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Calix[4]arenes containing urea and crown/urea moieties: effects of the crown ether unit and Na^+ towards anion binding ability

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Abstract—Calix[4]arenes containing urea and crown/urea moieties, **7** and **10**, respectively have been synthesized. ^{1}H NMR titrations of **7** and **10** with anions in DMSO-d_6 showed that **7** and **10** formed complexes with Cl^-, Br^-, NO_3^- and $H_2PO_4^-$ to a different extent. The association constants of **7** and **10** towards anions were calculated and found to vary as $H_2PO_4^-$>Cl^->Br^->NO_3^-. However, compared to **7** the presence of the crown unit in **10** resulted in a slightly higher affinity to Cl^- and Br^-, but a lower affinity to $H_2PO_4^-$. Upon addition of Na^+, the binding ability of **10** towards $H_2PO_4^-$ is increased due to ion-pair enhancement.

Anion recognition is an increasingly important research topic in supramolecular chemistry due to possible applications in selective ion receptors and sensors in biological and environmental systems.[1,2] Urea is used dominantly in neutral anion receptors because of its strong hydrogen bonding towards anions.[3,4] Umezawa and co-workers showed that urea receptors with a rigid xanthene spacer formed strong complexes with dihydrogen phosphate.[5] Very recently, cystine-based symmetrical cyclic oligoureas have been synthesized and found to bind Cl^-, Br^- and NO_3^- to a different extent.[6]

Calix[4]arene is one of the most important supramolecular building blocks because of its capability of being modified at both the wide and narrow rims. Recently, derivatives of calix[4]arene have been used as receptors for cations, anions and neutral molecules.[7] Budka et al. have synthesized a tetra-urea derivative of calix[4]arene in a 1,3-alternate conformation. It was found that this receptor, with two possible binding sites, exhibited a strong negative allosteric effect which led to the exclusive complexation of only one anion.[8] Reinhoudt and co-workers demonstrated that a calix[4]arene derivative containing ethyl ester groups and urea moieties on the narrow rim and on the wider rim, respectively, was able to bind Cl^- efficiently in the presence of Na^+.[9]

We are interested in synthesizing neutral anion receptors using calix[4]arene as the building block and attaching urea units as receptors for anions at the wider rim. In addition, in one of the target molecules, a crown ether group is attached to a calix[4]arene urea on the narrow rim. Anion binding studies of the hosts synthesized with various anions have been performed to investigate the effect of the crown ether unit and different cations towards anion binding ability.

Protection and deprotection strategies have been employed to generate a specifically functionalized calix[4]crown urea. Syntheses of calix[4]crown ureas were carried out as shown in Scheme 1. Calix[4]arene was reacted with 2 equiv. of benzoyl chloride in CH_3CN in the presence of Na_2CO_3 as base under N_2, and the reaction was heated at reflux for 2 h to give dibenzoyl calix[4]arene **2** in 90% yield.[10] Nitration of **2** with 65% HNO_3 and CH_3COOH in CH_2Cl_2 at room temperature yielded the dinitro compound **3** in 45% yield.[11] Methylation of **3** with CH_3I in CH_3CN using Na_2CO_3 as base and refluxing the reaction for 5 days resulted in the dimethyldinitro calix[4]arene **4** in 85% yield.[12] Removal of the benzoyl groups from **4** by excess NaOH resulted in a dimethyldinitro calix[4]arene building block **5** in 50% yield.[13] Reduction of the nitro groups in **5** with $SnCl_2{\cdot}2H_2O$ gave the dimethyldiamino calix[4]arene **6** in 70% yield.[14] The presence of the methyl groups at the positions *para* to the amine groups aids in stabilizing compound **6**. Nevertheless, compound **6** was immediately coupled with phenyl isocyanate in CH_2Cl_2 at room temperature. The white solid **7** precipitated out of the reaction in 60% yield.[15] The dimethoxydiurea calix[4]arene **7** is highly polar and dissolves only in polar solvents such as DMF and DMSO.

