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Stereospecific Fragmentation of 3-Dimethylaminocyclohexanols upon Electron Impact Ionization

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Stereoisomeric *cis*- and *trans*-1-butyl-3-dimethylaminocyclohexanols have been previously reported to exhibit different electron impact (EI) mass spectra. The *m/z* 100 $[C_6H_{14}N]^+$ ion is obtained only from the *cis*-isomer. The results of a collision-induced dissociation study are inconsistent with the previously proposed protonated dimethylaminocyclobutane structure (ion a) and suggest the *N,N*-dimethyl-1-butaneimmonium ($CH_3CH_2CH_2CH{=}N^+(CH_3)_2$) structure (ion b) for this ion. The mechanistic pathway proposed for this highly stereospecific process involves initial hydrogen migration from the hydroxy group to the radical site at the charged amino group as the stereospecific step, this being possible only for the *cis*-amino alcohol. The EI mass spectra of the corresponding stereoisomeric methyl ethers exhibit preferential elimination of formaldehyde from the *cis*-isomer, which is explained by initial hydrogen migration from the methoxy group to the N atom. The unsubstituted *cis*- and *trans*-1-methoxy-3-dimethylaminocyclohexanes do not show any stereospecificity in their behavior under EI.
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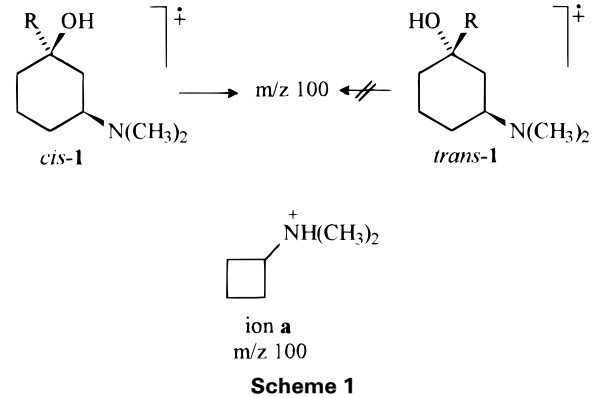
INTRODUCTION

Stereochemical effects in the chemistry of gas-phase ions have been one of the major objectives in the research activities of this laboratory.[1–3] Such effects have been applied in structural and mechanistic studies of ions in the gas phase and in configurational assignments of organic compounds in the condensed phase. In this context, our attention was caught by a report on the highly stereospecific fragmentation behavior of stereoisomeric 1-alkyl-3-dimethylaminocyclohexanols (**1**, R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *t*-C_4H_9, *n*-C_5H_{11}, *i*-C_5H_{11}) under electron impact ionization (EI).[4] The *cis*-isomers gave rise to *m/z* 100 $[C_6H_{14}N]^+$ and *m/z* 45 $[C_2H_7N]^{+\cdot}$ cations, which were absent in the EI mass spectra of the *trans*-analogs. The elemental compositions of the two ions have been confirmed by high-resolution measurements, and deuterium labeling experiment indicated the presence of the hydroxylic hydrogen in the *m/z* 100 ion. The structure of protonated dimethylaminocyclobutane (ion **a**) was proposed for the *m/z* 100 ion in the paper cited (see Scheme 1),[4] but no mechanistic pathway was suggested that would account for the high stereospecificity of its formation.

A similar stereospecific behavior has been reported by the same group in *cis*- and *trans*-3-alkyl-*N*-(3-hydroxycyclohexyl)piperidines.[5] The EI mass spectra of the *cis*-isomers exhibited *m/z* 140 and 85 ions, which were of much lower abundance in the spectra of the *trans* counterparts. Here again a cyclobutylamine structure (protonated *N*-cyclobutylpiperidine) was proposed for the characteristic *m/z* 140 ion,[5] but the origin of the stereospecific behavior of the *cis*- and *trans*-isomers was not dealt with.

