide **1** and thionyl chloride was heated to reflux for 1 h, the excess thionyl chloride was distilled off. The product obtained was used for further reaction without any purification m.p. 47-50°[3a].

Phenylenedioxydiacetamides **3** — *General Procedure*

The acid chloride **2** (1 equiv.) was dissolved in methylene dichloride at 0-5 °C and a solution of the amine in question (2 equiv.) was added dropwise.

The mixture was than kept stirring at room temperature for 1-1.5 h. After the reaction is over the mixture was washed with water several times and the organic solution was dried over anhydrous magnesium sulfate, the solvent was evaporated under vacuum to give the product.

o-Phenylenedioxydiacetamide **3 a**[9]

Acid chloride **2** (0.05 mol) was dissolved in 15 ml of dry acetone and 10 ml of concentrated ammonium hydroxide was added slowly at this temperature. The mixture was kept stirring at room temperature for 2 h. At the end of the reaction the mixture was cooled and filtered. The white crystals were washed several times with water, then with acetone; m.p. 205-208 °C; 59% yield. IR (KBr): 3380, 3195 and 1655 cm^{-1}. NMR (CD_3COOD); δ 4.68 (s, 4H, —OCH_2CO—), 7.02 (s, 4H, aryl) and 11.41 (s, 4H, —NH_2). UV: max 272 nm, $\varepsilon = 2029$. Anal. calc. for $C_{10}H_{12}N_2O_4$: C 53.57, H 5.39, N 12.49; found: C 53.76, H 5.44, N 12.23.

N,N'-diethyl-1,2-phenylenedieoxydiacetamide (**3 b**)

Obtained as a yellow oil, crystallized from CCl_4 to give white crystals, 80% yield, m.p. 130-131 °C. IR (KBr): 3380, 3290, 1655 cm^{-1}. NMR ($CDCl_3$): δ 1.18 (t, 6H, —CH_3, $J = 6.1$ Hz), 3.35 (q, 4H, —NCH_2—, $J = 6.1$ Hz), 4.52 (s, 4H, —OCH_2CO—), 6.98 (a singlet superimposed on a broad singlet, 6H, aryl and —NH—). UV: max 273 nm, $\varepsilon = 2030$. Anal. calc. for $C_{14}H_{20}N_2O_4$: C 59.98, H 7.19, N 9.99; found: C 60.00, H 7.15, N 9.80.

N,N'-dibutyl-1,2-phenylenedioxydiacetamide (**3 c**)

Obtained as light yellow crystals, recrystallized from CCl_4 to give white crystals, m.p. 85-87 °C, 83% yield. IR (KBr): 3320, 1665 and 1650 cm^{-1}. NMR ($CDCl_3$): δ 0.8-1.6 (m, 14H, —$CH_2CH_2CH_3$), 3.35 (q, 4H, $\rangle NCH_2$—, $J = 6.1$ Hz), 4.53 (s, 4H, —OCH_2CO—) and 6.96 (a singlet superimposed on a broad singlet, 6H, aryl and —NH—). UV: max 272 nm, $\varepsilon = 2243$. Anal. calc. for $C_{18}H_{28}N_2O_4$: C 64.26, H 8.39, N 8.33; found: C 64.50, H 8.27, N 8.22.

N,N'-di-t-butyl-1,2-phenylenedioxydiacetamide (**3 d**)

Obtained as light yellow crystals, recrystallized from CCl_4-hexane (1:1) to give white crystals, m.p. 85-87 °C, 71% yield. IR (KBr): 3320 and 1648 cm^{-1}. NMR ($CDCl_3$): δ 1.37 (s, 18H, —CH_3), 4.42 (s, 4H, —OCH_2CO—), 6.55 (broad singlet, 2, —NH—), 6.95 (s, 4, ary). UV: max 272 nm, $\varepsilon = 2114$. Anal. calc. for $C_{18}H_{28}N_2O_4$: C 64.26, H 8.39, N 8.33; found: C 64.01, H 8.15, N 8.20.

N,N'-dicyclopentyl-1,2-phenylenedioxydiacetamide (**3 e**)

Obtained as light yellow crystals, recrystallized from CCl_4 to give white crystals, m.p. 139-140 °C, 80% yield. IR (KBr): 3260, 1650 cm^{-1}. NMR ($CDCl_3$): δ 1.23-2.03 [m, 16H, —$(CH_2)_4$—], 4.1-4.5 (a singlet at 4.3 superimposed on a multiplet between 4.1-4.5, 6H, —OCH_2CO— and $\rangle N—CH\langle$), 6.5-7.0 (a singlet at 6.95 superimposed on a multiplet between 6.5-7.0, 6H, aryl and —NH—). UV: max 273 nm, ε 2000. Anal. calc. for $C_{20}H_{28}N_2O_4$: C 66.64, H 7.83, N 7.77; found: C 66.63, H 7.83, N 7.71.

