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SYNTHESIS AND ALKALI METAL PICRATE EXTRACTION STUDIES OF AN UNUSUAL CAGE-FUNCTIONALIZED CRYPTAND†

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Abstract- Novel cage-functionalized cryptand (**4**) which contains two formaldehyde acetal linkages was synthesized. The structure of **4** was estabilished unequivocally *via* application of X-Ray crystallographic techniques. Alkali metal picrate extractions were performed by using **4** as the host complexant, and the results thereby obtained were compared with the corresponding extraction efficiencies of two model crown ethers, i.e., (**8** and **9**) at the same concentraction. Host system (**4**) proved to be considerably more efficient than either **8** or **9** as an alkali metal picrate extractant. In addition, **4** displayed moderatly high selectivity toward extraction of Li^+ and Na^+ picrates.

INTRODUCTION

A wide variety of macrocyclic crown ethers and cryptands have been synthesized, and their use as "hosts" for selective complexation and transport of metal cations has been investigated in several laboratories worldwide.[1] Most of the crown ethers and cryptands that have been studied consist of ethano (OCH2CH2O) and/or propano ($OCH_2CH_2CH_2O$) bridges within a macrocyclic framework.[2,3] However, relatively few studies that involve host molecules of this type which contain bridging methano (i.e., formaldehyde acetal, OCH_2O) linkages have been reported.[4] In the present study, we report the synthesis and alkali metal picrate extraction capabilities of some new crown ethers and cryptands, all of which contain at least one OCH_2O linkage.

Recently, we reported the synthesis and the results of alkali metal picrate extraction studies of several cage-functionalized crown ethers and cryptands.[5] The presence of a cage moiety lends rigidity and a measure of lipophilicity to the resulting crown ethers with consequent impact upon the ability of such host systems to form complexes with a variety of neutral and ionic guest species.[6,7]

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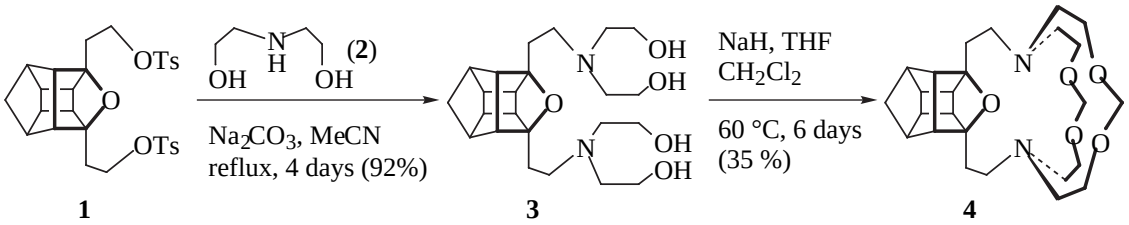
†Dedicated to Professor Shô Itô on the occasion of his 77th birthday.

RESULTS AND DISCUSSION

The method used to prepare a novel, cage-functionalized cryptand (**4**) that contains two OCH_2O linkages is described in Scheme 1. Thus, base promoted reaction of **1**[6b] with $HN(CH_2CH_2OH)_2$ (i.e., diethanolamine, **2**) afforded podand **3** in 92% yield (Scheme 1). Subsequent NaH promoted reaction of **3** with CH_2Cl_2 produced the corresponding cryptand, **4**, in 35% yield. The structure of **4** was established unequivocally *via* application of single crystal X-Ray crystallographic methods (*vide infra*).