The primary objective of this work was to investigate the structure of the *m/z* 100 $[C_6H_{14}N]^+$ ion obtained from *cis*-3-dimethylaminocyclohexanols (**1**) under EI



Scheme 1

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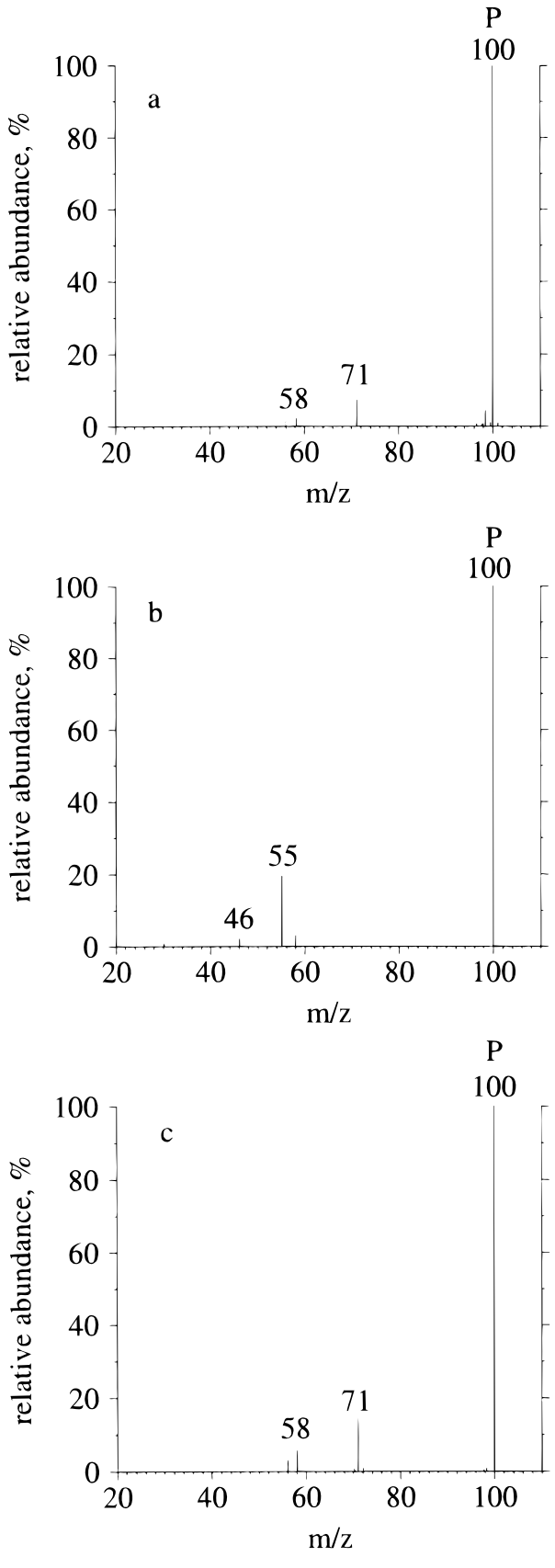

Figure 1. CID spectra of *m/z* 100 ions: (a) obtained from *cis*-1-butyl-3-dimethylaminocyclohexanol (*cis*-**1**, R = C_4H_9) under 70 eV EI conditions; (b) protonated (isobutane CI) dimethylaminocyclobutane (ion **a**); (c) CID spectrum of *m/z* 100 ion **b** obtained from 4-dimethylaminoheptane (**2**) upon EI.

and to propose a mechanism for its stereospecific formation.

RESULTS AND DISCUSSION

The *cis*- and *trans*-1-butyl-3-dimethylaminocyclohexanols *cis*-**1** and *trans*-**1** (R = *n*-C_4H_9) were synthesized by the reported route.[4] The EI mass spectral measurements reproduced the stereospecific formation of the *m/z* 100 ion from the *cis*-isomer *cis*-**1** (12% relative abundance). Collision-induced dissociation (CID) measurements on this ion and on the *m/z* 100 *N*,*N*-dimethylcyclobutylammonium ion **a**, obtained upon isobutane chemical ionization (CI) from dimethylaminocyclobutane, were performed in order to investigate its structure. The two CID spectra shown in Fig. 1 are entirely different, indicating different structures for these ions. The abundant *m/z* 55 ion in the CID spectrum of protonated dimethylaminocyclobutane, which presumably has the elemental composition $[C_4H_7]^+$, is consistent with the structure of ion **a**. The absence of the *m/z* 55 ion in the CID spectrum of the *m/z* 100 ion obtained in Fig. 1(c) suggests the absence of the cyclobutyl moiety in its structure.

