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## Supramolecular Chemistry

Publication details, including instructions for authors and subscription information:

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**To cite this Article** Bartsch, Richard A. , Kim, Jong Seung , Olsher, Uriel and Purkiss, David M.(1996) 'Conformational studies of dibenzo-16-crown-5 lariat ethers', *Supramolecular Chemistry*, 6: 3, 327 – 331

**To link to this Article:** DOI: 10.1080/10610279608032551

**URL:** <http://dx.doi.org/10.1080/10610279608032551>

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# Conformational studies of dibenzo-16-crown-5 lariat ethers

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(Received June 13, 1994)

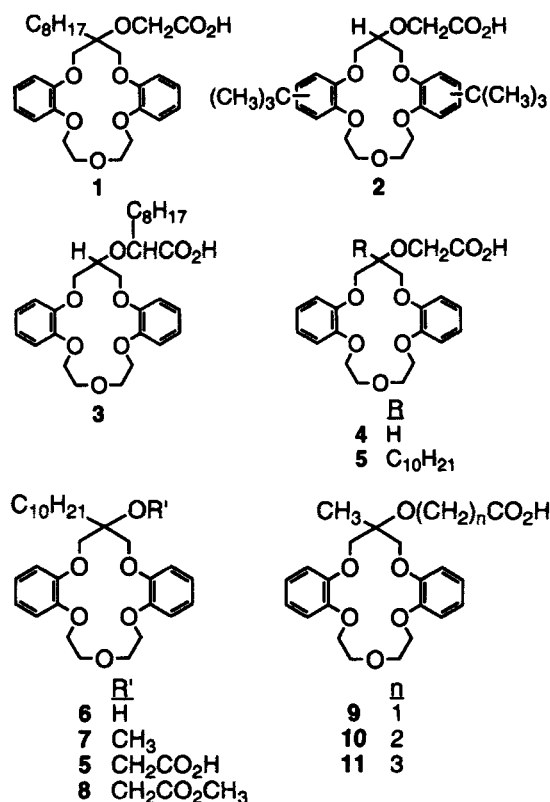
Conformations of *sym*-(R)(OR')dibenzo-16-crown-5 compounds with R = decyl and R' = H, CH<sub>3</sub>, CH<sub>2</sub>CO<sub>2</sub>H, and CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, as well as R = alkyl, fluoroalkyl, alkenyl, and alkynyl and R' = CH<sub>2</sub>CO<sub>2</sub>H, in solution have been probed by NMR spectroscopy. The difference in chemical shifts of the diastereotopic hydrogens for the methylene groups adjacent to the geminally substituted ring carbon is utilized to assess the ease of inversion of the three-carbon bridges. For lariat ethers with R = C<sub>10</sub>H<sub>21</sub>, the chemical shift difference is much larger when R' = CH<sub>2</sub>CO<sub>2</sub>H and CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub> than H and CH<sub>3</sub>. In non-hydrogen bonding solvents, the chemical shift difference for lariat ethers with R = C<sub>10</sub>H<sub>21</sub> is much larger when R' = CH<sub>2</sub>CO<sub>2</sub>H than CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, which demonstrates intramolecular hydrogen bonding of the carboxylic acid-containing side arm with a crown ether oxygen.

## INTRODUCTION

Lariat ethers are crown ethers to which a side arm bearing one or more potential coordination sites is attached.<sup>1</sup> In earlier work, we found that the Na<sup>+</sup> ion selectivity for competitive solvent extraction of alkali metal cations into chloroform by the ionized form of lipophilic lariat ether carboxylic acid **1** was considerably higher than that for the structural isomers **2** and **3**.<sup>2,3</sup> It was proposed that the presence of the geminal octyl group in **1** orients the carboxylic acid-containing side arm over the polyether cavity which preorganizes the binding site<sup>4</sup> and enhances the Na<sup>+</sup> extraction selectivity. In the solid-state structure of an analog of **1** which has a geminal decyl group in place of the octyl group, the carboxylic acid group is oriented over the cavity.<sup>5</sup> In the present study, conformations in solution of dibenzo-16-crown-5 lariat ethers with alcohol, ether, carboxylic acid, and ester side arms have been probed by NMR spectroscopy. In addition, the influence of structural variation within the geminal non-coordinating side arm has been examined for dibenzo-16-crown-5 lariat ether carboxylic acids.