Scheme 1

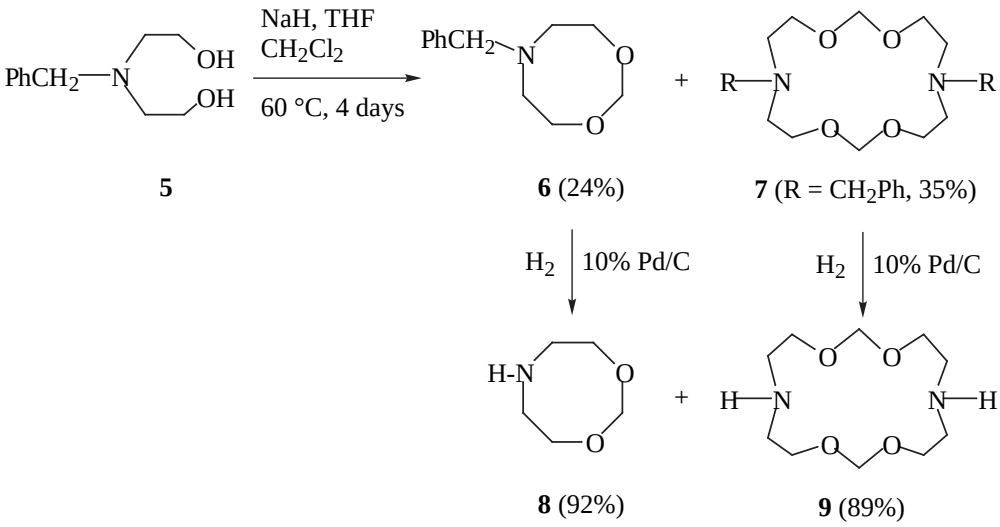


1 **3** **4**

Interestingly, the CI-HRMS spectrum of **4** revealed the presence of both the naked ligand and the corresponding Na^+ complex (see the EXPERIMENTAL). Since Na^+ is ubiquitous in a laboratory environment, it seems likely that this ion was captured during sample purification and/or during transfer of the sample of **4** into the mass spectrometer.

In order to evaluate the effects of cage-annulation on the complexation properties of cryptand (**4**), it was necessary to have available structually related model compounds, i.e., crown ethers that lack the cage moiety. The model systems that were chosen for study and the procedures that were used to prepare these compounds are shown in Scheme 2.

Scheme 2



5 **6** (24%) **7** (R = CH_2Ph, 35%)

8 (92%) **9** (89%)

Thus, base promoted reaction of *N*-benzyldiethanolamine (**5**)[8] with CH_2Cl_2 afforded the corresponding crown ethers, i.e., **6** and **7**, in 24% and 35% yield, respectively. Subsequent hydrogenolysis of the *N*-benzyl functionalities in **6** and **7** produced **8**[9] (92%) and **9** (89%), respectively. The structures of these

crown ethers were established *via* analysis of their respective ^{1}H NMR and ^{13}C NMR spectra and then were confirmed *via* analysis of their respective high-resolution mass spectra (see the Experimental Section).

X-RAY CRYSTAL STRUCTURE OF CRYPTAND (4)

An ORTEP-style structure drawing of the X-ray crystal structure of **4** is shown in Figure 1. Inspection of the solid state conformations suggests that no more than 3 or 4 coordinating atoms in the crown ether can be situated in a manner that permits them to interact simultaneously with an alkali metal cation guest. Constructive combinations in this regard might involve N(1), N(2), O(3), and possibly O(1). However, O(3) and O(2) cannot interact with the metal cation guest simultaneously, nor can O(4) and O(5). Instead, a sandwich-type 2:1 host-guest interaction might be more favorable. The C-O distances in the CC-O linkages [i.e., 1.439 (7) Å] are consistently larger than the corresponding OC-O distances [i.e., 1.402(6) Å], thereby resulting in unsymmetric C-O-C bonds. All N-C bonds in **4** are nearly equivalent.

