Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1125–1130

TETRAHEDRON: *ASYMMETRY*

Utility of crown ethers derived from methyl β-D-galactopyranoside and their lanthanide couples as chiral NMR discriminating agents

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Received 5 January 2001; accepted 15 March 2001

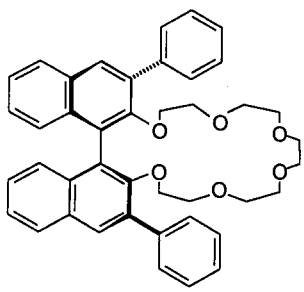
Abstract—Two chiral crown ethers derived from methyl β-D-galactopyranoside are examined as chiral NMR discriminating agents for protonated primary amines, amino alcohols, and amino acids. In combination, the solubility and use of the two crown ethers span a range of common NMR solvents including chloroform, acetonitrile, and methanol, which are compatible with the solubilities of various protonated amines. Enantiomeric discrimination is observed in the spectra of most substrates in the presence of the crown ethers. In several cases, the enantiomeric discrimination is larger than observed with previously reported chiral crown ethers. The crown ether **V** contains a β-diol unit capable of forming a chelate bond with lanthanide(III) ions. Adding ytterbium(III)nitrate to NMR samples in acetonitrile containing **V** causes substantial enhancements in the enantiodiscrimination in the spectra of several substrates.

1. Introduction

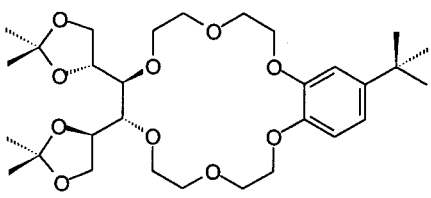
Crown ethers form stable inclusion complexes with protonated primary amines. Pioneering studies have demonstrated that chiral crown ethers can be used in conjunction with extraction,[1,2] NMR spectroscopy,[1,2] chromatographic separations,[3] and phase transfer systems[4] to differentiate the enantiomers of protonated chiral amines, amino alcohols, and amino acids.

Further uses of chiral crown ethers for enantioselection purposes have been described.[5] (2,3:4,5-Bis[1,2-(3-phenylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene) **I**, which contains an axial chiral binaphthyl moiety, is often the benchmark to which other chiral crown ethers are compared.[6] We have recently examined the utility of [3,4-*b*]{11,12-(4-*tert*-butylbenzo)-1,4,7,10,13,16-hexaoxacyclooctadeca-11-ene}-3,4-dideoxy-1,2:5,6-di-*O*-isopropylidene-D-mannitol **II**[7] and (2*R*,3*R*,11*R*,12*R*)-1,4,7,10,13,16-hexaoxacyclooctadecane-2,3,11,12-tetracarboxylic acid) **III**[8,9] as chiral NMR shift agents.

The scope and application of the crown ethers **I** and **II** in NMR spectroscopy is somewhat limited because their solubilities are restricted to chloroform and/or



I



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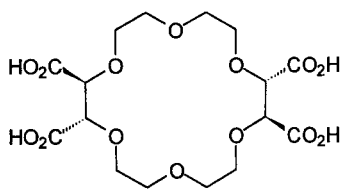

III

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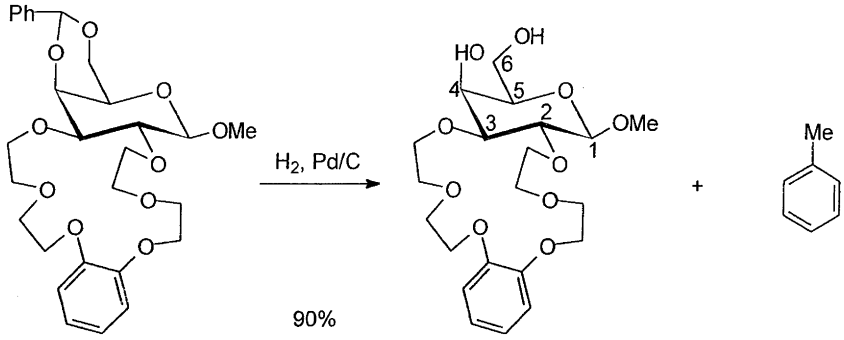