## RESULTS AND DISCUSSION

The <sup>1</sup>H NMR spectrum in the region of 3.0–5.5 δ for *sym*-dibenzo-16-crown-5-oxyacetic acid (**4**) in CDCl<sub>3</sub> is shown in in Figure 1. The methylene hydrogens (H<sub>c</sub>) in the side arm give a singlet at 4.48 δ with a relative area of 2.0. Interestingly the signals for the four methylene hydrogens (H<sub>a</sub> and H<sub>b</sub>) and one methine hydrogen (H<sub>d</sub>) of the three-carbon bridge appear as a singlet at 4.29 δ



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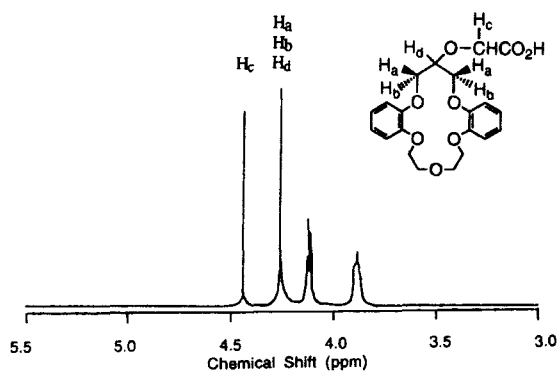


Figure 1 Proton magnetic resonance spectrum of *sym*-dibenzo-16-crown-5-oxyacetic acid (**4**).

with a relative area of 5.0. The absence of spin-spin coupling requires that the methylene and methine protons have identical chemical shifts. To ascertain this rather unusual circumstance, HOMO COSY and HETERO COSY spectra of **4** were taken in  $\text{CDCl}_3$ . In the HOMO COSY spectrum,<sup>6</sup> no cross-correlations were evident for  $H_a$ ,  $H_b$ , and  $H_c$ . The HETERO COSY spectrum<sup>6</sup> showed that the singlet assigned to  $H_a$ ,  $H_b$ , and  $H_c$  is coupled with two different types of carbons with absorptions at 79.6 ppm (the central carbon of the three-carbon bridge) and 71.4 ppm (the outer two carbons of the three-carbon bridge).

In the  $^1\text{H}$  NMR spectrum of *sym*-(decyl)dibenzo-16-crown-5-oxyacetic acid (**5**) in  $\text{CDCl}_3$  (Figure 2), the singlet for the methylene hydrogens in the oxyacetic acid side arm is shifted downfield to 4.85  $\delta$ . The absorption for the methylene hydrogens on the three-carbon bridge appear as a widely spaced AB pattern with a chemical shift difference<sup>7</sup> ( $\Delta\nu_{\text{AB}}$ ) of 205 Hz and a geminal coupling constant of 10 Hz. The HOMO COSY spectrum of **5** demonstrated that hydrogens  $H_a$  and  $H_b$  are indeed coupled to each other and a HETERO COSY spectrum showed that the outer carbons of the three-carbon bridge

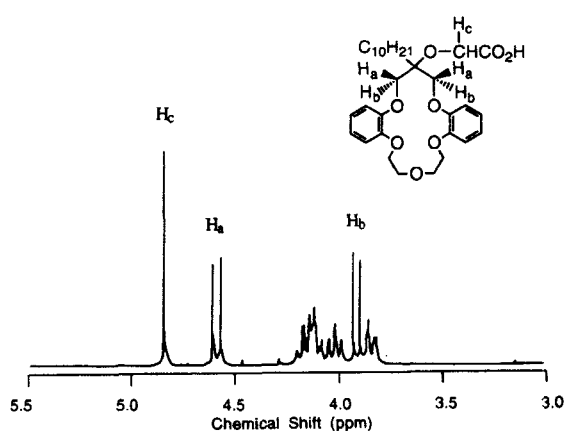


Figure 2 Proton magnetic resonance spectrum of *sym*-(decyl)dibenzo-16-crown-5-oxyacetic acid (**5**).

are coupled with  $H_a$  and  $H_b$ . Non-equivalence of the diastereotopic methylene hydrogens in **5** demonstrates that their interconversion by inversion of the three-carbon bridge (Figure 3) is slow on the NMR time scale. Thus the introduction of a *geminal*-decyl group into lariat ether carboxylic acid **4** produces a marked reduction in the ease of inversion of the three-carbon bridge.