N,N'-dicyclohexyl-1,2-phenylenedioxydiacetamide (**3 f**)

Obtained as light yellow crystals, recrystallized from CCl_4 to give white crystals, m.p. 145–147 °C, 85% yield. IR (KBr): 3320 and 1650 cm^{-1}. NMR ($CDCl_3$): δ 1.2-2.0 [m, 20 H, —$(CH_2)_5$—], 3.5-4.2 (m, 2 H, >N—CH<), 4.53 (s, 4 H, —OCH_2CO—), 6.5-6.9 (m, 2, —NH—) and 7.0 (s, 4 H, aryl). UV: max 272 nm, ε 2086. Anal. calc. for $C_{22}H_{32}N_2O_4$: C 68.01, H 8.30, N 7.21; found: C 67.84, H 8.20, N 6.93.

N,N,N',N'-tetra-ethyl-1,2-phenylenedioxydiacetamide (**3 g**)

Obtained as a light yellow oil, crystallized from CCl_4-ethyl ether (1:1) solution to give white crystals, m.p. 40–42 °C, 40% yield. IR: 1640 cm^{-1}. NMR ($CDCl_3$): δ 1.0-1.3 (m, 12 H, —CH_3) 3.40 (q, 8 H, >NCH_2—, J = 6.1 Hz), 4.72 (s, 4 H, —OCH_2CO—) and 6.9 (s, 4 H, aryl). UV: max 274 nm, ε = 3531. Anal. calc. for $C_{18}H_{28}N_2O_4$: C 64.26, H 8.39, N 8.33; found: C 64.50, H 8.27, N 8.22.

N,N'-diethyl-N,N'-diphenyl-1,2-phenylenedioxydiacetamide (**3 h**)

Obtained as light brown crystals, recrystallized from ether-hexane mixture to give a white solid, m.p. 104–105 °C, 55% yield. IR: 1640 cm^{-1}. NMR ($CDCl_3$): δ 1.10 (t, 6 H, —CH_3, J = 6.1 Hz), 3.72 (q, 4 H, >NCH_2—, J = 6.1 Hz), 4.35 (s, 4 H, —OCH_2CO—), 6.75 (s, 4 H, aryl), 6.9-7.6 (m, 10 H, aryl). UV: max 273 nm, ε = 4351. Anal. calc. for $C_{26}H_{28}N_2O_4$: C 72.20, H 6.52, N 6.48; found: C 71.69, H 6.22, N 5.89.

o-Phenylenedioxydiacetylpiperidine (**3 i**)

Obtained as light yellow crystals, recrystallized from CCl_4 to give white crystals, m.p. 97–99 °C, 72% yield. IR: 1650 cm^{-1}. NMR ($CDCl_3$): δ 1.6 [broad singlet, 12 H, —$(CH_2)_3$—], 3.52 (broad singlet, 8 H, >NCH_2—), 4.72 (s, 4 H, —OCH_2CO—), and 6.93 (s, 4 H, aryl). UV: max 272, ε = 2200. Anal. calc. for $C_{20}H_{28}N_2O_4$: C 66.64, H 7.83, N 7.77; found: C 66.56, H 7.93, N 7.69.

o-Phenylenedioxydiacetylmorpholine (**3 j**)

Obtained as light yellow crystals, recrystallized from CCl_4—CH_2Cl_2 (3:1) to give a white solid, m.p. 139–140 °C, 67% yield. IR: 1640 cm^{-1}. NMR ($CDCl_3$—CD_3COCD_3): δ 3.68 (broad singlet, 16 H, >NCH_2CH_2O—), 4.70 (s, 4 H, —OCH_2CO—), 6.96 (s, 4 H, aryl). UV: max 275 nm, ε 4115. Anal. calc. for $C_{18}H_{24}N_2O_6$: C 59.33, H 6.44, N 7.69; found: C 58.85, H 6.40, N 7.26.

N,N'-di-(β,β'-dimethoxyethyl)-1,2-phenylenedioxydiacetamide (**3 k**)

Obtained as light yellow crystalls, recrystallized from CH_2Cl_2-hexane (1:2) to give white crystals, m.p. 70–71 °C, 78% yield. IR (KBr): 3340, 1660 cm^{-1}. NMR ($CDCl_3$): δ 3.4 (s, 12 H, —OCH_3), 3.55 (d, 4 H, >NCH_2—, J = 6.0 Hz), 4.43 (t, 2 H, —OCHO—, J = 6.0 Hz), 4.60 (s, 4 H, —OCH_2CO—), 7.0 (broad singlet, 6 H, aryl and —NH—). UV: max 272 nm, ε 1986. Anal. calc. for $C_{18}H_{28}N_2O_8$: C 53.99, H 7.05, N 7.00; found: C 54.18, H 7.02, N 6.83.

