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Separation and identification of stereoisomeric cyclobutanediols by gas chromatography–mass spectrometry

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Abstract

A procedure is described for the separation and identification of *cis*- and *trans*-2,2,4,4-tetramethyl-1,3-cyclobutanediol. The separation of the isomeric diols was achieved by gas chromatography on an HP-1 capillary column under optimized conditions. The identification of the isomers was carried out through the mass spectrometric analysis of silyl derivatives prepared by using silylating agents of different steric demands. Striking reactivity differences of the isomers resulted in selective derivatization, permitting the unequivocal identification of the isomers. The results were supported by the analysis of authentic samples.

1. Introduction

The catalytic reduction of dimethylketene dimer resulted in the first synthesis of a mixture of *cis*- and *trans*-2,2,4,4-tetramethyl-1,3-cyclobutanediol [1]. The first separation of the isomers was performed on a preparative scale in the form of their formate esters. This method, however, required a large amount of starting material and provided only an appropriate isomer distribution, which is not satisfactory in most instances.

We were interested in studying the transformations of stereoisomeric cyclobutanediols, which required the reliable identification of the individual isomers. Moreover, the analysis of a large number of samples was expected, and a rapid and accurate analytical method was therefore needed. As substituted cyclic diols are important building blocks in organic synthetic [2], their separation and identification and the determination of their purity are of great general interest.

In this paper, we report the gas chromatographic (GC) separation of the above stereoisomeric cyclobutanediols and their identification by mass spectrometric (MS) analysis of their derivatives.

2. Experimental

2.1. Chemicals

All solvents were of spectroscopic grade (Reanal, Budapest, Hungary). The diol mixture with an isomeric ratio of about 1 was the product of City Chemical (New York, USA). Authentic *cis*-diol for comparison was prepared by treating the diol mixture with dilute sulphuric acid [3]. This treatment results in decomposition of the diols via dehydration. As the *trans* compound reacts much faster, the reaction permits the isolation of pure *cis*-diol. N,N-Diethyltrimeth-

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ylsilylamine and N *tert.*-butyldimethylsilyl-N-methyltrifluoroacetamide (MTBSTFA) (both from Fluka, Buchs, Switzerland) were used as silylating agents.

2.2. Derivatization

Silyl ethers were prepared according to the conventional method. A 5-mg sample of the diol mixture was dissolved in N,N-dimethylformamide (100 μl) and an excess of the silylating agent (200 μl) was added at room temperature. The reaction was complete within 15 min. A 5-μl volume of this mixture was used for analysis.

2.3. Chromatography

An HP 5890 gas chromatograph coupled with an HP 5970 MSD system (electron impact ionization at 70 eV, Hewlett-Packard, Avondale, PA, USA) was used for GC and MS measurements. Separation was carried out on free fatty acid phase (FFAP) (50 m × 0.2 mm I.D., 0.5 μm) and HP-1 (50 m × 0.2 mm I.D., 0.5 μm) capillary columns (both from Hewlett-Packard). Both columns were operated in the isothermal mode (oven temperatures 160°C for the FFAP and 150°C for the HP-1 column) with helium as carrier gas (flow-rate 0.85 cm^3/min). Calculations were carried out with an HP 59970 Chemstation (Hewlett-Packard).

3. Results and discussion

The GC separation of simple alcohols on packed columns usually gives satisfactory results [4–6]. The analysis of diols, in contrast, is more difficult. Therefore, it was not surprising that the application of packed columns with conventional partition liquids [Carbowax 20M, Apiezon, SE-52, 1,2,3-tris(2-cyanoethoxy)propane] did not result in the separation of the two cyclobutanediol isomers. In contrast, an FFAP capillary column specially designed for the analysis of hydroxy compounds [7] gave an excellent baseline separation of the two isomers. The long analysis time (more than 22 min), however, was inconvenient and further improvements were necessary.