To determine if the lower field doublet in the AB pattern arises from pseudoequatorial methylene hydrogens or pseudoaxial methylene hydrogens on the three-carbon bridge (Figure 3), a NOE experiment was conducted with **5** in  $\text{C}_6\text{D}_6$ .<sup>6</sup> Irradiation at 5.00 ppm ( $H_c$ ) enhanced the lower field doublet of the AB pattern. Examination of CPK space-filling models reveals that in the two limiting conformations shown in Figure 3, the pseudoequatorial methylene hydrogens are closer than the pseudoaxial methylene hydrogens to the methylene hydrogens in the oxyacetic acid side arm. Therefore, the absorptions identified as  $H_a$  and  $H_b$  are assigned to the pseudoequatorial and pseudoaxial methylene hydrogens, respectively, in lariat ether carboxylic acid **5**.

#### Pendent group and solvent variations for *sym*-(decyl)(OR')dibenzo-16-crown-5 compounds

It was surmised that the difference in chemical shifts for the diastereotopic hydrogens in the methylene groups on the three-carbon bridge,  $\Delta\nu_{\text{AB}}$ , might be used as a qualitative measure of the relative rates of conformational inversion of *sym*-(decyl)dibenzo-16-crown-5 derivatives **5-8**. Chemical shift differences for the diastereotopic methylene hydrogens in **5-8** in  $\text{DMSO-d}_6$  and  $\text{C}_6\text{D}_6$  are presented in Table 1.

For lariat ether alcohol **6** and its methyl ether **7**, the chemical shift difference is small and exhibits little change in going from  $\text{DMSO-d}_6$ , a hydrogen-bond accepting solvent, to  $\text{C}_6\text{D}_6$ , which can neither donate nor accept a hydrogen bond. In  $\text{DMSO-d}_6$ , the change from the hydroxy group in **6** and methoxy function in **7** to the oxyacetic acid group in **5** and the methyl oxyacetate group in **8** markedly enhances the chemical shift difference with a slightly larger chemical shift difference value for methyl ester **8** than for carboxylic acid **5**. Both are consistent with a ponderal effect. Thus inversion of the three-carbon bridges in **5** and **8** is judged to be less facile than that in **6** and **7**.

Although the magnitude of the chemical shift difference for lariat ether ester **8** is very nearly the same in  $\text{DMSO-d}_6$  and  $\text{C}_6\text{D}_6$ , the  $\Delta\nu_{\text{AB}}$  value for lariat ether carboxylic acid **5** increases from 87 Hz in  $\text{DMSO-d}_6$  to 244 Hz in  $\text{C}_6\text{D}_6$ . This anomalous effect for carboxylic acid **5** compared with lariat ethers **6-8** is attributed to *intramolecular* hydrogen bonding of the carboxylic acid group on the side arm with one of the crown ether ring oxygens in  $\text{C}_6\text{D}_6$ , which further diminishes the inversion