IV **V**

acetonitrile,[7] and unfortunately many protonated primary amines are insoluble in these solvents. However, the tetracarboxylic acid **III** is more broadly applicable since it is soluble in methanol, as are most protonated primary amines.[8,9]

Carbohydrates commonly serve as scaffolds for the preparation of chiral crown ethers[10] and several examples of crown ethers that utilize galactose moieties as the chiral unit have been reported.[11–19] Herein, we describe the examination of two galactose-derived crown ethers as chiral discriminating agents in ^{1}H NMR spectroscopy. Methyl 4,6-*O*-benzylidine [2,3-*b*]-(11,12-benzo-1,4,7,10,13,16-hexaoxacyclooctadeca-11-ene)-2,3-dideoxy-β-D-galactopyranoside **IV** was selected for investigation because preliminary studies indicated that it might exhibit enantiodiscriminating properties.[20] Methyl [2,3-*b*](11,12-benzo-1,4,7,10,13,16-hexaoxacyclooctadeca-11-ene)-2,3-dideoxy-β-D-galactopyranoside) **V**, which is prepared by deprotection of **IV**, was examined because the presence of the two hydroxy groups render it soluble in methanol. The presence of the β-diol unit in **V** also provides a site for chelate association with lanthanide ions.

Prior work has shown that achiral lanthanide species can be added to crown–substrate mixtures to enhance the extent of enantiomeric discrimination in the NMR spectrum of the substrate, thereby permitting better determination of e.e.[7,8] Lanthanide ions added as their nitrate salts to **III** directly associated with the carboxylate moieties of the crown.[8] With **II**, which does not have any sites for direct binding of lanthanide ions, a lanthanide tetrakis chelate anion of 2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedione $[Ln(fod)_4]^-$ was used.[7] The $Ln[(fod)_4]^-$, formed in situ by mixing $Ln(fod)_3$ and $Ag(fod)$,[21,22] associates with the ammonium ion and causes larger shifts in the spectrum of the enantiomer with the weaker association constant with the crown ether.[7]

Table 1. Enantiomeric discrimination ($\Delta\Delta\delta$) in Hz in the ^{1}H NMR spectra of substrates (0.0125 M) in the presence of **IV** (0.025 M) in chloroform-*d* at 20°C

Substrate	Resonance	$\Delta\Delta\delta$
Valine ethyl ester HCl	-$OCH_2\underline{CH_3}$	3.0
	-CH_3(A)	0
	-CH_3(B)	0
Alanine ethyl ester HCl	-CH_3	5.1
	-$OCH_2\underline{CH_3}$	24.6
Leucine methyl ester HCl	-OCH_3	6.0
1-Cyclohexylethyl amine HCl	-CH_3	0

Resonances listed are all of those for which enantiomeric discrimination was apparent.

2. Results and discussion

The acetal **IV** was found to be soluble in chloroform and sparingly soluble in both methanol and acetonitrile. Many protonated amines are insoluble in chloroform, which limits the number of substrates that can be examined with **IV**. The enantiomeric resolution in the spectra of several chloroform-soluble substrates with **IV** are reported in Table 1. Addition of **IV** generally causes slight upfield shifts of substrate resonances and enantiomeric discrimination is observed in the resonances of three of the four substrates.

In particular, the enantiodiscrimination of the ethoxy methyl resonance of alanine ethyl ester hydrochloride (Fig. 1) is unprecedented when compared to other crown ethers used as chiral NMR shift reagents.[7,8] The

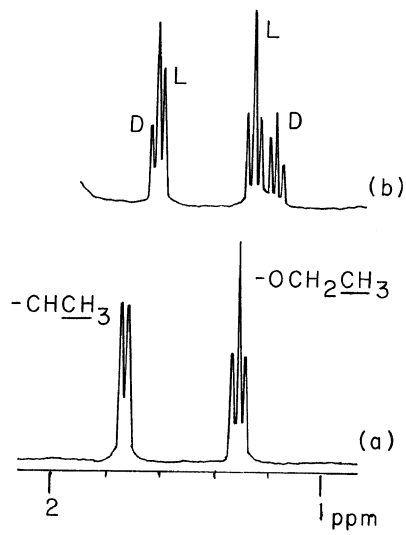

Figure 1. Resonances for the alanine methyl and ethoxy methyl groups in the ^{1}H NMR spectrum (300 MHz) of DL-alanine ethyl ester hydrochloride (0.0125 M, enriched in L-enantiomer) in chloroform-*d* at 20°C with (a) no **IV** and (b) 0.025 M **IV**.