As the stereoisomeric diols are centro- (*trans*) and planesymmetric (*cis*) and the molecular shape of both compounds is nearly spherical, near-zero dipole moments can be expected. We reasoned, therefore, that columns designed for the analysis of non-polar materials should be suitable for the separation of our diol isomers. A faster analysis was also expected owing to the weaker interaction between the partition liquid and the cyclobutanediols. Indeed, analysis on an HP-1 column required only about 10 min with the same excellent separation as on the FFAP column [Fig. 1B: peaks 6 (*cis*) and 7 (*trans*)]. Moreover, the retention indices [8] could easily be determined on HP-1 (Fig. 1A: peaks 1, 2, 3, 4 and 5; Table 1), in contrast with FFAP column, where this required the use of very high-molecular-mass hydrocarbons.

Whereas the above measurements can be carried out by means of simple detectors (flame ionization or thermal conductivity), more sophisticated techniques are needed to identify the individual compounds. Unfortunately, the MS detector used in our study operating at an ionization potential of 70 eV produced almost identical fragmentation patterns for the two diol isomers [Fig. 2A (*trans*) and B (*cis*) and Fig. 3], which is in accordance with literature data [9].

Derivatization of the diols appeared to be the solution to the problem. All our initial efforts with simple derivatives (different esters and ethers) failed to produce mass spectra suitable

Table 1
Retention indices of stereoisomeric cyclobutanediols and some derivatives on an HP-1 column at 150°C

Compound[a]	Retention index[b]
1a	1085.3
1b	1068.7
2a	1164.3
2b	1175.8
3a	1158.0

[a] See Figs. 2 and 3.
[b] *n*-Alkanes used for the determination of retention indices were C_9, C_{10}, C_{11}, C_{12} and C_{13}.

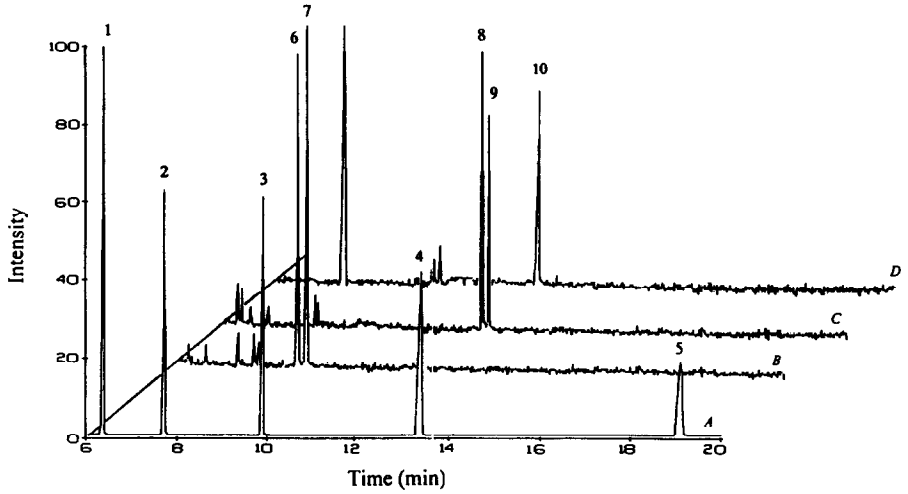

Fig. 1. Total ion chromatograms of the samples investigated. (A) Mixture of *n*-nonane (1), *n*-decane (2), *n*-undecane (3), *n*-dodecane (4) and *n*-tridecane (5); (B) mixture of *cis*- (6) and *trans*-diols (7); (C) mixture of *trans*- (8) and *cis*-bis-TMS (9) derivatives; (D) *trans*-(*tert.*-butyldimethylsilyl) ether (10) derivative.

for identification. Silyl derivatives were therefore prepared in a further attempt to apply them in identification studies [10–12]. The results of MS measurements of the trimethylsilyl and *tert.*-butyldimethylsilyl derivatives are given in Fig. 2. On the basis of these observations, the following main conclusions can be drawn: (i) both diols yield a bistrimethylsilyl derivative; (ii) there are no significant differences in the mass spectra of the trimethylsilyl derivatives at 70 eV (Fig. 3); and (iii) only one of the diol isomers reacts with MTBSTFA under the derivatization condition applied, the other isomer being unreactive (Fig. 1, total ion chromatogram D).