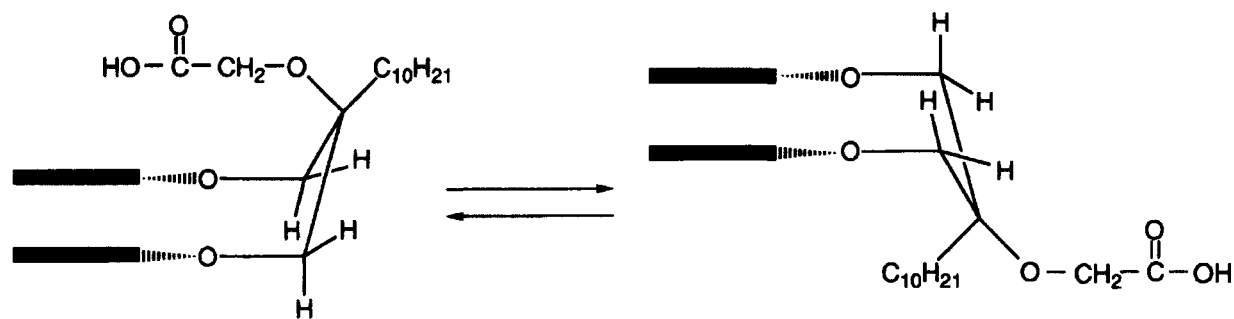


Figure 3 Conformational inversion of the three-carbon bridge in *sym*-(decyl)dibenzo-16-crown-5-oxyacetic acid (**5**).

propensity for the three-carbon bridge. This effect is not seen in DMSO- $d_6$  which can form *intermolecular* hydrogen bonds with the carboxylic acid group and thereby diminish the level of intramolecular hydrogen bonding.

Intramolecular hydrogen bonding of the pendent carboxylic acid group with a crown ether ring oxygen is possible only if the side arm is pseudoaxial and oriented over the crown ether cavity. Thus it appears that the side arm in **5** adopts a similar orientation in solution and in the solid state.<sup>5</sup> When the side arm is pseudoaxial, the alkyl-aryl ether oxygen and decyl groups are anti and an attractive *gauche* interaction<sup>8</sup> is possible between the alkyl-aryl ether oxygen and the ether oxygen in the side arm.

The NMR results described above were all obtained at room temperature. To further probe the intramolecular hydrogen bonding of the carboxylic acid group with a crown ether oxygen in **5**, the influence of temperature upon the  $\Delta\nu_{AB}$  values for lariat ether carboxylic acid **5** and the corresponding lariat ether methyl ester **8** was determined. The temperature dependence of the chemical shift difference for **5** and **8** in  $CDCl_3$  is recorded in Table 2. For both the **5** and **8**, the  $\Delta\nu_{AB}$  values decrease uniformly as the temperature is raised from 218 °K to 328 °K in ten-degree increments. However, the difference in the degree of change in  $\Delta\nu_{AB}$  for the two, closely related lariat ether compounds is striking. The chemical shift difference for the lariat ether ester decreases by 54%, whereas that for the lariat ether carboxylic acid is diminished by only 19%. The lower sensitivity to increased conformational mobility with temperature en-

Table 1 Chemical shift differences for diastereotopic methylene group hydrogens in *sym*-(decyl)(OR)dibenzo-16-crown-5 compounds **5-8**

Compound	R'	$\Delta\nu_{AB}$ (Hz) in	
		DMSO- $d_6$	$C_6D_6$
<b>6</b>	H	31	30
<b>7</b>	CH <sub>3</sub>	a	24
<b>5</b>	CH <sub>2</sub> CO <sub>2</sub> H	87	224
<b>8</b>	CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	109	118

<sup>a</sup>No AB pattern was evident.

hancement observed for lariat ether carboxylic acid **5** provides further evidence for *intramolecular* hydrogen bonding of the carboxylic acid group with one of the crown ether oxygens.

To further probe the solvent effect on the conformational mobility of lariat ether carboxylic acid **5**, <sup>1</sup>H NMR spectra were taken in a total of seven different deuterated solvents. Results are presented in Table 3. Focusing first on the five aprotic solvents, both the  $\Delta\nu_{AB}$  value and the chemical shift of the singlet for the methylene hydrogens in the carboxylic acid-containing side arm decrease as the solvent in varied benzene > chloroform > acetone  $\geq$  acetonitrile > DMSO. This ordering shows a rough correlation with the solvent polarity parameter  $E_T$ .<sup>N9</sup>

Table 2 Influence of temperature upon the chemical shift difference in  $CDCl_3$  for diastereotopic methylene group hydrogens in lariat ether carboxylic acid **5** and methyl ester **8**

Temperature (°K)	$\Delta\nu_{AB}$ (Hz) for lariat ether	
	<b>5</b>	<b>8</b>
218	228	196
228	226	188
238	225	179
248	222	170
258	217	160
268	215	150
278	212	141
288	208	129
298	204	121
308	199	110
318	192	100
328	185	91