ethoxy group must be in a configuration that is particularly influenced by the substituent group of the crown ether. The unusually large upfield shifts of the ethoxy resonances may indicate an orientation above the benzyl ring of **IV**, which is consistent with the geometry of other similar crown–substrate complexes.[13] It is interesting to note that the ethoxy methyl resonance of the D-enantiomer was shifted further upfield in the presence of **IV**, whereas the reverse order occurs for the alanine methyl resonance. Similar reversals have also been observed with other crown–substrate mixtures and suggest the importance of the diastereomeric nature of the complexes in explaining the enantiodifferentiation.[7,8] The enantiomeric discrimination of the ester resonances of the valine and leucine derivatives in the presence of **IV** in chloroform are also larger than previously observed with **II**.[7] Thus, **IV** is shown to be an effective chiral NMR discriminating agent for chloroform-soluble, protonated primary amines.

Since **IV** has no sites for direct association of lanthanide ions, a species such as $Eu[(fod)_4]^-$ must be added to shift the unassociated form of the substrate. Addition of small increments of $Eu[(fod)_4]^-$ to **IV**–substrate mixtures caused significant broadening of the resonances of all four substrates listed in Table 1. In prior work with similar crown–lanthanide systems, the broadening was primarily attributed to exchange effects and could be reduced to acceptable levels by warming the samples to 50°C.[7] Unfortunately, warming **IV**–substrate samples does not reduce the broadening sufficiently to observe coupling information in the spectrum. The potential of adding lanthanide ions to **IV**–substrate mixtures to enhance the enantiomeric discrimination was therefore of limited use.

The diol **V** was found to be readily soluble in acetonitrile and methanol, the latter of which is an especially good solvent for NMR studies on protonated primary amines. Adding **V** generally causes slight upfield shifts in the NMR spectra of substrates. Tables 2 and 3 list the enantiomeric discrimination observed in the NMR spectra of several substrates in the presence of **V** in methanol and acetonitrile, respectively. These results show that **V** is a broadly applicable chiral NMR shift reagent.

In comparison to prior NMR studies using **III**, which is also known to be an effective chiral shift agent in methanol, the size of the shifts for the methoxy resonance of alanine methyl ester hydrochloride, the CH resonance of tryptophan methyl ester hydrochloride, C(3′)H resonance of 1-(1-naphthyl)ethylamine hydrochloride, and the methyl resonance of (1*S*,2*R*)- and (1*R*,2*S*)-1-(4-hydroxyphenyl)-2-aminopropanol hydrochloride were larger when **V** was used. Similarly, the enantiodiscrimination with almost every substrate examined is greater with **V** than with **II**.

It is interesting to compare the enantiomeric discrimination of **IV** and **V** for a number of substrates (Tables 1 and 3). Whereas the ethoxy methyl resonance of alanine ethyl ester hydrochloride showed large discrimination with **IV** (24.6 Hz), there was no discrimination with **V**. In contrast, the valine methyl resonances of valine ethyl ester hydrochloride show sizeable discrimination in the presence of **V** but no discrimination with **IV**. Enantiomeric discrimination for the methyl resonance labelled A is larger than observed with other crown ether systems.[7,8] The pronounced differences that occur from changes at the acetal ring illustrates the subtleties of the discriminating effects of crown ether systems. These differences may result because the structure of the crown and/or the identify of the solvent is different.