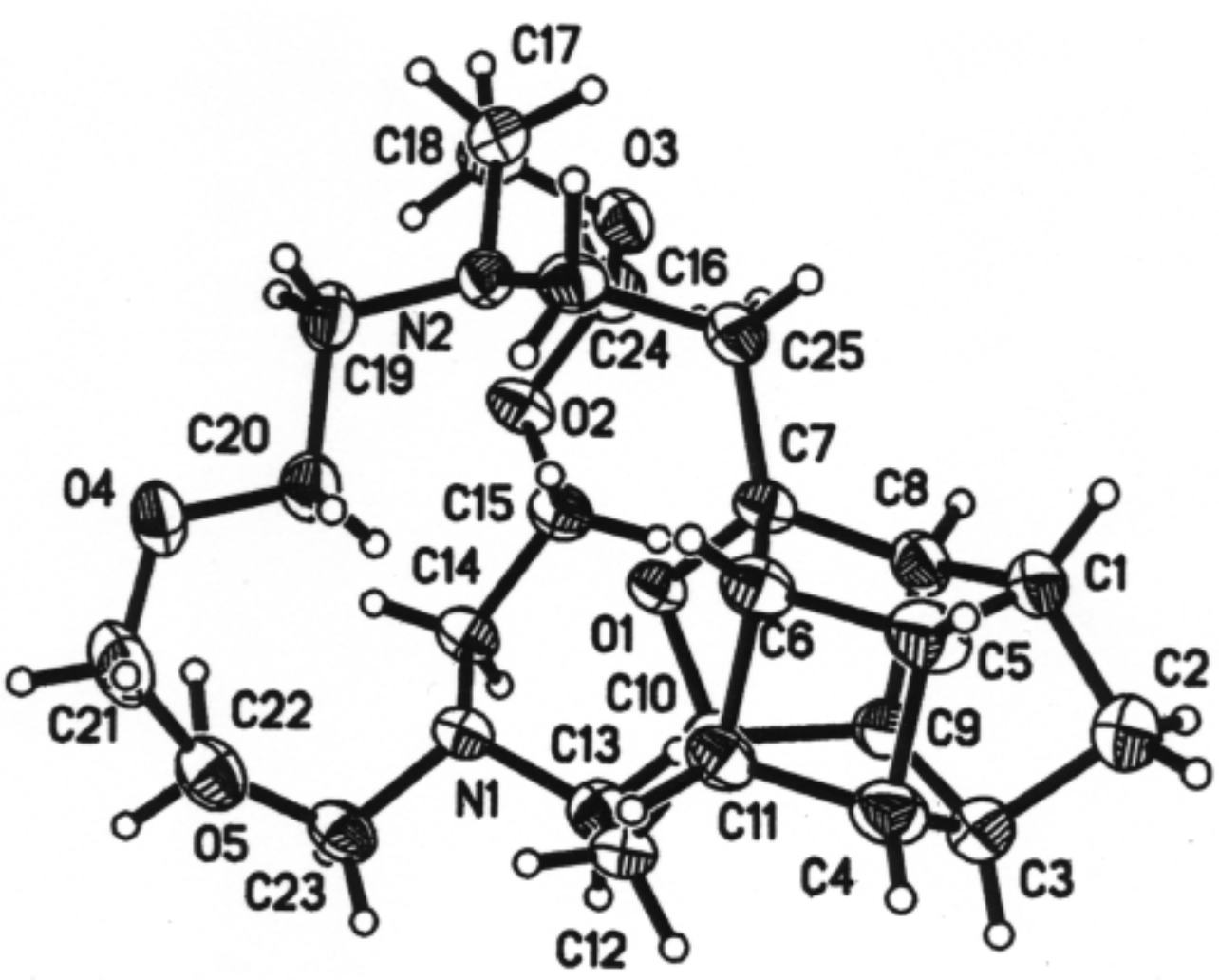


Figure 1. X-Ray structure drawing of **4**; the unit cell contains two identical molecules of **4**.

RESULTS OF ALKALI METAL PICRATE EXTRACTION STUDIES

Alkali metal picrate extraction studies have been performed by using cage-functionalized cryptand **4** and model compounds (**8**) and (**9**) as host systems in a CH_3Cl-H_2O liquid-liquid extraction medium. The results thereby obtained are shown in Table 1.

Table 1. Results of Alkali Metal Picrate Extraction Experiments.

