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GAS CHROMATOGRAPHIC ENANTIOSEPARATION OF ALLENES

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ABSTRACT: Enantioselective gas chromatography with modified cyclodextrins as stationary phases is successfully used to separate chiral allenic hydrocarbons - including kinetically labile 1,2-cyclooctadiene - and 1-halo-1,2-butadienes.

INTRODUCTION

During the last years there has been a wide-spread interest in the study of reactions of substituted allenes and their use in the synthesis of complex molecules. An increasing number of naturally occuring allenes has been isolated and characterised[1,2]. Although some natural products have been known for a long time there are still stereochemical and synthetic problems left to verify the constitution and the configuration of the allenic moiety[3]. Methods for enantioselective formation of optically active natural products - for example allenic pheromones[4] or allenyl prostaglandines[5] - have been published, but the authors were unable to directly determine the success of chirality transfer. It has been common practice to report enantiomeric purities based on chiroptical measurements. Unfortunately the results are often ambiguous[6] due to the lack of precise data

for the pure enantiomers. N.m.r. methods are generally of more fundamental applicability, but reports of the application of chiral shift reagents in allenic chemistry are rare[7,8,9]. Enantioselective chromatography is an alternative to these techniques. Although unsaturated compounds with axial and planar chirality have recently been separated[10], only some "functionalized" allenes have been resolved by liquid chromatography with cellulose triacetate as stationary phase[11,12] and just one example by gas chromatography with a cyclodextrin derivative[13]. Therefore, we have synthesized racemic 1-halo-1,2-butadienes and some "unfunctionalized" allenic hydrocarbons and wish to report their gas chromatographic enantioseparation using heptakis(2,6-di-O-methyl-3-O-n-pentyl)-β-cyclodextrin (2,6-me-3-pe-β-CD)[14], a new type of cyclodextrin derivative, heptakis(6-O-methyl-2,3-di-O-n-pentyl)-β-cyclodextrin (6-me-2,3-pe-β-CD) and octakis(6-O-methyl-2,3-di-O-n-pentyl)-γ-cyclodextrin (6-me-2,3-pe-γ-CD)[15].

EXPERIMENTAL

1-Halo-1,2-butadienes

The propargylic rearrangement is perhaps the most important synthetic method to prepare allenes[16]. 1-Halo-1,2-butadienes can be obtained almost instantaneously on treatment of 3-butin-2-ol with aqueous HX in the presence of CuX (X = Cl, Br, I). A more selective approach involves the conversion into the corresponding tosylate in the first step (**fig. 1.**)[17].

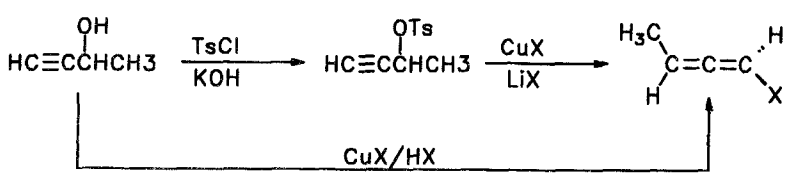

Fig. 1. Synthesis of 1-halo-1,2-butadienes

1-tert.Butyl-3-alkyl-allenes

The synthesis of this group of compounds is shown in **fig. 2.** After the tosylation of 3-propin-1-ol the keystep is again an anionic propargylic rearrangement, in this case with tert.butylmagnesiumchloride/CuBr. Tert.butylallene can easily be lithiated and directly converted with different electrophiles[18] to 1,3-disubstituted allenes. We used alkyl halides to obtain allenic hydrocarbons. Nearly no acetylenic impurities could be detected, because the lithiation of tert.butylallene proceeds regiospecifically.

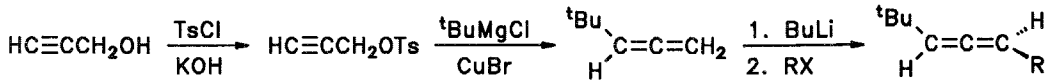

Fig. 2. Synthesis of 1-tert.butyl-3-alkyl-allenes

Synthesis of cyclic allenes

Cyclic allenes are conveniently synthesized via the carbenoid route developed by *Doering, Moore* and *Skattebøl* (**fig. 3.**)[19]. In the first step bromoform is added to a cooled slurry of the cyclic olefin, potassium tert.butylate and pentane. The cycloaddition products react with methyllithium to the desired allenes. The starting olefin for the next higher homologue can be prepared by reduction of the allene with sodium in liquid ammonia[20].

