Studies on the Origin of Asymmetry. Part 1.[1] Optically Active Crystals as Selective Adsorbents

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Solid samples (powders and crystals) of optically active sodium chlorate, bromate, periodate trihydrate, uranyl acetate, of benzil, and of nickel sulphate hexahydrate have been used in attempts to secure selective absorption or reaction with several racemic compounds, such as tris(pentane-2,4-dionato)cobalt(III) and α-lipoic acid. No genuine optical rotation has been observed. The origin of the spurious rotations reported in the literature in such systems (and readily reproduced here) is discussed.

RESOLUTION by selective adsorption of enantiomers on to an optically active crystal is often thought to be relevant in discussion of the origin of molecular asymmetry in living systems. Bonner and his co-workers [2-4] have recently shown, using labelled amino-acids and their derivatives, that there is a perceptible difference in absorption of the enantiomers from organic solvents by optically active quartz.

The possibility of such resolutions (checked by polarimetry) on inorganic crystals is well known, but controversial. In fact, although some successful resolutions were claimed [5-10] (based on observations of optical rotations) using optically active crystals of quartz or sodium chlorate as absorbents, all such results were denied by Amariglio *et al.*[11,12] after they had tried some similar experiments under quite carefully considered and controlled conditions.†

Quartz and sodium chlorate belong [14] to that class of compounds which exhibit optical activity in the crystalline state only. The molecules are arranged in a helical way in the crystal lattice and are related by a screw axis, which can be either right or left handed. It is their helical symmetry which gives the crystal its rotatory power. We sought some clear polarimetric evidence for stereospecific interactions of such dissymmetric crystals with enantiomeric substances.

Chiral single crystals of sodium chlorate, sodium bromate, sodium periodate trihydrate, nickel(II) sulphate hexahydrate, sodium uranyl acetate, and benzil were used as absorbents in attempts at solid-state resolution of such racemic and resolvable systems as chromium(III) and cobalt(III) tris(pentane-2,4-dionate), α-lipoic acid, penicillamine, and tartaric acid.‡ Some of these crystals were also used for attempted stereospecific reactions on their surfaces.

RESULTS

Crystal Growth.—Chiral single crystals of sodium chlorate, sodium bromate, sodium periodate trihydrate, nickel sulphate hexahydrate, sodium uranyl triacetate, and benzil were grown from their saturated solutions using techniques described in detail in the Experimental section.

TABLE 1

Chirality of Na[ClO$_3$] crystals grown from saturated aqueous solutions

					Seeded solutions							
	Unseeded solutions				D Seeded solutions				L Seeded solutions			
	D crystals		L crystals		D crystals		L crystals		D crystals		L crystals	
Experiment no.	No. of crystals grown	% of the total	No. of crystals grown	% of the total	No. of crystals grown	% of the total	No. of crystals grown	% of the total	No. of crystals grown	% of the total	No. of crystals grown	% of the total
1	1	25	3	75	234	87	34	13	80	13	550	87
2	6	43	8	57	404	63	237	37	220	36	395	64
3	50	29	125	71	18	90	2	10	560	52	520	48
4	122	88	17	12	213	56	170	44	2	40	3	60
5	11	42	15	58	63	53	55	47				
6	13	42	18	58	20	91	2	9				
7	3	60	2	40	11	33	22	67				
8	70	89	18	21								
9	5	63	3	37								
10	2	67	1	33								
11	80	84	15	16								
12	8	67	4	33								
13	0	0	3	100								
14	40	43	54	57								
15	50	83	10	17								
16	37	57	28	43								
17	25	63	15	37								
18	23	56	18	44								
19	115	59	80	41								
20	65	57	50	43								
Total	727	60	487	40	965	65	522	35	862	37	1 468	63

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† There is no doubt that crystals of enantiomeric molecules (*e.g.* lactose [13]) do manifest such selective interactions.

‡ α-Lipoic acid = 1,2-dithiolan-3-valeric acid; penicillamine = 3-mercaptovaline.

D and L crystals of sodium chlorate and sodium bromate could easily be separated using an appropriate polariscope. In Tables 1 ($Na[ClO_3]$) and 2 ($Na[BrO_3]$) the numbers of crystals of each chirality obtained from seeded and non-seeded solutions are compared. It again appears that seeding the solutions of $Na[ClO_3]$ with crystals of a particular chirality tends to induce the preferential growth of crystals of the same handedness. However, seeding is not a necessary condition for the preferential growth of crystals of one hand, since some solutions gave 100% of crystals with a single chirality without being seeded.* Although the limited number of results available is not enough to infer the expected behaviour of a large population, it is suggested that spontaneous generation of chirality is possible in localized elements of a given population.