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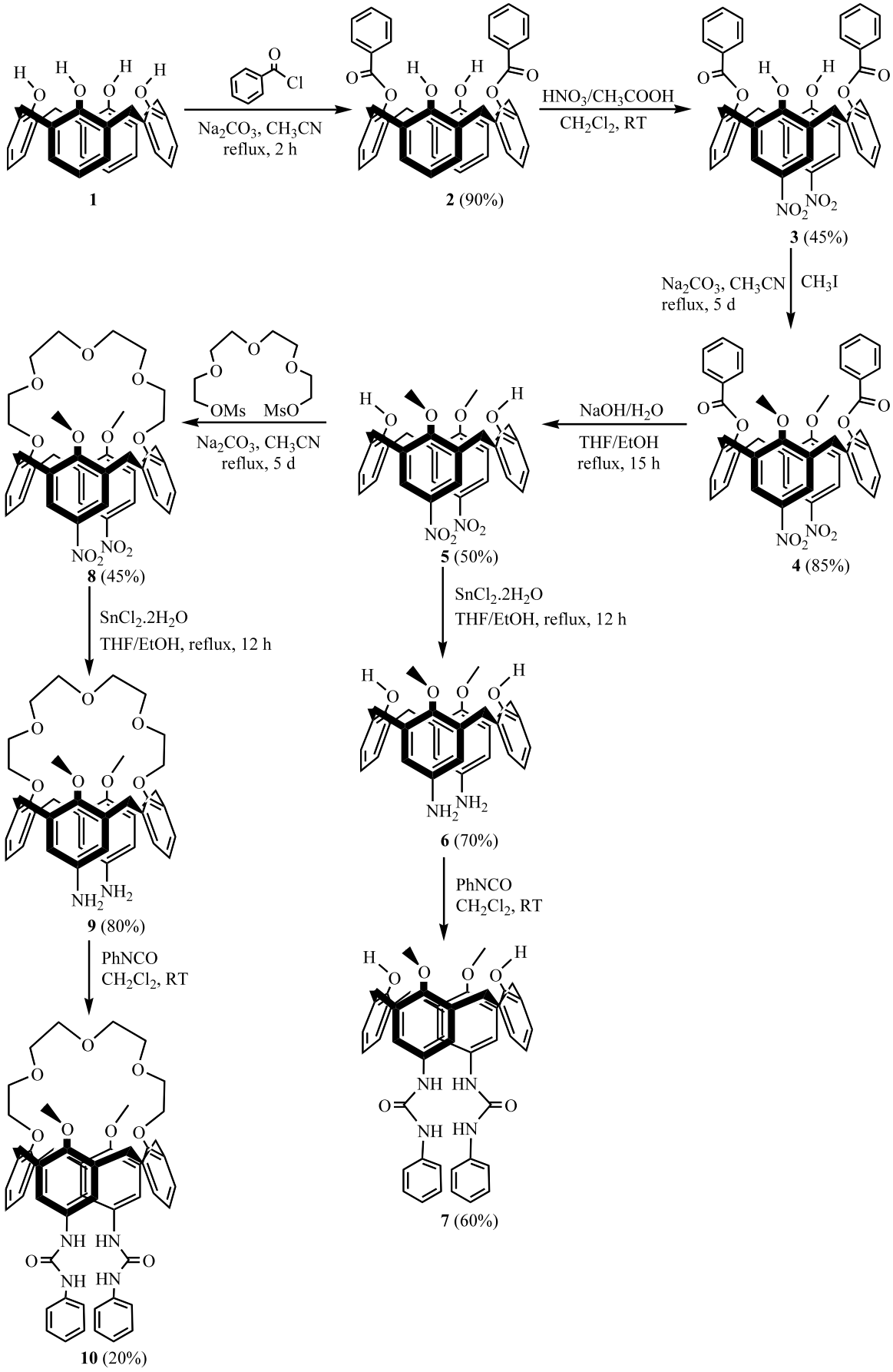
1
Na2CO3, CH3CN
reflux, 2 h
2 (90%)
HNO3/CH3COOH
CH2Cl2, RT
3 (45%)
Na2CO3, CH3CN
reflux, 5 d
CH3I
4 (85%)
NaOH/H2O
THF/EtOH
reflux, 15 h
5 (50%)
OMs MsO
Na2CO3, CH3CN
reflux, 5 d
8 (45%)
SnCl2.2H2O
THF/EtOH, reflux, 12 h
6 (70%)
SnCl2.2H2O
THF/EtOH, reflux, 12 h
9 (80%)
PhNCO
CH2Cl2, RT
7 (60%)
PhNCO
CH2Cl2, RT
10 (20%)

Scheme 1.