The CID spectrum of the *m/z* 100 ion obtained from *cis*-**1** was found to be similar to the CID spectrum of *N*,*N*-dimethyl-1-butaneimmonium cation (ion **b**) formed from 4-dimethylaminoheptane (**2**) upon EI [Scheme 2 and Fig. 1(c)] (the tandem mass spectrometric behavior of immonium ions has been described in two recent papers[6]). This finding suggests the structure of ion **b** for the product of the stereospecific fragmentation of *cis*-**1**.

$$(CH_3CH_2CH_2)_2CHN(CH_3)_2 \xrightarrow{EI} CH_3CH_2CH_2C{=}\overset{+}{N}(CH_3)_2$$

2 ion **b**

Scheme 2

A plausible mechanism for the formation of ion **b** from *cis*-**1** is proposed in Scheme 3. The initial hydrogen migration from the hydroxy group to the radical site at the charged amino group is the stereospecific step, this being possible only for the *cis*-isomer *cis*-**1**.

As expected, based on the above mechanism, the EI mass spectra of *cis*- and *trans*-1-butyl-1-methoxy-3-dimethylaminocyclohexanes *cis*- and *trans*-**3** (R = C_4H_9) (shown in Fig. 2) do not exhibit the analogous *m/z* 114 ion (Scheme 4). The formation of such an ion would require migration of a methyl group from the oxygen to the nitrogen atom. A significant difference in the behavior of these two stereoisomeric amino ethers **3** appears in the relative abundances of the *m/z* 182 and 183 $[M - CH_3O]^+$ and $[M - CH_2O]^{+\cdot}$ ions. The preferential elimination of formaldehyde observed in *cis*-**3** suggests the occurrence of a hydrogen transfer from the methoxy group to the cation radical site at the N atom, which is possible only in the *cis*-isomer, unless ring cleavage is involved in this process. A mechanistic pathway for this fragmentation is proposed in Scheme 5.

In contrast to *cis*-**1** and *trans*-**1**, the unsubstituted *cis*- and *trans*-3-dimethylaminocyclohexanols *cis*- and *trans*-**4** give rise to similar EI mass spectra (Fig. 3).

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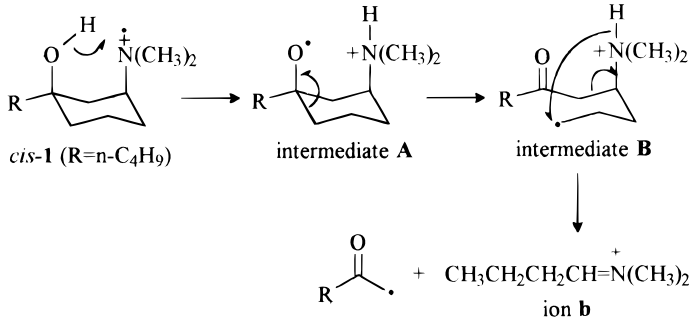
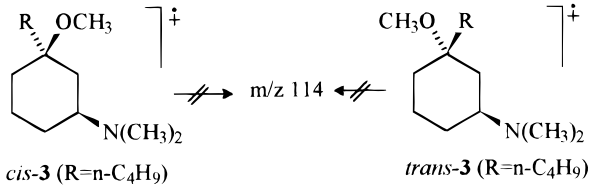


Scheme 3



Scheme 4

High-resolution mass spectral measurement of the mixture of *cis*- and *trans*-**4** shows the presence of two *m/z* 100 ions. The major $[C_5H_{10}NO]^+$ ion (*m/z* 100.0755, calculated 100.0762, most abundant in the mass spectrum) is formed presumably by the standard fragmentation process[7] shown in Scheme 6. The minor $[C_6H_{14}N]^+$ ion (*m/z* 100.1128, calculated 100.1126,