TABLE 2

Chirality of $Na[BrO_3]$ crystals grown from aqueous saturated solutions in non-seeded experiments *

Experiment no.	D crystals: No. of crystals grown	D crystals: % of the total	L crystals: No of crystals grown	L crystals: % of the total
1	90	78	25	22
2	3	~1	>400	~99
3	106	89	13	11
4	17	63	10	37
5	0	0	75	100
6	1	13	7	87
7	2	67	1	33
8	45	21	170	79
9	100	38	160	62
10	36	47	40	53
Total	400	31	901	69

* In one experiment using D seeds, 60 D and 40 L crystals were obtained.

Optically Active Crystals as Adsorbents.—In all the reported experiments which claimed effective resolution with quartz or sodium chlorate crystals [5-10] a solution of the racemic compound was shaken with a certain amount of the powdered optically active solid for some time, then the solution was separated from the solid and its rotation read. The experiments in which this method was used are in Supplementary Publication No. SUP 22565 (5 pp.).† Amariglio *et al.*[12] tried to resolve a few compounds in a column packed with optically active quartz powder, with no success. This method was also used here for a few systems which appear in SUP 22565. The French authors attributed the rotations reported in earlier literature either to the presence of finely divided particles in the solution, or to very intense absorptions by the liquid. In trying to eliminate these effects, solutions were filtered and centrifuged before reading rotations. We also avoided concentrated solutions. Rotation values were sometimes obtained, but they were not reproducible and usually disappeared after filtering the solution more carefully. Even in passing solvent alone through the column, finite rotations were sometimes observed, particularly in the case of benzene.‡ For this, it sufficed to have some humidity at the polarimeter cell walls to get some reasonably high readings. However, no clear and reproducible rotations could be seen.

Reactions with Optically Active Crystals.—Some reactions on solid surfaces have been described as being stereospecific in the sense that a reaction in a crystal with chiral structure can lead to chiral product molecules, even if the monomeric reactants are achiral. Penzien and Schmidt [15] exposed an optically active single crystal of 4,4′-dimethylchalcone to bromine vapour and got an optically active dibromo-derivative, the optical yield being *ca.* 6%. Miller *et al.*[16] have also succeeded in observing such effects in a variety of systems. Some reactions with optically active crystals were tried in the present work, in an attempt to see a preferential interaction with one of the enantiomers of a racemic mixture.

2,2′-Bipyridyl co-ordinates to nickel(II) ions, giving the tris(2,2′-bipyridyl)nickel(II) ion, which gives a rose-violet solution in water, methanol, ethanol, or acetone. So the reaction of optically active crystals of nickel(II) sulphate hexahydrate with 2,2′-bipyridyl was studied with the ligand dissolved in different solvents, and at different temperatures, in an attempt to see one enantiomer of $[Ni(bipy)_3]^{2+}$ appearing faster than the other. No rotation was found. The conditions and results are summarized in SUP 22565.

Benzil and 1,2-diaminopropane react in ethanol, giving 2,3-dihydro-2-methyl-5,6-diphenylpyrazine in good yield. Reactions in solution with DL- and with L-1,2-diaminopropane gave the DL and L product respectively. This reaction was modified as follows. DL-1,2-Diaminopropane vapour was passed through optically active benzil crystals and the unchanged diamine was collected. If one enantiomer of the diamine reacted faster we should be able to observe optical rotation in the collected unchanged diamine, and in the solid product of reaction there will be some optically active 2,3-dihydro-2-methyl-5,6-diphenylpyrazine. Reactions were carried on at low pressure and with solid benzil maintained at temperatures between 75 and 85 °C, with no success.

Some preliminary experiments with crystalline sodium periodate trihydrate were essayed in attempts to oxidize DL-serine and DL-butane-2,3-diol stereospecifically, but no evidence was seen for this, although oxidation of serine by periodic acid in solution is said [17] to take place rapidly (1 min) and with good yield at 20 °C and pH 7.5:

$$CH_2OH{\cdot}CH(NH_2){\cdot}CO_2H + 3HIO_4 \xrightarrow{Na[HCO_3]} 3\,HIO_3 + HCHO + CHO{\cdot}CO_2H$$

DISCUSSION

The few apparently positive results which appeared in our attempts to use optically active crystals as resolving agents are genuine. They are due wholly to small particles in the solution, and, in a few cases, to very concentrated solutions. To see what kind of mistaken information could appear through those spurious effects (*i.e.* how big and reproducible can totally sham rotations be?) values were registered for carefully prepared, genuine, optically active solutions (Table 3) and for some solutions, deliberately containing solid particles, Table 4, and for concentrated coloured solutions. Curiously, quite reproducible results are found in each set of observations of the effect of solid particles, but no consistent values are observed for the more concentrated

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* Although, in a sense, the first crystal from a homogeneous solution is a seed for the next one.

† For details see Notices to Authors No. 7, *J.C.S. Dalton*, 1978, Index issue.