Table 3 Solvent dependence of the chemical shift difference for diastereotopic methylene group hydrogens in *sym*-(decyl)dibenzo-16-crown-5-oxyacetic acid (**5**)

Solvent	$E_T^N$	$\Delta\nu_{AB}$ (Hz)	Chemical shift for -OCH <sub>2</sub> CO <sub>2</sub> H (ppm)
Benzene- $d_6$	0.111	244	5.004
Chloroform- $d$	0.259	205	4.848
Acetone- $d_6$	0.355	134	4.766
Acetonitrile- $d_3$	0.460	137	4.620
DMSO- $d_6$	0.444	87	4.462
Acetic Acid- $d_4$	0.648	142	4.852
Ethanol- $d_6$	0.654	108	4.677

Results for the two protic solvents, acetic acid and ethanol, do not fit within the ordering defined by the aprotic solvents.

#### Geminal group variation for *sym*-(R)dibenzo-16-crown-5-oxyacetic acids

To probe the influence of the R group upon the conformational mobility of *sym*-(R)dibenzo-16-crown-5-oxyacetic acids,  $^1\text{H}$  NMR spectra were measured in DMSO- $d_6$  and  $\text{C}_6\text{D}_6$  for compounds with linear alkyl, branched alkyl, sterically hindered alkyl, perfluoroalkyl, alkenyl, and alkynyl R groups. The  $\Delta\nu_{\text{AB}}$  values are recorded in Table 4.

As R is varied from methyl to butyl to octyl to decyl (Entries 1-4, respectively, in Table 4), only slight changes are noted for the  $\Delta\nu_{\text{AB}}$  values in DMSO- $d_6$  and in  $\text{C}_6\text{D}_6$ . Thus even methyl, the smallest alkyl group, produces diminished conformational flexibility of the three-carbon bridge compared with that for lariat ether carboxylic acid **4** which does not have a geminal alkyl group. Also, the length of the geminal, normal alkyl group is found to have no influence upon the propensity for intramolecular hydrogen bonding for the lariat ether carboxylic acids in  $\text{C}_6\text{D}_6$ . Similarly the  $\Delta\nu_{\text{AB}}$  values when R is a branched alkyl (isopropyl) or sterically hindered alkyl (neopentyl) group (Entries 5 and 6, respectively, in Table 4) are very similar to those observed for the normal alkyl groups.

The change from a non-polar octyl geminal group to a polar perfluorooctyl group (compare Entries 3 and 7, respectively, in Table 4) produces a substantial decrease in the  $\Delta\nu_{\text{AB}}$  value in  $\text{C}_6\text{D}_6$  and a barely perceptible diminution in DMSO- $d_6$ . The increased conformational flexibility for the three-carbon bridge in *sym*-(perfluorooctyl)dibenzo-16-crown-5-oxyacetic acid in  $\text{C}_6\text{H}_6$  may result from enhanced attraction of the polar perfluoroalkyl group to the polar polyether portion of the molecule.

Indication that the conformational mobility of *sym*-(R)dibenzo-16-crown-5-oxyacetic acids is affected by the hybridization of the first atom of the R group is provided by the data for 2-methyl-1-propenyl and 1-octynyl

groups (Entries 8 and 9, respectively, in Table 4). In both DMSO- $d_6$  and  $\text{C}_6\text{D}_6$ , there is a marked diminution in the  $\Delta\nu_{\text{AB}}$  values when an alkyl geminal group is replaced by an alkenyl function. A further substitution of a geminal alkynyl group for the alkenyl unit produces another substantial decrease in the  $\Delta\nu_{\text{AB}}$  values. These results suggest that the number of atoms which are attached to the first carbon of the geminal R group has an important influence on the ease of inversion of the three-carbon bridge.

#### Variation of side arm length for lariat ether carboxylic acids

Lariat ether carboxylic acids **9-11** have common structures except for the number of methylene groups in the functional side arm.  $^1\text{H}$  NMR spectra for **9-11** were taken in DMSO- $d_6$  and  $\text{C}_6\text{D}_6$  and the  $\Delta\nu_{\text{AB}}$  values are recorded in Table 5. In both solvents, the  $\Delta\nu_{\text{AB}}$  values are in the order **9**  $\gg$  **10**  $>$  **11**. Thus elongation of the side arm from oxyacetic acid to 3-oxypropanoic acid markedly enhances the conformational flexibility of the three-carbon bridge in the lariat ether carboxylic acid. Further elongation to incorporate three methylene groups in the side arm produces an additional increase in the conformational flexibility.