Table 2. Enantiomeric discrimination ($\Delta\Delta\delta$) in Hz in the ^{1}H NMR spectra of substrates (0.025 M) in the presence of **V** (0.025 M) in methanol-d_4 at 20°C

Substrate	Resonance	$\Delta\Delta\delta$
Alanine methyl ester HCl	-OCH_3	2.4
Phenylglycine methyl ester HCl	-OCH_3	5.1
	-CH	6.3
Tryptophan methyl ester HCl	-H_1	3.0
	-CH	7.2
1-(1-Naphthyl) ethylamine HCl	-CH_3	6.3
	-CH	9.3
	-$H_{2'}$	4.8
	-$H_{3'}$	8.1
1-Cyclohexylethyl amine HCl	-CH_3	5.4
(1*S*,2*R*)- and (1*R*,2*S*)-1-(4-Hydroxyphenyl)-2-aminopropanol HCl	-CH_3	3.9
	$H_{3'}$	1.2

Resonances listed are all of those for which enantiomeric discrimination was apparent.

Table 3. Enantiomeric discrimination ($\Delta\Delta\delta$) (Hz) in the ^{1}H NMR spectra of substrates (0.025 M) in the presence of **V** (0.025 M) in acetonitrile-d_3 at 20°C with and without added ytterbium(III)

Substrate	Resonance	$\Delta\Delta\delta$	$\Delta\Delta\delta$ (with Yb)
Valine ethyl ester HCl	-CH_3(A)	16.5	29.1 (0.010)
	-CH_3(B)	2.7	4.5 (0.010)
	-$OCH_2\underline{CH_3}$	1.8	3.6[a] (0.050)
Alanine ethyl ester HCl	-CH_3	0	21.3 (0.050)
	-$OCH_2\underline{CH_3}$	0	0
1-Phenylethyl amine HCl	-CH_3	7.5	–[b]
	-Aromatic (*ortho*)	0	18.6 (0.030)

Resonances listed are all of those for which enantiomeric discrimination and enhancements occurred. Concentration of Yb(III) is listed in parentheses.

[a] The resonances of the two enantiomers coalesce and then reverse order in the spectra as increasing quantities of Yb(III)nitrate are added.

[b] The resonance overlaps with the solvent resonance on addition of Yb(III).

The effect of adding ytterbium(III)nitrate to solutions of **V** and alanine ethyl ester hydrochloride or (1*S*,2*R*)- and (1*R*,2*S*)-1-(4-hydroxyphenyl)-2-aminopropanol hydrochloride was examined. It is well known that β-diol units of carbohydrates associate with lanthanide ions in a chelate manner.[26] In prior work, the addition of Yb(III)nitrate to solutions of substrates with **III** in methanol was often effective at enhancing enantiomeric discrimination in the NMR spectrum.[8] The Yb(III) bound with the carboxylate groups of **III**, which accounted for the shifts. Using **V** in methanol, the lanthanide-induced shifts in the spectra of either the crown or the substrate range from small (<10 Hz) to non-existent. Addition of Dy(III)nitrate to a solution of **V** and alanine methyl ester hydrochloride in methanol causes essentially no broadening and no observable shifts in the spectrum of either the crown or substrate. This was surprising since Dy(III) is one of the strongest shifting lanthanide metals.[26] Broadening is also more significant with an ion such as Dy(III).[26] The absence of any shifts or broadening in the presence of Dy(III) indicates that the lanthanide does not associate with the crown in methanol. It is assumed that the presence of abundant hydroxyl groups from the methanol lead to a preferential solvation of the positive lanthanide(III) ions, thereby inhibiting any significant association with the neutral β-diol moiety of **V**.

In acetonitrile, which would be expected to associate less strongly with lanthanide(III) ions in comparison to methanol, the likelihood that Yb(III) will associate at the β-diol functionality of **V** is increased. The effect of adding Yb(III)nitrate to **V**–substrate mixtures is summarized in Table 3. Substantial lanthanide-induced shifts and enhancements in enantiomeric discrimination are observed in the spectra of all three substrates. The shifts almost certainly result from association of the Yb(III) at the β-diol moiety of **V**, since Yb(III) would not be expected to directly bind with a protonated amine. Also, the resonances of the crown exhibit significant shifting and broadening, whereas the resonances of the substrate show little broadening on addition of Yb(III)nitrate. Addition of $Yb(fod)_3$, which is also acetonitrile-soluble, to a mixture of **V** and alanine ethyl ester hydrochloride causes marked broadening of both the crown and substrate resonances. Presumably the exchange rate of the larger $Yb(fod)_3$ is slower than that of Yb(III) nitrate with **V**, thereby accounting for the broadening. This is consistent with observations of prior crown–lanthanide systems that involve chelates of fod and Yb(III)nitrate.[7,8]