These data, in accordance with our earlier results of a comprehensive study of the derivatization of these isomeric diols [13], can be accounted for as follows. Silylation of diols is certainly a stepwise process. Reaction of sterically demanding silylating agents with these highly

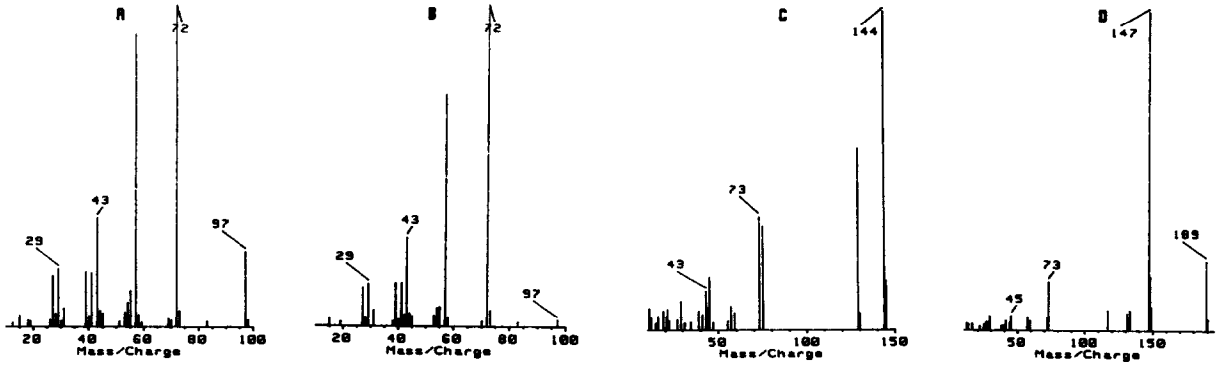

Fig. 2. Mass spectra of the compounds studied. (A) *trans*-2,2,4,4-Tetramethyl-1,3-cyclobutanediol (**1a**); (B) *cis*-2,2,4,4-tetramethyl-1,3-cyclobutanediol (**1b**); (C) *trans*-2,2,4,4-tetramethyl-cyclobutanediol bis-TMS ether (**2a**); (D) *trans*-2,2,4,4-tetramethylcyclobutane-1-*tert.*-butyldimethylsilyloxy-3-ol (**3a**).