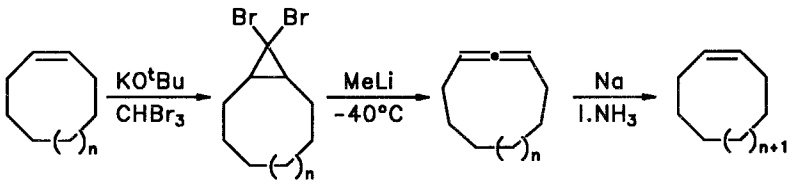

Fig. 3. Synthesis of 1,2-cyclononadiene and its homologues (n=1-8)

Gas chromatography

25 m Fused silica capillaries were coated by the static procedure[21] after leaching with diluted aqueous HCl (2%), treatment with Silanox[22] and high temperature silylation of the inner wall surface with diphenyltetramethyldisilazane (DPTMDS) according to *K. Grob*[23]. The synthesis of the cyclodextrin derivatives and its properties have been described previously[14,15]. A 1:1 mixture of modified cyclodextrin and the polysiloxane OV 1701 (w/w) has been used for coating.

Gas chromatography was performed with a Carlo Erba Model 2150 AC and a Carlo Erba HRGC 5300 Mega Series instrument equipped with split injector and flame ionisation detector. The gas chromatograms were recorded by a Merck-Hitachi Integrator D-2500. Hydrogen was used as carrier gas at 55 kPa.

RESULTS AND DISCUSSION

Haloallenes are versatile synthetic intermediates in organic chemistry. Their utility for the preparation of leukotrienes, allenic hydrocarbons, and naturally occuring allenediynes is well documented[24]. Although some methods for preparing optically active haloallenes are known, their optical purity has never been precisely determined. In **fig. 4.** the enantioseparation of 1-halo-1,2-butadienes is shown. Excellent separations were achieved on a 25m fused silica capillary column coated with 6-me-2,3-pe-β-CD.

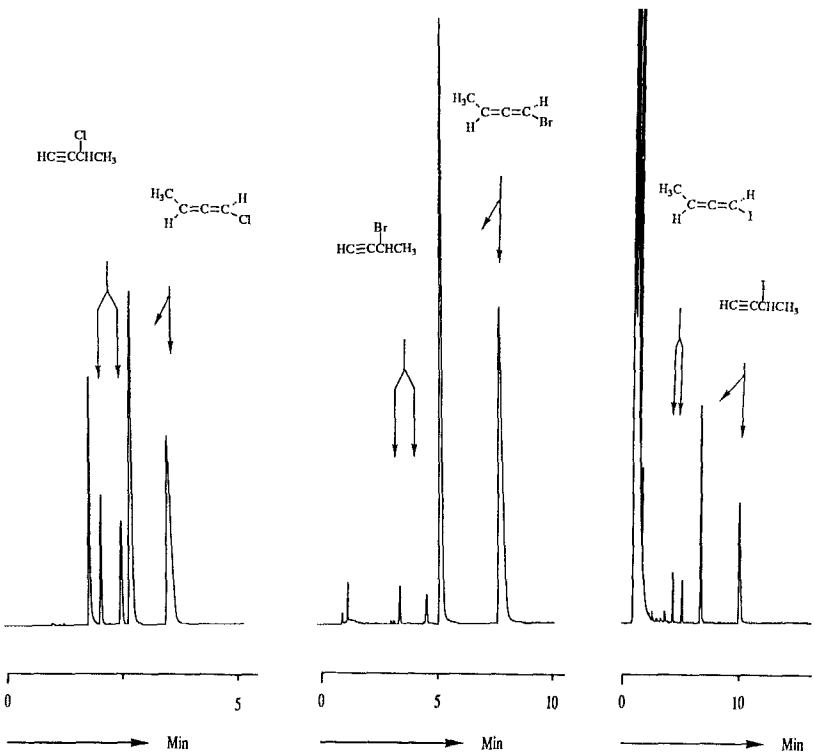

Fig. 4. Separation of 1-halo-1,2-butadienes on a 25 m fused silica capillary column coated with 6-me-2,3-pe-β-CD: carrier gas, hydrogen, 55 kPa.
left: 1-Chloro-1,2-butadiene at 30°C, headspace injection
center: 1-Bromo-1,2-butadiene at 35°C, headspace injection
right: 1-Iodo-1,2-butadiene at 45°C
(The allene/alkyne assignment was confirmed by n.m.r. analysis)