An example of the improved enantiodiscrimination that can be obtained by adding Yb(III) is shown in Fig. 2 for the methyl resonance of alanine ethyl ester hydrochloride. It is interesting that the Yb(III)-induced shifts are downfield, which is the opposite to the effect previously observed when Yb(III) was added to alanine methyl ester hydrochloride–**III** mixtures.[8] Yb(III)-induced shifts in the spectrum of valine ethyl ester hydrochloride with **V** are also downfield over the entire series of Yb(III) additions (up to 0.05 M). The ethoxy methyl resonances of valine ethyl ester hydrochloride actually reverse their order as the Yb(III) is added.

With a mixture of 1-phenylethylamine hydrochloride and **V**, initial added increments of Yb(III) (up to 0.02 M) caused downfield shifts in the methyl and *o*-aromatic resonances. Further increments of Yb(III) (0.03 M and higher) led to a gradual upfield shift of these two substrate resonances. This trend was previously observed when lanthanides were added to **II**–substrate mixtures in chloroform.[7] In this prior report, when the concentration of the lanthanide ion was higher than that of the crown and substrate, it was unequivocally shown that the lanthanide associated in the crown cavity and displaced the substrate. The same effect appears to occur with 1-phenylethylamine and **V** at higher Yb(III) concentrations. Nevertheless, substantial enhancement of the enantiomeric discrimination of the *o*-aromatic resonance of 1-phenylethylamine is observed for Yb(III) concentrations up to 0.03 M. Thus, addition of Yb(III)nitrate to **V**–substrate mixtures in acetonitrile offers considerable potential for enhancing enantiomeric discrimination in ^{1}H NMR.

3. Conclusion

Two crown ethers derived from β-galactopyranoside are effective chiral NMR shift agents for protonated primary amines. **IV** is useful for protonated amines which are soluble in chloroform, whereas **V** is useful for the enantiodiscrimination of acetonitrile- and

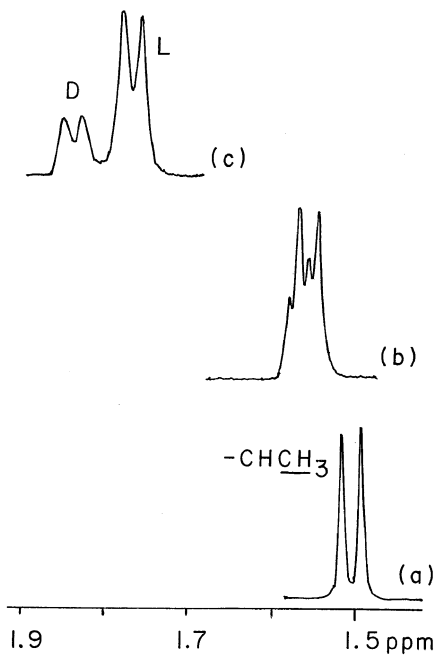

Figure 2. Resonances for the alanine methyl group in the ^{1}H NMR spectrum (300 MHz) of DL-alanine ethyl ester hydrochloride (0.025 M, enriched in L-enantiomer) in acetonitrile-d_3 at 20°C with 0.025 M **V** and (a) no ytterbium(III)nitrate; (b) 0.02 M ytterbium(III)nitrate, and (c) 0.05 M ytterbium-(III)nitrate.

methanol-soluble protonated amines. In several cases, **IV** and **V** effect greater enantiodifferentiation in the ^{1}H NMR spectra of substrates than those observed with previously reported chiral crown ethers. Addition of ytterbium(III) nitrate to mixtures of **V** with protonated primary amines in acetonitrile often enhances the enantiodiscrimination. It is assumed that the Yb(III) associates with the β-diol moiety of **V**.