	Percent of Picrate Extracted (%)[a]				
Host Molecule	**Li^+**	**Na^+**	**K^+**	**Rb^+**	**Cs^+**
8	2.4 ± 0.4	1.8 ± 0.6	2.5 ± 0.7	0.4 ± 0.3	0.9 ± 0.3
9	10.8 ± 0.6	9.4 ± 0.1	8.4 ± 0.6	8.8 ± 0.4	7.1 ± 0.1
4	68.4 ± 0.8	61.9 ± 0.6	42.0 ± 0.3	31.6 ± 0.5	30.1 ± 0.8

[a] Averages and standard deviations calculated for data obtained from three independent extraction experiments.

Inspection of the data in Table 1 indicates that both 6-aza-1,3-dioxacyclooctane (i.e., monoaza-8-crown-3, **8**) and 6,14-diaza-1,3,9,11-tetraoxaoctadecane (i.e., 6,11-diaza-16-crown-6, **9**) are relatively inefficient and non-selective alkali metal picrate extractants. By way of contrast, cryptand (**4**) is a relatively avid extractant toward all five alkali metal picrates studied. In addition, **4** appears to enter into selective complex formation with Li^+ and Na^+ picrates, unlike its corresponding model compound (**9**).

SUMMARY AND CONCLUSIONS

In this study, methylene (i.e., OCH_2O) bridged crown ethers (**8**) and (**9**) and cryptand (**4**) have been synthesized, and their respective alkali metal picrate extraction profiles have been determined in $CHCl_3$-H_2O medium. Of particular significance is our observation that cryptand (**4**) clearly functions as the most effective alkali metal cation complexing agent among the three host molecules whose extraction profiles have been studied herein. This result is not surprising,[5,6] since **4** is the most highly preorganized of these three host systems. Interestingly, whereas **4** displays relatively high avidity toward all of the alkali metal cations studied, it appears to form complexes selectively with Li^+ and Na^+.

EXPERIMENTAL

Melting points are uncorrected. Absorption intensities of alkali metal picrate solutions were measured at λ = 374 nm by using a Hewlett-Packard Model 84524 Diode Array UV-visible spectrophotometer. High-resolution MS data reported herein were obtained by Professor Jennifer S. Brodbelt at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin by using a ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

Synthesis of 3. A mixture of **1** (500 mg, 0.9 mmol), diethanolamine (**2**, 198 mg, 1.9 mmol), anhydrous Na_2CO_3 (524 mg, 4.95 mmol), and CH_3CN (10 mL) was refluxed with stirring during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The solid residue was washed with $CHCl_3$ (100 mL). The filtrate was concentrated *in vacuo*, and the residue was purified *via* column chromatography on silica gel by eluting with 20% methanol-EtOAc. Pure **3** (346 mg, 92%) was thereby obtained as a colorless oil: IR (film) 3454 (br, s), 2957 (s), 1602 (m), 1434 (w), 1320 cm^{-1} (w); ^1H NMR ($CDCl_3$) 1.49 (d, J = 10.2 Hz, 1 H), 1.71-1.98 (m, 5 H), 2.37 (br s, 2 H), 2.47-2.72 (m, 18 H), 3.53 (t, J = 5.1 Hz, 8 H), 3.81 (br s, 4 H); ^{13}C NMR (CDCl) 29.3 (t), 41.2 (d), 43.2 (t), 43.9 (d), 47.4 (d), 49.7 (t), 56.2 (t), 57.9 (d), 59.2 (t), 96.3 (s); Exact MS (CI HRMS) Calcd for $C_{23}H_{38}N_2O_5$: $[M_r + H]^+ m/z$ 423.28590. Found: $[M_r + H]^+ m/z$ 423.28599.

