

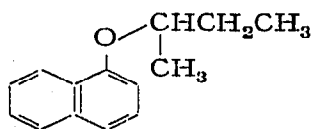
OPTICAL RESOLUTION BY MOLECULAR COMPLEXATION CHROMATOGRAPHY

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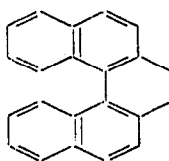
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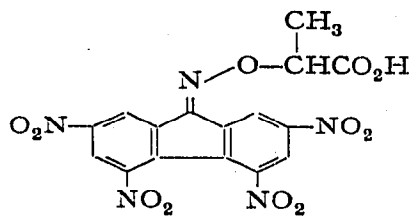
In a previous paper¹ we described the use of columns of silicic acid impregnated with picric acid or 2,4,7-trinitrofluorenone for adsorption chromatography of mixtures of aromatic hydrocarbons. It was proposed that the process of adsorption was identifiable with molecular compound formation between the aromatic hydrocarbon and the polynitro complexing agent held monomolecularly on the surface of the silicic acid. We now report the successful extension of such method to the optical resolution of two racemic compounds, 1-naphthyl 2-butyl ether (I) and 3,4,5,6-dibenzo-9,10-dihydrophenanthrene (II), by use of the optically active complexing agent (+)- or (—)- α -(2,4,5,7-tetranitro-9-fluorenylideneaminoxy)-propionic acid (III) as impregnant.



(I)



(II)



(III)

Synthesis of (III) and its use in optical resolution of (I) and other racemates by means of fractional crystallization or precipitation of molecular complexes from solution has been effected by NEWMAN AND LUTZ² and NEWMAN AND LEDNICER³. Optically active (II) has been previously obtained only by chemical transformation of resolved 1,1'-binaphthyl-2,2'-dicarboxylic acid⁴. The use of columns of alumina impregnated with various naturally occurring optically active compounds for accomplishing partial resolution of racemates has been described recently by KARAGOUNIS, CHARBONNIER AND FLÖSS⁵, who have also presented a bibliography on optical resolution by means of chromatography on pure optically active absorbents.

EXPERIMENTAL

Preparation of impregnated adsorbent

To a column (4.5 × 41 cm) of Mallinckrodt reagent-grade 100-mesh silicic acid (packed dry in an all-glass tube, shielded from light by means of aluminum foil

wrapping, and under the vacuum provided by a water aspirator) was added, in succession, 100 ml of reagent-grade chloroform (prewash), a solution of 31.4 g of (—)-III², m.p. 151.5–155°, $[\alpha]_D^{24} - 82.5^\circ$ (*c* 0.813, dioxane), in 250 ml of chloroform, 50 ml of chloroform, and 1 l of Mallinckrodt reagent-grade 30–60° petroleum ether. Thereafter, air was sucked through the column for 12 h. Small portions at the top and bottom of the column were dug out and discarded. The main part of the impregnated silicic acid was dried further in a vacuum desiccator for 24 h, pulverized by means of a mortar and pestle, and stored in a brown bottle, yield 354 g of impregnated adsorbent containing 8.9% (by weight) of (—)-III ($2.1 \cdot 10^{-4}$ moles of III per g). Silicic acid impregnated with (+)-III was prepared in the same manner.

Chromatography

Using the suction of a water aspirator a 1.9-cm (diameter) tube was packed dry with successive layers of 1–2 cm of plain silicic acid, 40 cm (75–85 g) of impregnated silicic acid, and 1 cm of purified sand. The column was prewashed with 100–200 ml of petroleum ether. A solution of the racemic or partially resolved compound in the minimum volume of petroleum ether was added to the column (still under suction) and development and elution were conducted with the same solvent. Development of the chromatogram was readily observed by the formation of a dark red to brown color (molecular compound) which gradually expanded downward on the column. As soon as this color reached the bottom of the column, samples of effluent were collected arbitrarily (3–8 fractions) and evaporated to dryness in a stream of nitrogen. Each resultant residue was redissolved in approximately 5 ml of a suitable solvent (petroleum ether for I, benzene for II), transferred to a 2-dm polarimeter tube, diluted with the same solvent to fill the tube, measured polarimetrically, transferred quantitatively to a tared flask, re-evaporated, dried *in vacuo* for 1–2 h, and weighed. By selective recombination and re-chromatography of effluent fractions, samples of (I) and (II) in various degrees of optical purity were obtained; maximum $[\alpha]_D^{24}$ values found, $+ 7^\circ$ (*c* 0.143, petroleum ether) for (I), $- 1300^\circ$ (*c* 0.014, benzene) for (II); reported $[\alpha]_D^{29} - 7.4^\circ$ (*c* 2.03, ethyl acetate)² for (I), $[\alpha]_{5791}^{22} - 1307^\circ$ (*c* 0.525, benzene)⁴ for (II). Recovery of at least 90% of the adsorbate charged to the column was usually accomplished in these runs. Illustrative data are presented in Table I. Also in an exploratory run using (+)-III and racemic methyl α -(1-anthryl) propionate² (IV), it was found that (—)-IV was eluted first.

In a test run 18.4 mg of (II), $[\alpha]_D^{23} + 584^\circ$, was passed through a 0.9×23 -cm column of plain silicic acid. The total collected effluent contained 16.0 mg of residue, $[\alpha]_D^{24} + 574^\circ$. Analogous results were obtained with a column of alumina.