"Unfunctionalized" chiral allenic hydrocarbons are not only interesting natural target molecules. The stereochemistry of the formation of the allenic moiety and the various reactions are of current interest. Intensive investigations of the stereochemical features of (2+2) cycloaddition reactions of optically active and racemic allenes are reported (for example[25]). For mechanistic studies an analytical tool to determine the enantiomeric excess of the chiral allenes would be necessary. We synthesized 1-tert.butyl-3-alkyl-allenes - where alkyl is ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, isopentyl, cyclopentyl, n-hexyl, n-heptyl and n-octyl - as model compounds for enantioselective gas chromatography. We successfully separated all compounds on different chiral stationary phases. Good to excellent results can especially be observed with 25 m fused silica columns coated with 2,6-me-3-pe-β-CD and 6-me-2,3-pe-γ-CD (**fig. 5.**).

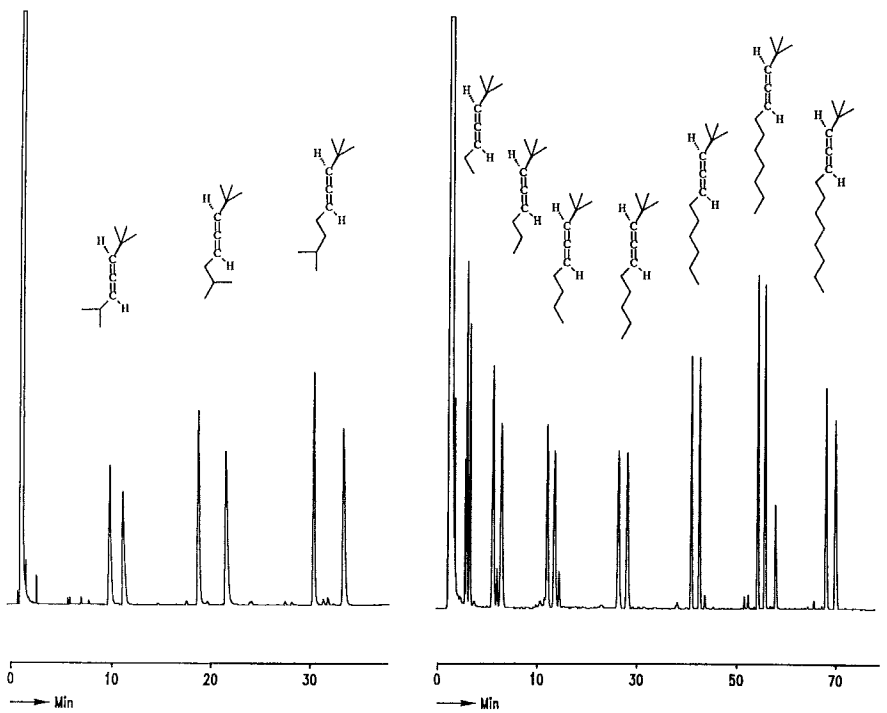

Fig. 5. Right: Separation of enantiomers of 1-tert.butyl-3-ethyl-allene, 1-tert.butyl-3-n-propyl-allene, 1-tert.butyl-3-n-butyl-allene, 1-tert.butyl-3-n-pentyl-allene, 1-tert.butyl-3-n-hexyl-allene, 1-tert.butyl-3-n-heptyl-allene and 1-tert.butyl-3-n-octyl-allene on a fused silica capillary column coated with 2,6-me-3-pe-β-CD: Carrier gas, hydrogen, 55 kPa. Temperature programming: After 20 minutes at 60°C 1°C/min up to 100°C.