Examination of CPK space-filling models reveals that for the 4-oxybutanoic acid pendent group in **11**, the side arm extends across the crown ether ring and is too long for effective intramolecular hydrogen bonding of the carboxylic acid group with a crown ether ring oxygen. In agreement, the  $\Delta\nu_{\text{AB}}$  values for **11** are the same in  $\text{C}_6\text{D}_6$  and in DMSO- $d_6$  which reveals that intramolecular hydrogen bonding is unimportant for this lariat ether carboxylic acid. The weak intramolecular hydrogen bonding which is evident for **10** also indicates that the side arm is too long for effective intramolecular hydrogen bonding. On the other hand, the much larger  $\Delta\nu_{\text{AB}}$  value for **9** in  $\text{C}_6\text{D}_6$  than in DMSO- $d_6$  is consistent with pronounced intramolecular hydrogen bonding in  $\text{C}_6\text{D}_6$  of the carboxylic acid group with a crown ether oxygen.

$^1\text{H}$  NMR spectra for a variety of dibenzo-16-crown-5 compounds with geminal substituents (one a hydrocarbon group and the other with potential coordinating sites) on the central carbon of the three-carbon bridge exhibit

**Table 4** Influence of R group upon the chemical shift difference for diastereotopic methylene group hydrogens in *sym*-(R)dibenzo-16-crown-5-oxyacetic acids

Entry	R	$\Delta\nu_{\text{AB}}$ (Hz) in	
		DMSO- $d_6$	$\text{C}_6\text{D}_6$
1	$\text{CH}_3$	85	259
2	$\text{C}_4\text{H}_9$	90	245
3	$\text{C}_8\text{H}_{17}$	85	247
4	$\text{C}_{10}\text{H}_{21}$	87	243
5	$\text{CH}(\text{CH}_3)_2$	108	241
6	$\text{CH}_2\text{C}(\text{CH}_3)_3$	98	224
7	$\text{C}_8\text{F}_{17}$	77	132
8	$\text{CH}=\text{C}(\text{CH}_3)_2$	28	158
9	$\text{C}\equiv\text{CC}_6\text{H}_{13}$	19	98

**Table 5** Influence of side arm length variation upon the chemical shift difference for diastereotopic methylene group hydrogens in lariat ether carboxylic acids **9-11**

Lariat ether	$\Delta\nu_{\text{AB}}$ (Hz) in	
	DMSO- $d_6$	$\text{C}_6\text{D}_6$
<b>9</b>	85	259
<b>10</b>	25	44
<b>11</b>	15	14

AB splitting patterns for the diastereotopic methylene group hydrogens. The magnitude of the difference in chemical shifts for the diastereotopic hydrogens provides a qualitative measure of the ease of inversion of the three-carbon bridge.

## EXPERIMENTAL

### Materials

Deuterated NMR solvents were obtained from commercial suppliers and were used directly. Lariat ethers **1**,<sup>10</sup> **4**,<sup>11</sup> **5**,<sup>3</sup> **6**,<sup>12</sup> **8**,<sup>3</sup> and **9**<sup>13</sup> were prepared by the reported methods. Other lariat ether carboxylic acids were prepared by adaptations of the methods reported for the synthesis of **1**, **5**, and **9**. Lariat ether **7** was prepared by reaction of **6** with NaH then iodomethane in THF.

### NMR spectral measurements

The NMR spectra were obtained with a 300 MHz Bruker NMR spectrometer. Chemical shifts are reported downfield from TMS in ppm ( $\delta$ ). The chemical shift of the AB patterns were calculated by the "weighted average chemical shift" method.<sup>7</sup>

## ACKNOWLEDGEMENT

This research was supported by the Division of Chemical Sciences of the Office of Basic Energy Sciences of the U.S. Department of Energy (Grant DE-FG03-94ER14416).

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