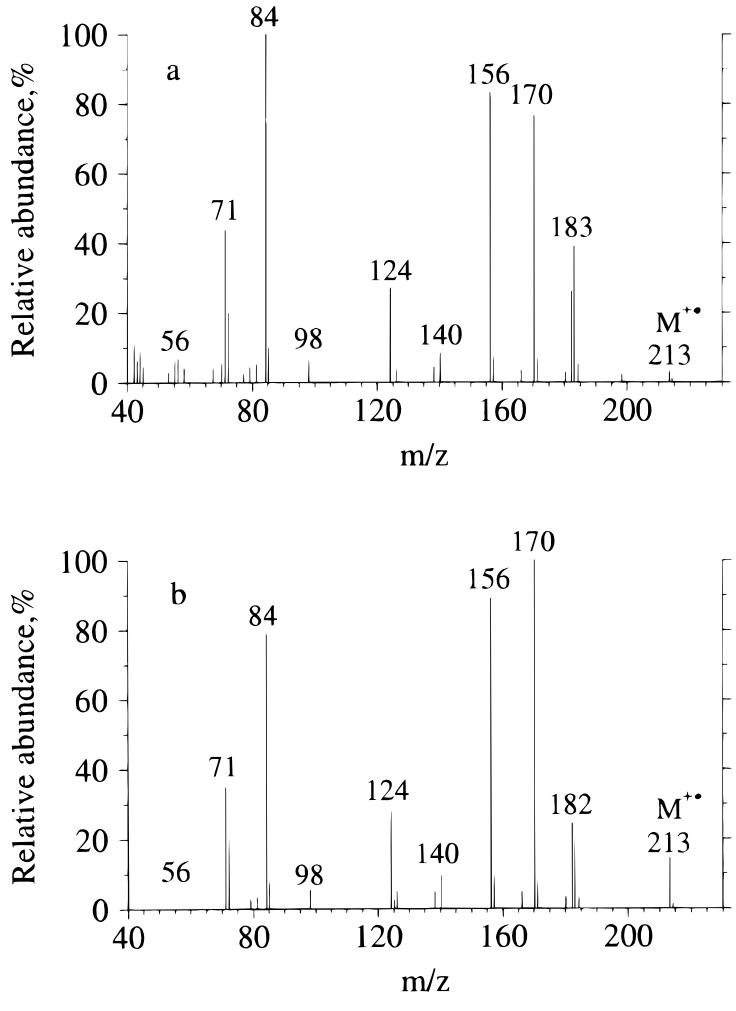


Figure 2. EI mass spectra of stereoisomeric 1-butyl-1-methoxy-3-dimethylaminocyclohexanes *cis*- and *trans*-**3** (R = C_4H_9).

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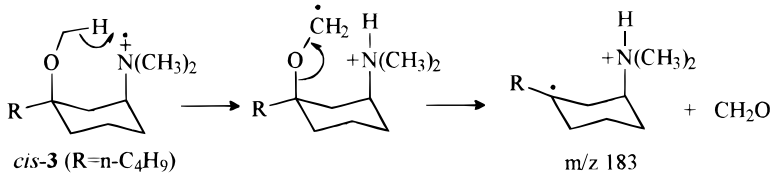


cis-**3** (R=n-C_4H_9) m/z 183

Scheme 5

10% relative abundance), corresponding to ion **b**, is presumably formed from *cis*-**4** via a route similar to that shown in Scheme 3. This presumably different behavior of the unsubstituted *cis*- and *trans*-3-dimethylaminocyclohexanols *cis*- and *trans*-**4** is hidden in their low-resolution EI mass spectra.