1,1',3,3'-tetramethyl-1,1'-(o-phenylenedioxydiacetyl)diurea (**3l**)

Obtained as light yellow crystals, recrystallized from $CHCl_3$ to give a white solid, m.p. 178-180 °C, 62% yield. IR (KBr): 3330, 1655 cm^{-1}. NMR ($CDCl_3$): δ 2.80 (s, 3H, $>NCH_3$), 2.90 (s, 3H, NCH_3), 3.29 (s, 6H, —$CONCH_3CO$—), 4.92 (s, 4H, —OCH_2CO—), 8.75 (broad singlet, 2H, —NH—), 6.92 (s, 4H, aryl). UV: max 271 nm, ε 1971. Anal. calc. for $C_{16}H_{22}N_4O_6$: C 52.45, H 6.05, N 15.29; found: C 52.19, H 6.05, N 15.29.

N,N'-diphenyl-1,2-phenylenedioxydiacetamide (**3m**)[9]

Obtained as white crystals, m.p. 195-196 °C without purification, 76% yield. IR (KBr): 3370, 3270, 1685 cm^{-1}. NMR (*DMSO-d_6*): δ 4.78 (s, 4H, —OCH_2CO—), 6.9-7.78 (m, 14H, aryl) and 10.0 (s, 2H, —NH—). UV: max 240, ε 32292. Anal. calc. for $C_{22}H_{20}N_2O_4$: C 70.20, H 5.36, N 7.44; found: C 70.37, H 5.36, N 7.56.

N,N'-di-(1-naphthyl)-1,2-phenylenedioxydiacetamide (**3n**)

Obtained as white crystals, m.p. 210-211 °C, 63% yield. IR (KBr): 3400, 3250, 1690, 1670 cm^{-1}. NMR (*DMSO-d_6*): δ 4.98 (s, 4H, —OCH_2CO), 7.10-8.06 (m, 18H, aryl), 10.10 (s, 2H, —NH—). UV: max 269 nm, ε 15961. Anal. calc. for $C_{30}H_{24}N_2O_4$: C 75.61, H 5.08, N 5.88; found: C 75.50, H 5.12, N 5.77.

N,N'-di-(α-methyl-β-methoxycarbonyl)vinyl-1,2-phenylenedioxydiacetame (**3o**)

Obtained as a brown oil, crystallized from CCl_4 to give a white solid, m.p. 134-136 °C, 64% yield. IR (KBr): 3260, 1718, 1680 cm^{-1}. NMR ($CDCl_3$): δ 2.4 (s, 6H, —CH_3), 3.62 (s, 6H, —OCH_3), 4.68 (s, 4H, —OCH_2CO), 4.95 (s, 2H, =CH), 7.03 (s, 4H, aryl), 11.85-11.95 (broad singlet, 2H, —NH—). UV: max 266, ε 35238. Anal. calc. for $C_{20}H_{24}N_2O_8$: C 57.14, H 5.75, N 6.66; found: C 57.29, H 5.75, N 6.47.

N,N'-di-(o-acetylphenyl)-1,2-phenylenedioxydiacetamide (**3p**)

Obtained as light brown crystals recrystallized from CCl_4-*Me*OH (1:1) to give bright yellow crystals, m.p. 143-144 °C, 73% yield. IR (KBr): 3500, 3200, 1678, 1648 cm^{-1}. NMR ($CDCl_3$): δ 2.32, 2.67 (s, 6H, —CH_3 in proportion of 3:1), 4.66, 4.74 (s, 4H, —OCH_2CO— in proportion of 1:3), 6.80-7.98 (m, 12H, aryl), 8.7, 8.8 (s, 2H, —NH—). UV: max 318, ε 80000; 257 ε 234385. Anal. for $C_{26}H_{24}N_2O_6$: C 67.82, H 5.25, N 6.08, found: C 67.60, H 5.19, N 5.80.

Direct UV titration method

Anhydrous NaCl, NaI, KI, KSCN, NH_4Cl, $CaCl_2$, and other salts were used as received. Ligand solutions in anhydrous methanol were prepared by diluting a 0.1 *M* stock solution to the expected suitable concentration. Cation solution (0.01 *M*, 0.1 *M* or 1.0 *M*) was added via a 10 µl syringe so that volume changes could be neglected. After each addition the cuvet was thoroughly shaken before the UV spectrum was recorded.

Picrate extraction procedure

Aqueous picrate solutions were made up from standardized stock solution of sodium hydroxide, potassium hydroxide or other inorganic reagents and

picric acid. Calcium picrate, for example, was prepared by neutralization picric acid with calcium chloride at $7.0 \times 10^{-5}\,M$ added to a final Ca^{++} of $1.0\,M$, or by adding excess calcium chloride solution to picric acid. the diamide ligands were dissolved in methylenedichloride. Equal volumes of the two solutions in stopped centrifuge tubes were mixed well by hand for five minutes to ensure complete equilibration. Centrifugation was needed for complete phase separation. The extractions were conducted at 28 ± 1 °C. Equilibrium picrate concentrations in both phases were measured by UV spectrophotometer.

This same extraction was carried out in the absence of picric acid. The equilibrium cation concentration in both phases were measured by atomic absorption with a Perkin-Elmer model 503 spectrophotometer.

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