‡ An observation strikingly reminiscent of an early claim (later refuted) that γ-irradiation of benzene gives an optically active liquid!

TABLE 3

Optical rotations of malic acid solutions measured by a NPL type 243 Automatic Polarimeter (precision and accuracy of results)

Experiment	θ_c/°C	Concentration [a] of malic acid solution mol dm^{-3}	t [b]/h	No. of measurements [c]	Best estimate (× 10⁴) of true value [d]	of precision [e]	of standard error [f]
1A	35	0.41	0	90	−147.9	0.75	0.08
B	35	0.20	0	70	−75.5	1.5	0.20
C	35	0.086	0	103	−42.7	1.5	0.15
2A	28	0.40	0	66	−147.5	1.3	0.16
B	28.5	0.40	1	52	−147.5	1.5	0.22
C	28.5	0.40	2.5	26	−145.3	1.0	0.20
D	28.5	0.40	4	26	−143.5	1.0	0.20
E	28.5	0.40	5	26	−143.1	1.0	0.20
F	28.5	0.40	8	26	−141.0	1.0	0.20
3A	28.5	0.24	0	72	−86.6	3.4	0.40
B	28.5	0.24	1	27	−84.6	1.0	0.20
C	28	0.24	2.75	27	−83.7	0.6	0.12
4	28.5	0.06	0	48	−25.2	1.4	0.20
5	28	0.0392	0	112	−12.6	2.10	0.20

[a] The concentrations were checked by titration. [b] Time from the preparation of the solution to the reading of rotations. [c] All rotations were measured at 546 nm, using a 10-mm cell. This number of measurements is n. [d] $X_n = \frac{1}{n}\Sigma x_i$. [e] $s_n(x) = [(x_i - x_n)^2]^{\frac{1}{2}}/(n-1)^{\frac{1}{2}}$. [f] $S_n(x) = s_n(x)/n^{\frac{1}{2}}$.

solutions of K[Co(edta)] (edta = ethylenediaminetetraacetate).

Some of the work from the literature is summarized in SUP 22565. No filtration is mentioned in some of the experiments [listed under (5) and (18) [18]], and very long cells were used in one experiment [(18)] but the cell length is not mentioned in the others. Presumably such use of long cells would be common in trying to see the lowest rotations possible.

Where benzene is used as solvent [experiment (19) [19]], the results are of the same order as some of our spurious rotations in Table 4 and vary with time in a way qualitatively identical to that here observed, increasing and then diminishing with time. In an experiment not mentioned in SUP 22565, Ferroni and Cini [10] found that by shaking bis(benzoylacetonato)beryllium(II) solution in benzene with D-Na[ClO$_3$] powder, a rotation of +0.067 ± 0.03° was observed in the mother liquid, after filtering it. Similar experiments with L-Na[ClO$_3$] powder did not give any rotation, but Merck Na[ClO$_3$] gave a rotation of 0.071 ± 0.003 and a 50 : 50 mixture of D- and L-Na[ClO$_3$] gave a rotation of 0.017 ± 0.002°. These results (odd if we are dealing with a genuine resolution of the beryllium complex) are not extraordinary if compared with those of Table 4 and considered as due to the presence of fine particles. It seems then that the criticisms by Amariglio and Duval [11,12,20] of such results must be confirmed, and that the diastereoisomeric interactions of the two enantiomers with these optically active crystals have not sufficiently different energies to be observed by our present chiroptical experimental means.

The success in getting stereospecific reactions with optically active crystals already achieved for some systems was not repeated here. It seems that benzil is not a suitable reagent for this kind of work, since Curtin and Stein [21] also got no chiral products from the reactions of its asymmetric crystals with lithium reagents and metal hydrides.

The conclusion from this work (and that, relating to α-quartz, of the French workers) must be that there is no unequivocal case of a resolution (*i.e.* an observable

TABLE 4

Typical spurious rotations due to fine particles {L-Na[BrO$_3$] in benzene}

Sample	No. of measurements [a]	t [b]/h	Best estimate (× 10⁴) of true value	of precision	standard error
Water	33	0	+0.6	0.1	0.02
Benzene in the dried cell	33	0	+3.3	4.2	0.7
Benzene after contact with L-Na[BrO$_3$] powder without filtration:					
sample 1	46		−10.6	2.5	0.35
2	59		−27.6	1.1	0.14
3	49		+17.5	1.4	0.20
4	26		+1.7	1.1	0.23
5	26	0	+50.3	1.5	0.31
	26	0.25	+80.4	1.0	0.20
	26	1.5	+35.0	1.0	0.20
	26	3.0	+31.3	1.0	0.20
	22	17.75	+15.2	1.0	0.20

[a] All the readings were made at 546 nm and with a 10-mm cell. [b] Time the solution was left in contact with the optically active solid before reading rotations.

rotation) obtained by differential interaction of two enantiomers with the surface of a solid which owes its dissymmetry to crystal packing rather than molecular dissymmetry. While there are many indications * that such resolutions should in principle be possible, it is doubtful whether any have yet been reproducibly achieved.