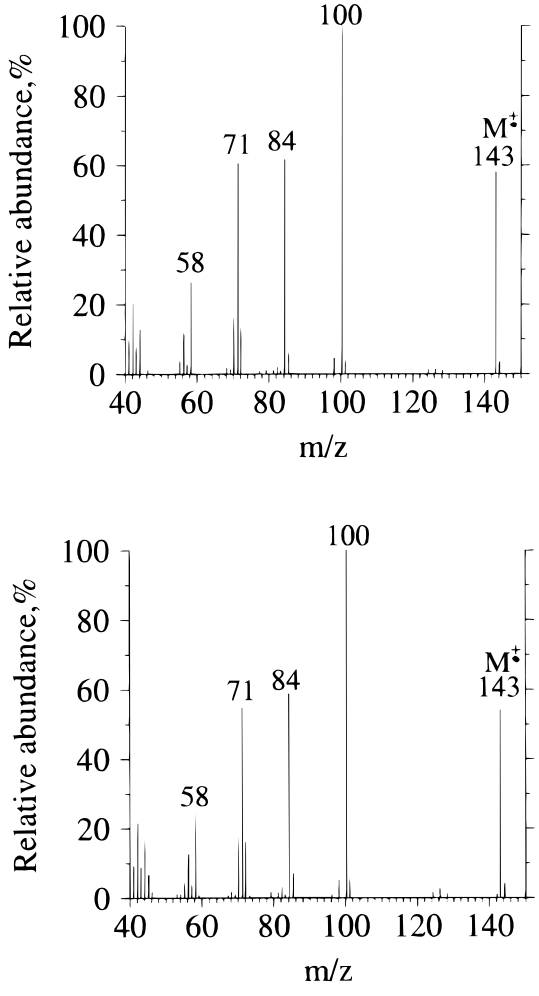
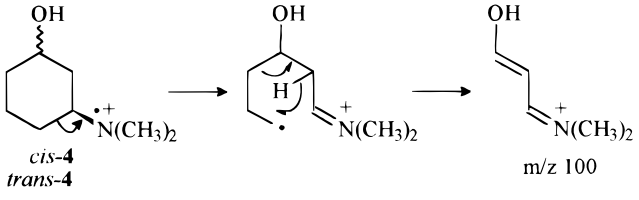
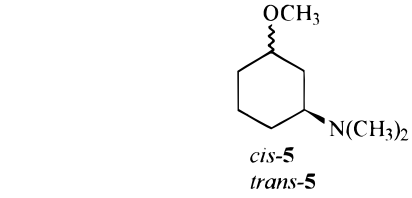


Figure 3. EI mass spectra of stereoisomeric unsubstituted 3-dimethylaminocyclohexanes *cis*- and *trans*-**4**.



cis-**4**
trans-**4**
m/z 100

Scheme 6



cis-**5**
trans-**5**

The unsubstituted *cis*- and *trans*-1-methoxy-3-dimethylaminocyclohexanes *cis*- and *trans*-**5** afford indistinguishable EI mass spectra (shown in Fig. 4). In