Compound **5** underwent nucleophilic substitution with tetraethylene glycol dimethanesulfonate in CH_3CN using Na_2CO_3 as base and heating at reflux for 5 days to yield the dimethyldinitro crown calix[4]arene **8** in 45% yield.[16]

Reduction of the nitro groups of **8** with $SnCl_2{\cdot}2H_2O$ gave the crown dimethyldiamino calix[4]arene **9** in 80% yield.[17] The ^1H NMR spectra of compounds **8** and **9** showed very complicated signals in the aromatic and alkyl proton regions that signified aryl ring inversion in the calix[4]arene unit.[18] This behavior stems from the lack of intramolecular hydrogen bonding in **8** and **9**. The coupling reaction between **9** and phenylisocyanate at room temperature resulted in the precipitation of the calix[4]arene crown urea **10** in 20% yield.[19] Although **10** lacks intramolecular hydrogen bonding, the substituents on the urea nitrogen prohibit the ring inversion. Compound **10** is hardly soluble in common organic solvents such as CH_2Cl_2 and $CHCl_3$. It dissolves only in highly polar solvents such as DMSO. Spectroscopic data and elemental analysis support the structures of all the compounds synthesized.

We aimed to compare the binding ability of compounds **7** and **10** towards anions. Because of their importance in environmental and biological systems, anions such as $H_2PO_4^-$, NO_3^-, Cl^-, Br^- and I^-, were chosen for study. The anion binding studies of compounds **7** and **10** were carried out by ^1H NMR titrations.[20] Addition of tetrabutylammonium iodide anion to a DMSO-d_6 solution of the receptors **7** and **10** did not cause any shifts of the NH or other proton resonances which indicated that **7** and **10** could not form complexes with I^-. However, addition of a tetrabutylammonium salt of a guest anion such as $H_2PO_4^-$, Cl^-, Br^- and NO_3^- to a DMSO-d_6 solution of the receptors **7** and **10** resulted in significant downfield shifts of the NH resonances at room temperature, which is consistent with the formation of hydrogen-bonded complexes. The plots between the mole ratios of anion: **7** and the NH chemical shift of compound **7** are illustrated in Figure 1. Job plot analysis indicates that **7** and **10** bind $H_2PO_4^-$, Cl^-, Br^- and NO_3^- in a 1:1 ligand/anion ratio. Association constants of **7** and **10** towards $H_2PO_4^-$, Cl^-, Br^- and NO_3^- calculated by the program EQNMR[21] are collected in Table 1.

The results in Table 1 indicate that both compounds **7** and **10** bind Cl^-, Br^-, NO_3^- and $H_2PO_4^-$ albeit to a different extent. Both compounds form most stable complexes with $H_2PO_4^-$ and least stable complexes with NO_3^-. Compound **10** binds Cl^- and Br^- more strongly than **7** does. However, **7** forms a more stable complex with $H_2PO_4^-$ than compound **10**. These results indicate that the presence of the crown bridging group in compound **10** has increased the binding ability towards Cl^- and Br^- slightly and decreased the binding ability towards $H_2PO_4^-$.

Recently, ion-pair recognition has attracted chemists' attention. Beer and colleagues have discovered that the presence of a suitable cation increases the binding ability of anion receptors containing cation binding units.[22] Compound **10** includes a crown-5 unit which is well known to form stable complexes with Na^+.[7] We are also interested to see the effect of the ion-pair enhancement in the binding ability of compound **10** towards $H_2PO_4^-$. Upon adding 1.2 equiv. of $NaPF_6$ to a DMSO-d_6 solution of the receptor **10**, we observed large chemical shifts in the region of the proton resonance of the crown ether unit suggesting complex formation between Na^+ and the crown ether unit. Addition of nBu$_4$NH$_2$PO$_4$ to the solution caused the NH peak to shift downfield. The association constant was then calculated by the program EQNMR to be 1028.4 M^-.[1] The presence of Na^+ thus increases the binding ability of **10** towards $H_2PO_4^-$. Potentially, this type of receptor can be modified to be a metal-ion controlled anion receptor or sensor in the future.