4. Experimental

4.1. Reagents

The sources of substrates and deuterated NMR solvents were described in prior reports.[7–9] The nitrate salts of lanthanides were prepared by established procedures.[23] The lanthanide fod chelates [Ln(fod)$_3$][24] and silver(I)fod[25] were prepared and purified by established procedures. **IV** was prepared according to a literature method.[20]

4.2. Procedures

The appropriate amount of crown ether and substrate were weighed and dissolved in deuterated NMR solvent (1 mL). Increments of lanthanide(III)nitrate or Ln(fod)$_3$ were added either by weight or by 10 μL additions of a 0.5 M stock solution. Increments of Ln[(fod)$_4$]$^-$ were added by weighing the appropriate amounts of Ln(fod)$_3$ and Ag(fod) into a small test-tube, adding the solution with the crown and substrate, and shaking for 1 min. The silver chloride precipitate that formed was removed by centrifugation and decantation of the supernatant into an NMR tube. All chemical shift values were referenced to internal tetramethylsilane. NMR spectra of crown ether–substrate mixtures were recorded on a General Electric QE 300 MHz NMR spectrometer at ambient probe temperature unless otherwise stated.

4.3. Synthesis of methyl [2,3-*b*](11,12-benzo-1,4,7,10,13,16-hexaoxacyclooctadeca-11-ene)-2,3-dideoxy-β-D-galactopyranoside V

Compound **IV** (1.064 g, 2 mmol) was dissolved in a MeOH/$CHCl_3$ mixture (25 mL, 9:1) at rt. After argon was bubbled through the solution for 5 min (in order to remove oxygen), Pd/C (10%, 50 mg) was added and the mixture immediately shaken in a Parr hydrogenator under H_2 (around 4×10^5 Pa) for 3 h. The resulting mixture was filtered through a Celite pad. The reactor and pad were exhaustively rinsed with a mixture of CH_2Cl_2/EtOH (1:1), the resulting filtrate solution was concentrated under reduced pressure to a gum, which crystallized on standing. Recrystallization from hot EtOAc afforded **V** as colorless crystals (799 mg, 90%). Mp (uncorr.) 130–131°C, $[\alpha]_D^{20}=-3.2$ (*c* 3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (dd, 1H, CH_2-O*H*), 2.8 (s, 1H, CH-O*H*), 3.3 (dd, 1H, $J_{3\text{-}4}$ 3.3 Hz, $J_{2\text{-}3}$ 9.5 Hz, H-3), 3.43 (bt, 1H, $J_{4\text{-}5}\sim0$ Hz, $J_{5\text{-}6}\sim J_{5\text{-}6'}\sim6$ Hz, H-5), 3.47 (dd, 1H, $J_{1\text{-}2}$ 7.7 Hz, H-2), 3.52 (s, 3H, OC*H*$_3$), 3.72 (t, 2H, *J* 4.8 Hz, 2OC*H*H), 3.77–3.9 (m, 12H, H-6, -6′, 2OCH*H*, 4OCH$_2$), 4.04 (d, 1H, H-4), 4.1–4.19 (m, 4H, 2OCH$_2$), 4.21 (d, 1H, H-1), 6.89–6.95 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 149.1 (C-1, -2 catechol), 121.8, 121.7 (C-4, -5 catechol), 114.7, 114.65 (C-3, -6 catechol), 104.6 (C-1 Gal), 81.3 (C-3 Gal), 79.1 (C-2 Gal), 74.0 (C-5 Gal), 72.3, 71.1, 71.0, 69.85, 69.8, 69.7, 69.6, 69.3 (85O*C*H$_2$), 62.3 (C-6 Gal), 57.1 (O*C*H$_3$). $C_{21}H_{32}O_{10}$ requires: C, 56.74; H, 7.26. Found C, 56.84; H, 7.28%. EIMS$^+$ (70 eV): $C_{21}H_{32}O_{10}$ requires 444.2, found 444.3 (20%) $[M]^{\bullet+}$, 323.2 (100%).

Acknowledgements

We thank the National Science Foundation (Research at Undergraduate Institutions Program, Grant CHE-8921335 and CHE-0070007) for supporting this work. Parts of this project were also funded by a grant to Bates College from the Howard Hughes Medical Institute. We appreciate the assistance of Mrs. Eliane Eppiger in recording the NMR spectra of the reaction products.

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