Optical resolution by crystallization

Excess hydrocarbon was allowed to crystallize from a solution containing 200 mg of (±)-II and 150 mg (*ca.* 0.5 molar equivalent) of (+)-III in 5 ml of benzene. The crystalline precipitate was collected by filtration, washed with 2 drops of benzene,

TABLE I
SELECTED DATA ON OPTICAL RESOLUTION BY MOLECULAR COMPLEXATION CHROMATOGRAPHY

Run	Adsorbate used		Adsorbate solution ml	Optical sign of impregnant	Time of run h	No.*	Effluent fraction				
	formula	mg					$[\alpha]_D^{24}$ (degrees)	ml	mg of residue	observed** α (degrees)	$[\alpha]_D^{24}$ (degrees)
A	(I)	2500	15	—	27	1	40	1439	-0.06	-	0.3
						2	100	570	+0.02	+	0.2
						3	250	378	+0.03	+	0.5
B	(I)	150	5	—	23	1	40	41	-0.02	-	3
						3	50	34	+0.02	+	4
						4	350	18	+0.02	+	7
						1	250	131	+0.54	+	26
C	(II)	1000	2000	+	16	3	450	197	0.00	-	0
						6	250	87	-0.64	-	46
						1	20	2.2	+0.08	+	230
D	(II)	87	110	+	4.5	2	30	8.1	+0.26	+	200
						4	100	38.9	-0.97	-	150
						1	50	11.1	-0.73	-	40
E	(II)	131	250	—	38.5	2	35	13.1	-0.35	-	170
						6	80	17.2	+0.78	+	280
						7	100	7.4	+0.40	+	340
						1	50	1.2	-0.22	-	1100
F	(II)	37.0	15	—	56.1	2	50	3.0	-0.55	-	1100
						3	50	3.5	-0.59	-	1000
						4	75	5.3	-0.71	-	830
						7	300	5.5	0.00	-	0
G	(II)	12.8	10	—	25.5	1	200	1.8	-0.38	-	1300
						2	200	6.2	-1.16	-	1200
						3	450	3.2	-0.37	-	720

* Fractions are numbered consecutively in order of appearance.

** For a solution of the total residue.

and dissolved in 10 ml of benzene. The benzene solutions were washed with excess saturated sodium bicarbonate and measured polarimetrically in the aforementioned manner. From the precipitated fraction was obtained 20.1 mg of II, $[\alpha]_D^{24} + 568^\circ$; from the filtrate, 172.7 mg of II, $[\alpha]_D^{24} - 64.1^\circ$.

DISCUSSION

During each chromatographic run with impregnated silicic acid (*cf.* Table I) the effluent was observed either to change sign of optical rotation or (where such change of sign did not occur) to decrease in absolute magnitude. It is thus clear that optical resolution was effected by the column. However, observed polarimeter readings were too small in the case of (I) to ascertain accurately the optical purities of the samples. For (II), on the other hand, optical purity of at least 80% would appear to have been achieved in some samples. There seems to be little reason to doubt that extension of our procedure could give considerably larger samples of complete optical purity.

The optical sign of the impregnant determines which enantiomorph is retained more selectively on the column. Thus for (II), when (+)-III was used on the column (—)-II was more strongly retained; while when (—)-III was used, (+)-II was more strongly retained. In all runs with (I), where only (—)-III was used, excess (—)-enantiomorph appeared in the first portions of effluent. Combined with the fact that silicic acid by itself causes neither further optical resolution nor racemization of partially resolved (II), these data confirm the presumption that it is the optically active impregnant (and not the silicic acid) which is responsible for the observed optical resolution. Moreover, the intense colors produced on the columns plus the chemical natures of (I)–(IV) are strong indications that this resolution is effected through *bona fide* molecular compound formation on the surface of the silicic acid, from which (III) is not removed by washing with petroleum ether. It was pointed out previously¹ that adsorbability on impregnated silicic acid is independent of relative values of melting point for the adsorbate components or the molecular compounds formed. It has also been postulated⁶ that neither relative melting point nor relative solubility is pertinent to adsorption on alumina. Likewise, in the present studies the enantiomorphs are separated despite the fact that their melting points and solubilities would be identical. Moreover, since the complexing agent does not move on the column (*i.e.* does not enter the mobile phase), the relative solubilities of the molecular compounds formed *in situ* cannot be pertinent to the chromatographic process. Thus in glacial acetic acid (—)-III·(+)-I is more soluble than (—)-III·(—)-I, and (+)-III·(—)-IV is more soluble than (+)-III·(+)-IV². Though comparison is confused by the fact that different solvents were used in the resolution by chromatography and by crystallization, in the case of I the enantiomorph which forms the less soluble complex is eluted first and in the case of IV that which forms the less soluble complex is eluted last.

Examination of Table I (runs C, E and F) indicates that the highest efficiency of resolution is gained by using small weights of adsorbate (and/or small volumes of

adsorbate solution) and slow flow rates through the column. These are conditions conducive to fractionation *via* virtual equilibrium processes such as

and



where relative adsorbabilities of the enantiomorphs are determined fundamentally by the relative thermodynamic stabilities of their adsorbed molecular compounds. Since our total column contains $1.7 \cdot 10^{-2}$ moles of impregnant and the percentage of these molecules complexed at any one time may be small, it follows that our method can scarcely be expected to compete with optical resolution by fractional precipitation methods on a macro-preparative scale. On the other hand our procedure would appear to be feasible for (a) the resolution of relatively small amounts of material, (b) the determination of relative stabilities of the diastereoisomeric molecular compounds, and (c) possibly, in the last analysis, assignment of absolute configuration(s) to the impregnant or the adsorbate enantiomorphs used.

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SUMMARY

Partial optical resolutions of three racemic aromatic compounds have been achieved by chromatography on silicic acid impregnated with optically active α -(2,4,5,7-tetranitro-9-fluorenylideneaminoxy)-propionic acid using petroleum ether as solvent. The success of this method is ascribed to the occurrence of molecular complexation (between the widely dispersed molecules of the impregnant and the aromatic compound) on the surface of the silicic acid support.

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