Sodium Hydride Promoted Reaction of 3 with Methylene Chloride. To a suspension of NaH (obtained as a 60% suspension in mineral oil, 151 mg, 4.97 mmol) in dry THF (20 mL) under argon was added with stirring a solution of **3** (290 mg, 0.69 mmol) in dry THF (5 mL), and the resulting mixture was stirred during 20 min. To the reaction mixture was added dropwise CH_2Cl_2 (1.37 g, 16.2 mmol), and the resulting mixture was gradually heated to 60 °C and stirred at that temperature during 6 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The solid residue was washed with THF (15 mL). The filtrate was concentrated *in vacuo*, and the residue was purified *via* column chromatography on silica gel by eluting with 5% MeOH-CH_2Cl_2. Workup of the eluate afforded **4** (40 mg, 35%) which subsequently was recrystallized from CH_2Cl_2-hexane. Pure **4** was thereby obtained as a colorless microcrystalline solid, mp 141-142 °C; IR (film) 2942 (s), 2858 (m), 1742 (m), 1455 (m), 1115 cm^{-1} (m); ^1H NMR ($CDCl_3$) 1.49 (*AB*, J_{AB}= 11.8 Hz, 1 H), 1.72-1.98 (m, 5 H), 2.24-2.83 (m, 20 H), 3.42-3.74 (m, 4 H), 3.80-4.04 (m, 4 H), 4.53-4.75 (m, 4 H); ^{13}C NMR ($CDCl_3$) 30.7 (t), 41.4 (d), 43.5 (t), 43.8 (d), 48.3 (d), 51.4 (d), 55.0 (t, 2 C), 58.7 (d), 65.5 (t), 65.6 (t), 93.6 (t), 93.7 (t), 95.6 (s). Exact MS (CI HRMS) Calcd for $C_{25}H_{38}N_2O_5Na^+$ $M_r^+ m/z$ 469.26784. Found: $M_r^+ m/z$ 423.26908; Calcd for $C_{25}H_{38}N_2O_5$: $[M_r + H]^+ m/z$ 447.27590. Found: $[M_r + H]^+ m/z$ 447.28652.

X-Ray Crystal Structure of 4. A colorless prism of dimensions $0.1 \times 0.1 \times 0.3$ mm^3 was used to collect X-Ray data at ambient temperature on a Bruker SMART™ CCD-based diffractometer. A total of 1321 frames were collected at 10 seconds per frame, and the frames were integrated with the *SAINT* software package[10] by using a narrow-frame algorithm. The structure was solved by using the SHELXTL[11] program package and subsequently was checked by using PLATON.[12] There are two independent molecules in the unit cell.The compound crystallizes in the triclinic system with space group P-1. The unit cell

dimensions are a = 11.472 (12), b = 14.806 (16), c = 16.215 (18) Å, α = 98.44 (2), β = 100.89 (2), and γ = 112.68 (2)°with V = 24212 (4) $Å^3$, Z = 4, D_{calc} = 1.225 mg-m^{-3}, μ = 0.085 mm^{-1}. A total of 10,951 reflections were collected of which 6,806 were independent. Full-matrix least-squares refinement on F^2 with 578 parameters gave R_1 = 0.0492, wR_2 = 0.0656 for I > 2σ(I) and R_1 = 0.1679 and wR_2 = 0.0880 for all data.

Sodium Hydride Promoted Reaction of 5 with Methylene Chloride. To a suspension of NaH (obtained as a 60% suspension in mineral oil, 134 mg, 2.79 mmol) in dry THF (5 mL) under argon was added with stirring a solution of **5**[8] (182 mg, 0.93 mmol) in dry THF (5 mL), and the resulting mixture was stirred at ambient temperature during 20 min. To the reaction mixture was added dropwise CH_2Cl_2 (634 mg, 9.46 mmol). The resulting mixture was heated gradually to 60 °C and subsequently was stirred at that temperature during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The solid residue was washed with THF (10 mL). The filtrate was concentrated *in vacuo*, and the residue was purified *via* column chromatography on silica gel by eluting with 60% EtOAc-hexane. Pure *N*-benzyl-6-aza-1,3-dioxacyclooctane (**6**, 46 mg, 24%) was thereby obtained as a colorless oil; IR (film) 2943 (s), 1468 (m), 1350 (m), 1129 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 2.86 (t, *J* = 5.1 Hz, 4 H), 3.74 (t, *J* = 5.1 Hz, 4 H), 3.84 (s, 2 H), 4.82 (s, 2 H), 7.18-7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$) d 55.9 (t), 60.8 (t), 68.0 (t), 96.0 (t), 126.9 (d), 128.2 (d), 128.7 (d), 139.6 (s). Exact MS (CI HRMS) Calcd for $C_{13}H_{17}NO_2$: $[M_r + H]^+$*m/z* 208.13375. Found: $[M_r + H]^+$*m/z* 208.13414.