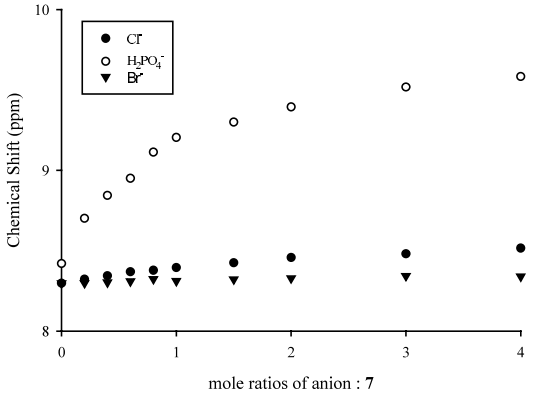

Figure 1. Plots between mole ratios of anion **7** and the NH chemical shifts.

Table 1. Association constants of ligands **7** and **10** towards $H_2PO_4^-$, Cl^-, Br^- and NO_3^- using nBu$_4$N$^+$ as countercation[a]

Anion	Association constants (M^{-1})	
	7	**10**
$H_2PO_4^-$	250	200
Cl^-	43	60
Br^-	30	31
I^-	No binding	No binding
NO_3^-	13	11

[a] All experiment were carried out at 298 K, errors estimated to be less than 15%.

In summary, we have synthesized calix[4]arene ureas **7** and **10**. Anion binding studies by ^1H NMR showed that both **7** and **10** bind $H_2PO_4^-$ selectively. The incorporation of the crown ether unit in the calix[4]urea results in a slightly higher affinity of **10** for Cl^- and Br^-, but a lower affinity for $H_2PO_4^-$. The presence of Na^+ is found to enhance the affinity of **10** for $H_2PO_4^-$. We are currently synthesizing other derivatives of calix[4]arene containing crowns/ureas and studying their anion binding and sensing ability. These results will be reported in due course.