Left: Separation of enantiomers of 1-tert.butyl-3-isopropyl-allene, 1-tert.butyl-3-isobutyl-allene and 1-tert.butyl-3-isopentyl-allene on a fused silica capillary column coated with 6-me-2,3-pe-γ-CD: Carrier gas, hydrogen, 55 kPa. Temperature programming: After 10 minutes at 30°C 1°C/min.

Asymmetric synthesis and the determination of optical purity of cyclic allenes have been investigated for a long time[26,27,28]. Today mechanistic aspects are systematically studied. Above all thermal[29] and photochemical[30] reactions are described. No elegant method to measure the optical purity has yet been reported. **Fig. 6.** shows the separation of the enantiomers of 1,2-cyclononadiene and the higher homologues up to 1,2-cyclohexadecadiene. The best results have been achieved with 2,6-me-3-pe-β-CD as stationary phase.

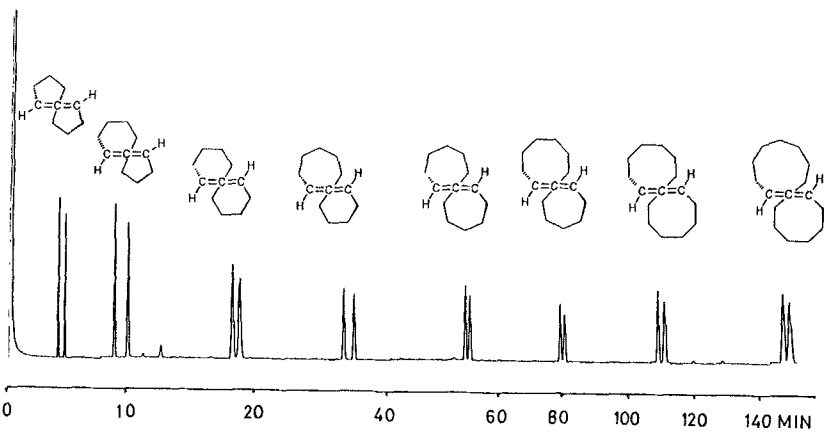

Fig. 6. Separation of 1,2-cyclononadiene and its homologues up to 1,2-cyclohexadecadiene on a fused silica capillary column coated with 2,6-me-3-pe-β-CD: Carrier gas, hydrogen, 55 kPa. Temperature programming: After 30 minutes at 95°C, 1°C/min up to 110°C, 35 minutes isothermal, then 1°C/min to 120°C and after additonal 35 minutes 1°C/min to 125°C.

Strained cyclic cumulenes have been a longstanding challenge to chemists[31]. Whereas 1,2-cyclononadiene is stable at room temperature, the smaller cycloallenes are known to be of limited stability. Due to the ring strain they have a tendency to dimerisation. To date, the only isolable 1,2-cyclooctadiene is the 1-tert.butyl derivative. It is remarkable that we have been able to resolve unsubstituted 1,2-cyclooctadiene (**fig. 7.**) and to investigate the dimerisation kinetics. For the first time the chirality of this compound has been formally proved. The 1-methyl, 1-ethyl and 1-isopropyl derivatives of 1,2-cyclooctadiene enjoy an increasing kinetic stability, but do all dimerize at ambient temperatures. Further studies on mechanistic aspects of the dimerisation of kinetically labile cycloallenes are in progress .