EXPERIMENTAL

Circular dichroism measurements were made using a Roussel–Jouan model 1B Dichrographe. Ultraviolet and visible spectra were recorded on a Unicam SP 800. The polarimeter used for detecting optical rotation in most experiments was an NPL type 243 Automatic Polarimeter, whose precision is 0.000 1° (Table 3). Commercially available chemicals of high purity were used without further purification.

Crystal Growth.—Crystals of sodium chlorate, sodium bromate, and sodium uranyl triacetate were grown by slow evaporation of their saturated solutions in water. Some of them were obtained at controlled evaporation rate and temperature through the number of holes in the lids and by keeping the evaporating vessels in a water-bath, respectively. The separation of the relatively large single isotropic crystals of those compounds into the D and L forms was easily made in an appropriate polariscope.

Single crystals of nickel sulphate hexahydrate were grown from saturated solution in water, usually at *ca.* 40 °C. Seeds were obtained by evaporating such solutions and collecting the best crystals formed on the bottom of the flasks. These little crystals are glued to the end of small glass rods, stuck into little blocks of polystyrene foam. Saturated solutions of nickel sulphate in water were then prepared at *ca.* 39 °C, filtered several times, and then put into screw-topped glass bottles (diameter 5—6 cm), previously heated to *ca.* 40 °C. Usually, four or five holes of diameter *ca.* 2—3 mm were bored in the lid to allow evaporation. The polystyrene floats were then put on the solution in such a way that the seed crystals (edge 2—3 mm) were at 2—3 cm below the surface of the solution. These bottles were allowed to stand for *ca.* 20 d at a controlled temperature (water-bath or oven). Several single crystals were obtained in this way, with edges 2.5—3.5 cm.

Crystals of sodium periodate trihydrate with edges greater than 2—3 mm were not easily obtained, but crystals up to that size could be grown by slow evaporation of saturated solutions, usually at *ca.* 35 °C. A few crystals of suitable dimensions were obtained by a method similar to that used for the nickel sulphate with the best little single crystals as seeds.

Benzil crystals with the 0001 face most developed were grown by slow evaporation of ether solutions at room temperature, L and D forms being distinguishable by observing them in the principal axis direction on the same polarimeter used for $Na[ClO_3]$ and $Na[BrO_3]$ crystals.

Racemates. Tris(pentane-2,4-dionato)cobalt(III) was prepared by the method of Bryant and Fernelius [22] (Found: C, 50.65; H, 5.75. Calc.: C, 50.55; H, 5.95%), m.p. 206 °C. Tris(pentane-2,4-dionato)chromium(III) was prepared by the method of Fernelius and Blanch [23] (Found: C, 52.35; H, 6.00. Calc.: C, 51.55; H, 6.05%), m.p. 213—214 °C. The salt $[Ni(bipy)_3]Cl_2 \cdot 6H_2O$ was prepared by the method of Schweitzer and Lee [24] (Found: C, 52.3; H, 4.65; Cl, 10.8; N, 12.45. Calc.: C, 51.05; H, 5.10; Cl, 10.4; N, 11.9%).

L-2,3-*Dihydro*-2-*methyl*-5,6-*diphenylpyrazine*.—Benzil (10 g) was dissolved in ethanol and anhydrous liquid L-1,2-diaminopropane (4.2 cm^3) was added. The mixture was heated (*ca.* 95 °C) for *ca.* 17 h. The brownish product gave (after several crystallizations from ethanol) an n.m.r. spectrum in $CDCl_3$ which coincides with that given by Beak and Miesel [25] for the DL form [multiplet at $\delta \sim 7.28$ (relative area 10), aryl H; 4.20—2.84 (relative area 3), $CHCH_2$; and a doublet at 1.44 (relative area 3), CCH_3] (Found: C, 81.85; H, 6.65; N, 11.1. Calc.: C, 82.2; H, 6.50; N, 11.3%), m.p. 112—113 °C.† A negative Cotton effect was observed with λ at *ca.* 368 nm, near the maximum (365 nm) of lower energy in the electronic spectrum.

We thank the Instituto de Alta Cultura for a fellowship, and the University of Aveiro for leave of absence to J. D. P. da L. de J.

[7/564 *Received*, 31*st March*, 1977]

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* For example: (*i*) the growth of crystals of natural vitamin B_{12} upon (−)quartz is epitaxial, whereas upon (+)quartz, it is not; (*ii*) the etch figures produced by enantiomeric solutions upon a handed crystal are enantiomorphous.

† The literature values 116—118° (ref. 25) and 111—112 °C (ref. 26) are for the DL compound.