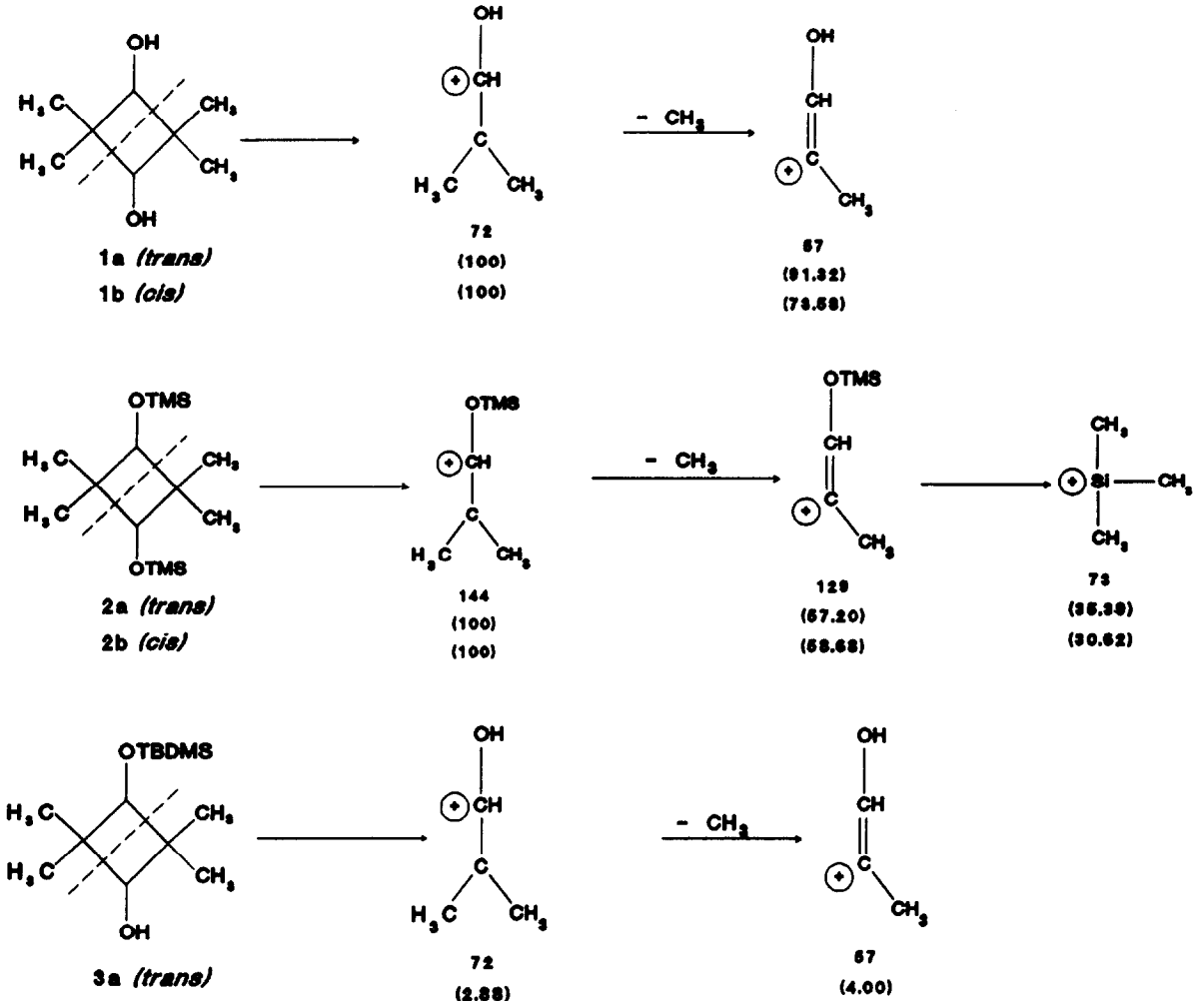

Fig. 3. Fragmentation patterns and the relative intensities of mass peaks of *trans*- (**1a**), and *cis*-2,2,4,4-tetramethyl-1,3-cyclobutanediol (**1b**), *trans*- (**2a**) and *cis*-2,2,4,4-tetramethyl-1,3-cyclobutanediol bis-TMS ether (**2b**) and *trans*-2,2,4,4-tetramethylcyclobutane-1-*tert*.-butyldimethylsilyloxy-3-ol (**3a**).

sterically hindered diols results in striking differences in reactivity. Simple reagents (acid halides, methyl iodide and reagents producing trimethylsilyl derivatives) react readily with both hydroxyl groups in each diol, yielding the corresponding bis derivatives. This does not occur, however, with hindered reagents, which result in severe steric interactions during the derivatization reaction. Neither of the two closely situated hydroxy groups in the *cis*-diol reacts with MTBSTFA, whereas the *trans* compound produces only the monosilylated derivative (Fig. 3). This interpretation was unequivocally confirmed by the attempted silylation of the authentic *cis*-diol sample, which was also unreactive under the reaction conditions employed.

In conclusion, it has been demonstrated that appropriate chromatographic conditions selected on the basis of chemical and steric characteristics permit the GC separation of stereoisomeric 2,2,4,4-tetramethyl-1,3-cyclobutanediols. Unequivocal identification of the individual isomers

was achieved with the utilization of reactivity differences in the silylation of the stereoisomeric diols with sterically demanding reagents.

4. Acknowledgement

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