Acknowledgements

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10. **2**: ^{1}H NMR spectrum (200 MHz, $CDCl_3$) δ 8.36 (d, $J=8$ Hz, 4H, Ar$\boldsymbol{H}_{\text{benzoyl}}$), 7.72 (t, $J=8$ Hz, 2H, Ar$\boldsymbol{H}_{\text{benzoyl}}$), 7.53 (t, $J=8$ Hz, 4H, Ar$\boldsymbol{H}_{\text{benzoyl}}$), 7.07 (d, $J=4$ Hz, 4H, Ar$\boldsymbol{H}$), 6.66–6.94 (m, 8H, Ar$\boldsymbol{H}$), 5.50 (s, 2H, ArO$\boldsymbol{H}$), 3.98 (d, $J=14$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar), 3.52 (d, $J=14$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar).
11. **3**: ^{1}H NMR spectrum (200 MHz, $CDCl_3$) δ 8.21 (d, $J=8$ Hz, 4H, Ar$\boldsymbol{H}$), 7.97 (s, 4H, Ar$\boldsymbol{H}$), 7.76 (t, $J=7$ Hz, 2H, Ar$\boldsymbol{H}$), 7.53 (t, $J=7$ Hz, 4H, Ar$\boldsymbol{H}$), 7.01 (m, 6H, Ar$\boldsymbol{H}$), 6.33 (s, 2H, ArO$\boldsymbol{H}$), 3.99 (d, $J=14$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar), 3.66 (d, $J=14$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar).
12. **4**: ^{1}H NMR spectrum (200 MHz, $CDCl_3$) δ 6.75–8.19 (m, 20H, Ar$\boldsymbol{H}$), 3.35–3.82 (m, 14H, ArOC$\boldsymbol{H}_3$, ArC$\boldsymbol{H}_2$Ar).
13. **5**: ^{1}H NMR spectrum (200 MHz, $CDCl_3$) δ 7.80 (s, 4H, Ar$\boldsymbol{H}$), 7.52 (s, 2H, ArO$\boldsymbol{H}$), 7.14 (d, $J=7$ Hz, 4H, Ar$\boldsymbol{H}$), 6.75 (t, $J=6$ Hz, 2H, Ar$\boldsymbol{H}$), 4.33 (d, $J=13$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar), 4.05 (s, 6H, ArOC$\boldsymbol{H}_3$), 3.51 (d, $J=13$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar). FAB MS (m/z): 542.84 [M^+].
14. **6**: ^{1}H NMR spectrum (200 MHz, $CDCl_3$) δ 7.88 (s, 2H, ArOH), 7.02 (d, $J=7$ Hz, 4H, Ar$\boldsymbol{H}$), 6.64 (t, $J=7$ Hz, 2H, Ar$\boldsymbol{H}$), 6.18 (s, 4H, Ar$\boldsymbol{H}$), 4.21 (d, $J=14$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar), 3.89 (s, 6H, ArOC$\boldsymbol{H}_3$), 3.27 (d, $J=14$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar), 1.78 (br, 4H, -N$\boldsymbol{H}_2$).
15. **7**: ^{1}H NMR spectrum (200 MHz, DMSO-d_6) δ 8.42 (s, 2H, ArN$\boldsymbol{H}$-), 8.30 (s, 2H, ArN$\boldsymbol{H}$-), 8.17 (s, 2H, ArO$\boldsymbol{H}$), 7.08–7.33 (m, 16H, Ar$\boldsymbol{H}$), 6.89 (t, $J=7$ Hz, 2H, Ar$\boldsymbol{H}$), 6.60 (t, $J=7$ Hz, 2H, Ar$\boldsymbol{H}$), 4.15 (d, $J=13$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar), 3.89 (s, 6H, ArOC$\boldsymbol{H}_3$), 3.46 (d, $J=13$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar). ESI MS (m/z): 720.99 [M^+]. Anal. calcd for **7** ($C_{44}H_{40}$ N_4O_6): C, 73.32; H, 5.59; N, 7.77. Found: C, 73.16; H, 5.63; N, 7.74.
16. **8**: ^{1}H NMR spectrum (200 MHz, $CDCl_3$) δ 8.28–8.04 (m, 4H, Ar$\boldsymbol{H}$), 6.50–6.94 (m, 6H, Ar$\boldsymbol{H}$), 4.42 (d, $J=13$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar), 3.24–4.20 (m, 26H, ArOC$\boldsymbol{H}_3$, -OC$\boldsymbol{H}_2$C$\boldsymbol{H}_2$O- and ArC$\boldsymbol{H}_2$Ar). ESI MS (m/z): 723.40 [M^++Na^+].
17. **9**: ^{1}H NMR spectrum (200 MHz, $CDCl_3$) δ 6.47–6.97 (m, 10H, Ar$\boldsymbol{H}$), 4.33 (d, $J=12$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar), 4.01 (s, 6H, ArOC$\boldsymbol{H}_3$), 3.28–3.92 (m, 16H, -OC$\boldsymbol{H}_2$C$\boldsymbol{H}_2$O-), 2.99 (d, $J=12$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar), 2.74 (br, 4H, ArN$\boldsymbol{H}_2$).
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19. **10**: ^{1}H NMR spectrum (200 MHz, DMSO-d_6) δ 8.59 (s, 2H, ArN$\boldsymbol{H}$-), 8.37 (s, 2H, ArN$\boldsymbol{H}$-), 7.44 (d, $J=8$ Hz, 4H, Ar$\boldsymbol{H}_{\text{ph}}$), 7.26 (t, $J=8$ Hz, 6H, Ar$\boldsymbol{H}_{\text{Ph}}$), 6.94 (t, $J=7$ Hz, 2H, Ar$\boldsymbol{H}$), 6.45–6.59 (m, 8H, ArH), 4.30 (d, $J=12$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar), 4.03 (s, 6H, ArOC$\boldsymbol{H}_3$), 3.34–3.84 (m, 16H, -OC$\boldsymbol{H}_2$C$\boldsymbol{H}_2$O-), 3.13 (d, $J=13$ Hz, 4H, ArC$\boldsymbol{H}_2$Ar). ESI MS (m/z): 901.69 [M^++Na^+]. Anal. calcd for **10**·$2H_2O$ ($C_{52}H_{58}N_4O_{11}$): C, 68.26; H, 6.39; N, 6.12. Found: C, 68.05; H, 5.96; N, 6.65.
20. Solutions of **7** and **10** (0.01 M) in DMSO-d_6 were prepared. To a solution of a ligand in each NMR tube was added 0.0–4.0 equiv. of a 0.25 M tetrabutylammonium salt of the anion. The result of the experiment was a plot of displacement in chemical shift as a function of the amount of added anion. The program EQNMR was then used to analyze the resulting titration curves and to calculate stability constant values in M^{-1}.
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