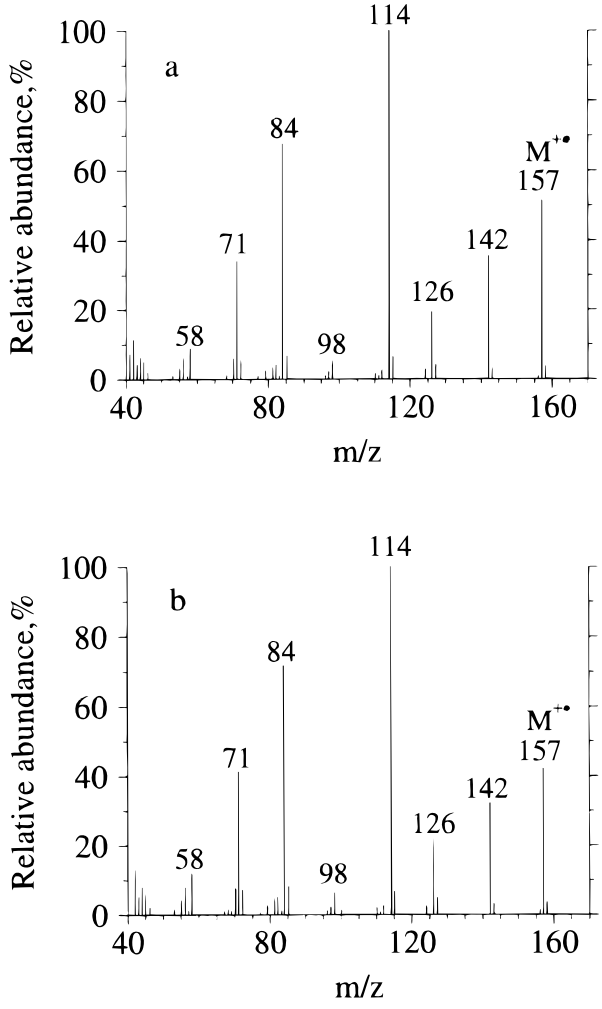


Figure 4. EI mass spectra of stereoisomeric 1-methoxy-3-dimethylaminocyclohexanes *cis*- and *trans*-**5**.

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contrast to the 1-alkyl-substituted amino ethers **3**, none of the stereoisomers *cis*- and *trans*-**5** exhibits elimination of formaldehyde.

CONCLUSION

It has been shown a long time ago that stereoisomeric 3- and 4-arylcyclohexylamines give rise to identical EI mass spectra.[1,8] This non-stereospecific behavior has been ascribed to the low energy required for the ring cleavage in cycloalkylamines (α-cleavage of the C(1)—C(2) bond), which results in identical structures of the fragmenting $M^{+\cdot}$ ions of the *cis*- and *trans*-isomers.[1,8,9] The results of this investigation show that the additional hydroxy and methoxy groups at position 3 induce additional fragmentation channels initiated by a hydrogen transfer between the oxygen and nitrogen functions. These additional fragmentation processes occur preferentially in the *cis*-isomers, where the distance between the two interacting functions is small.

EXPERIMENTAL

Mass spectrometry

Gas chromatographic/mass spectrometric analyses and CID measurements were carried out on a Finnigan TSQ-70B triple-stage quadrupole mass spectrometer. The stereoisomeric pairs were introduced as mixtures, and separations were performed on a DB-5 (0.25 μm film thickness) 30 m × 0.25 mm i.d. capillary column. The column temperature was programmed from 60 to 260 °C at 15 °C min^{-1}. The scan rate was 1 scan s^{-1}.

EI measurements were performed at a 150 °C ion source temperature and 70 eV electron energy. CID measurements were performed with argon as the target gas (0.3 mTorr, indicated (1 Torr = 133.3 Pa)) at 40 eV collision energy (indicated) in order to ensure reliable comparisons.

Materials

1-Butyl-3-dimethylaminocyclohexanols (1). A mixture of *cis*- and *trans*-**1** (R = *n*-C_4H_9) was synthesized from 3-dimethylaminocyclohexanone and *n*-butyllithium by the literature procedure.[4]

1-Butyl-1-methoxy-3-dimethylaminocyclohexane (3). A mixture of *cis*- and *trans*-**1** (R = C_4H_9) (0.2 g, 1 mmol) was added to a suspension of NaH (0.03 g, 12 mmol) in 2 ml of dry tetrahydrofuran (THF). After stirring for 20 min at 40 °C, iodomethane (0.4 g, 3 mmol) was added, and the mixture was stirred for 4 h. Addition of water (3 ml) followed by evaporation of THF and methylene chloride extraction yielded a mixture of *cis*- and *trans*-**3** (R = C_4H_9) (70%).

4-Dimethylaminoheptane (2). 4-Aminoheptane was prepared by lithium aluminum hydride reduction of heptan-4-one oxime.[10] Eschweiler–Clarke methylation[11] with formaldehyde and formic acid gave **2** (yield 65%).

Dimethylaminocyclobutane. This was obtained by Eschweiler–Clarke methylation[11] of aminocyclobutane (Aldrich).

3-Dimethylaminocyclohexanols (4). A mixture of *cis*- and *trans*-**4** was prepared by sodium borohydride reduction of 3-dimethylaminocyclohexanone.

1-Methoxy-3-dimethylaminocyclohexanes (5). A mixture of *cis*- and *trans*-**5** was obtained from **4** by the procedure described above for the preparation of **3**.

Acknowledgement

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