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Note

Direct gas chromatographic resolution of enantiomers on optically active mesophases

I. Smectic carbonyl-bis-(D-leucine isopropyl ester)

CHARLES H. LOCHMÜLLER* and REX W. SOUTER

P. M. Gross Chemical Laboratory, Duke University, Durham, N.C. 27706 (U.S.A.)

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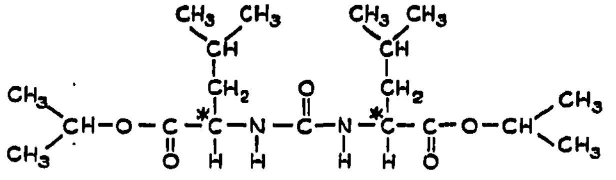
Two general classes of optically active stationary phases have been extensively studied as agents for the direct resolution of enantiomers by gas chromatography, *viz.* dipeptide amido-esters[1,2] and carbonyl-bis(amino acid esters)[3–5]. In many cases these structural types have been shown to be active liquid stationary phases for the direct resolution of chiral amides and amino acid esters[6–8]. In addition, the solid form of carbonyl-bis(L-valine isopropyl ester) was shown to give enhanced resolution factors for selected amides compared to the liquid form[5].

While it has been suggested that optically active liquid crystals should be capable of resolution of enantiomers if used as stationary phases for gas chromatography[9,10], the successful use of a chiral mesophase for this purpose has never been reported. Liquid crystals have been studied extensively as stationary phases for the resolution of positional isomers[11]. In the case of smectic-type liquid crystals, the high viscosity and highly-ordered structure significantly affects the selectivity and the retention[10,12].

The authors wish to report here the first enantiomer separations on an optically active mesophase, as such. Carbonyl-bis(D-leucine isopropyl ester) contains two asymmetric centers of the same optical configuration and has the following structure:



Baseline or near-baseline separations were achieved with this mesophase for a variety of racemic mixtures.

MATERIALS AND METHODS

Separations were effected using a 6 ft. × $^1/_8$ in. glass column packed with acid-washed, dimethylchlorosilanized (AW-DMCS) Chromosorb G (100–120 mesh) which

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* To whom correspondence should be addressed.

was coated 5.00% by weight with the optically active phase. Racemic derivatives (solutes) were N-perfluoroacyl-2-aminoethyl benzenes: trifluoroacetyl (TFA), pentafluoropropionyl (PFP), and heptafluorobutyryl (HFB). The stationary phase and the solutes were prepared as described earlier[3,13]. Calorimetric data for the carbonyl-bis(D-leucine isopropyl ester) were determined by use of a Perkin-Elmer DSC-1 differential scanning calorimeter.

RESULTS AND DISCUSSION

Calorimetric data are presented for the stationary phase in Table I and were determined by using indium metal as the standard. Carbonyl-bis(D-leucine isopropyl ester) exists as a mesophase over a 55° temperature range until it turns to isotropic liquid at 110°. For a particular mesomorphic compound, if the percentage of the total entropy gain (over all transitions) is high for the transition to isotropic liquid, then the mesophase preceding that transition is very probably smectic. Such is the case for carbonyl-bis(D-leucine isopropyl ester) indicating that the mesophase existing from 55°–110° is smectic[14].

Good separations of a variety of solutes were observed over the whole mesophase temperature range in the gas chromatographic experiments, and typical results at one temperature are presented in Table II. Values of α were calculated from the

TABLE I

THERMAL TRANSITION PROPERTIES OF CARBONYL-BIS(D-LEUCINE ISOPROPYL ESTER)

Transition temperature (°K)*	*Transition heat Q (kcal/mole)*	*Transition entropy $\Delta S = Q/T$ (cal/mole °K)*	*% total ΔS for 383°K transition*
$C \xrightarrow{328°} S$	5.38	16.4	
$S \xrightarrow{383°} I$	0.54	1.40	7.9

* C = crystalline, S = smectic, I = isotropic.

TABLE II

COMPARISON OF GAS CHROMATOGRAPHIC DATA FOR DIFFERENT N-PERFLUOROACYL 2-AMINOETHYLBENZENES

Conditions: 6 ft. × 1/8 in. glass column; 5.00% carbonyl-bis(D-leucine isopropyl ester) by weight on AW-DMCS Chromosorb G; helium carrier gas pressure, 22.95 p.s.i.; column temperature, 88.51°C (361.67°K).

Compound	α	$\Delta(\Delta G^0)$ *(cal/mole)*
N-PFP 2-aminoethylbenzene	1.658	−363
N-HFB 2-aminoethylbenzene	1.399	−241
N-TFA 2-aminoethylbenzene	1.119	− 81

relation $\alpha = (t_{r2} - t_m)/t_{r1} - t_m)$ where t_{r2} and t_{r1} are the retention times of the most-retained and the least-retained species, respectively, and t_m is the retention time of a species known to be essentially unretained. Methane was chosen as the unretained species for these experiments. The difference in standard free energy of association of the optical antipodes with the chiral stationary phase was calculated from $\Delta(\Delta G^0) = -RT \ln\alpha$. The longest-retained species on the D stationary phase were the L(−) solutes. In terms of absolute configuration, both asymmetric centers of the stationary phase are of the R configuration, while the D(+)-2-aminoethylbenzenes have an absolute S configuration.

The reported chromatographic values are quite large indicating a significant degree of interaction between solutes and the mesophase. High viscosity (which would affect diffusion) and a very high degree of order (approaching that of the crystalline form) of the smectic mesophase may play a role in determining selectivity towards the solutes[10,12]. The separations were best for the most highly fluorinated (N-PFP and N-HFB), most volatile solutes.

Enantiomer separations on optically active liquid stationary phases are believed to occur via formation of transient diastereomeric hydrogen-bonded association complexes between the stationary phase and the solute molecules. Selectivity is best when hydrogen bonds form in close proximity to the chiral centers. For carbonyl-bis(amino acid esters), the ester carbonyls have been shown to be the important sites of hydrogen bonding which occurs to the amido protons of the solutes[3].

Studies of enhanced separations on optically active mesophases such as reported here, and of separations on such compounds as isotropic liquids, can provide clues to the mechanisms of asymmetric solute–solvent interactions, and can provide a basis for structural design of optically active stationary phases useful for fast, efficient, preparative-scale separations of particular enantiomeric species.

The effects on selectivity of substituent changes and of length-to-width ratio changes in chiral mesophases of chromatographic importance are topics under active investigation at the present time.

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