Continued elution of the chromatography column with 100% EtOAc afforded *N,N'*-dibenzyl-6,14-diaza-1,3,9,11-tetraoxaocta-decane (**7**, 62 mg, 35%) as a colorless oil; IR (film) 2962 (s), 2871 (s), 1468 (m), 1115 (m), 1037 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 2.77 (t, *J* = 6.0 Hz, 8 H), 3.63 (t, *J* = 6.0 Hz, 8 H), 3.69 (s, 4 H), 4.63 (s, 4 H), 7.14-7.36 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ53.8 (t), 59.9 (t), 66.4 (t), 95.5 (t), 126.9 (d), 128.1 (d), 128.8 (d), 139.4 (s). Exact MS (CI HRMS) Calcd for $C_{24}H_{34}N_2O_4$: $[M_r + H]^+$*m/z* 415.25968. Found: $[M_r + H]^+$*m/z* 415.25991.

Hydrogenolysis of the *N*-Benzyl Group in 6. To a solution of **6** (136 mg, 0.65 mmol) in EtOH (10 mL) was added 10% palladized charcoal (20 mg, catalytic amount). The resulting mixture was subjected to hydrogenolysis on a Parr shaker hydrogenation apparatus by agitation with excess H_2 (g) at 55 psig at ambient temperature during 24 h. The reaction mixture was filtered through Celite®, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on neutral alumina by eluting with 10% MeOH-EtOAc. Pure **8** (68 mg, 92%) was thereby obtained as a colorless oil; IR (film) 2930 (s), 2871 (s), 1657 (m), 1454 (m), 1129 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 1 H), 2.84 (t, *J* = 5.2 Hz, 4 H), 3.74 (t, *J* = 4.2 Hz, 4 H), 4.66 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 49.7 (t), 68.1 (t), 95.8 (t). Exact MS (CI HRMS) Calcd for $C_5H_{11}NO_2$: $[M_r + H]^+$*m/z* 118.08680. Found: $[M_r + H]^+$*m/z* 118.08824.

Hydrogenolysis of the *N*-Benzyl Groups in 7. To a solution of **7** (152 mg, 0.36 mmol) in EtOH (10 mL) was added 10% palladized charcoal (20 mg, catalytic amount). The resulting mixture was subjected to hydrogenolysis on a Parr shaker hydrogenation apparatus by agitation with excess H_2 (g) at 55 psig at ambient temperature during 24 h. The reaction mixture was filtered through Celite®, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on neutral alumina by eluting with 15% MeOH-EtOAc. Pure **9** (79 mg, 89%) was thereby obtained as a colorless oil; IR (film) 2943 (s), 1702 (w), 1454 (w), 1128 (w), 1037 cm^{-1} (w); ^{1}H NMR ($CDCl_3$) δ 2.24 (br s, 2 H), 2.82 (t, *J* = 5.2 Hz, 8

H), 3.63 (t, J = 5.2 Hz, 8 H), 4.77 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 49.2 (t), 67.3 (t), 95.6 (s). Exact MS (CI HRMS) Calcd for $C_{10}H_{22}N_2O_4$: $[M_r + H]^+$*m/z* 235.16578. Found: $[M_r + H]^+$*m/z* 235.16528.

Alkali Metal Picrate Extraction Experiments. The extraction experiments were performed by using 5mM solutions of each compounds in $CHCl_3$. The procedure that was used for this purpose has been described elsewhere.[5a]

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