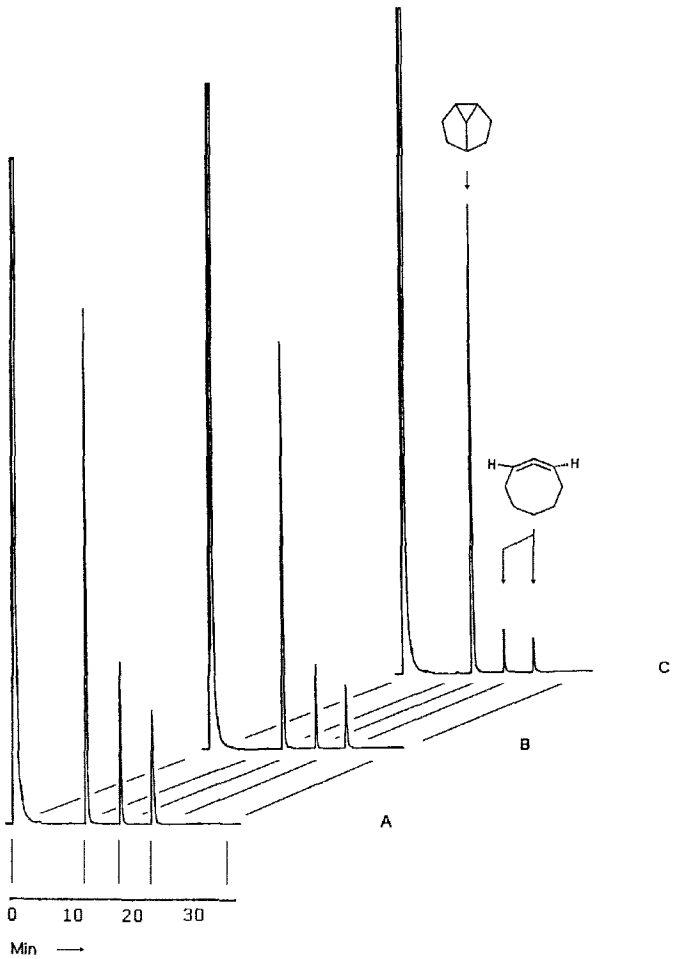

Fig. 7. Separation of 1,2-cyclooctadiene (isothermal at 40°C) on a 25 m fused silica capillary column coated with 6-me-2,3-pe-β-CD:carrier gas, hydrogen, 55 kPa.
A: Directly after quenching the reaction mixture (see **fig. 3.**)
B: After one hour C: After five hours

Table 1. Separation Factors of Allenic Coumpounds at Different Stationary Phases

Stationary phase	Separated compound	T in [K]	α-value	Retention time of the first eluted enantiomer in [min]
6-me-2,3-pe-β-CD	1,2-cyclononadiene	323	1.198	11.55
	1,2-cyclodecadiene	333	1.127	15.32
	1,2-cycloundecadiene	323	1.030	68.14
	1,2-cyclododecadiene	333	1.072	66.61
	1,2-cyclotridecadiene	333	1.025	157.12
	1,2-cyclotetradecadiene	353	1.023	77.57
	1,2-cyclooctadiene	338	1.161	8.04
	1-methyl-1,2-cyclooctadiene	313	1.392	14.22
	1-ethyl-1,2-cyclooctadiene	323	1.368	27.67
	1-isopropyl-1,2-cyclooctadiene	338	1.148	14.82
	1-chloro-1,2-butadiene	313	1.385	1.04
	1-bromo-1,2-butadiene	313	1.524	2.69
	1-iodo-1,2-butadiene	318	1.233	3.31
2,6-me-3-pe-β-CD	1-tert.butyl-1,2-cyclooctadiene	353	1.411	1748
	1-tert.butyl-3-ethyl-allene	333	1.124	2.01
	1-tert.butyl-3-propyl-allene	333	1.209	4.30
	1-tert.butyl-3-n-butyl-allene	333	1.153	10.84
6-me-2,3-pe-γ-CD	1-tert.butyl-3-isopropyl-allene	303	1.147	9.75
	1-tert.butyl-3-isobutyl-allene	313	1,183	11.29
	1-tert.butyl-3-isopentyl-allene	323	1.129	14.07
	1-tert.butyl-3-cyclopentyl-allene	323	1.070	20.88
	1-tert.butyl-3-n-pentyl-allene	323	1.138	20.43
	1-tert.butyl-3-n-hexyl-allene	338	1.050	18.73
	1-tert.butyl-3-n-heptyl-allene	343	1.039	30.37
	1-tert.butyl-3-n-octyl-allene	348	1.034	48.18
	ethyl-3,4-hexadienoate	323	1.087	24.92
2,6-me-3-pe-γ-CD	1,2-cyclopentadecadiene	388	1.029	56.36
	1,2-cyclohexadecadiene	398	1.030	65.58

CONCLUSION

Gas chromatographic separations of enantiomers of "unfunctionalized" allenes have not previously been reported. This universal method for the determination of enantiomeric purity may be applied as a versatile tool in allenic chemistry. Large separation factors (α-values) enable precise answers to stereochemical features (**table 1**). Noteworthy are the studies on configurationally labile compounds.

Acknowledgement

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