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Spontaneous Generation of Optical Activity in Urea Inclusion Compounds *vis-a-vis* Current Theories†

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A novel test of recent theories of the origin of optical activity has been designed based on the inclusion of certain alkyl 2-methylhexanoates into urea channels.

The origin of the pronounced chiral bias of the biosphere has been the focus of intense speculation and inquiry in recent decades, with both ‘chance’ and ‘determinate’ theories having been proposed.[1] According to one determinate theory, the chiral bias derives from the ‘electroweak force’, an ubiquitous but extremely weak chiral influence which renders unto enantiomeric molecules slightly differing energy contents, characterised as the ‘parity violating energy difference’ (PVED). The electroweak effect has been estimated to be as weak as 10^{-20} E_h, so that it is normally undetectable, although an efficient amplification process may make it manifest.

Interestingly, it has been proposed that such amplification could occur during the crystallisation of effectively achiral compounds that form chiral crystals.[2] [The resulting enantiomeric excess (ee) is then proportional to $n\varepsilon$, where n is the number of unit cells and ε is a measure of the PVED per unit cell.] In fact, a 1% ee of l(−) quartz has been observed in terrestrial samples, lending weight to the above proposal.[1e,2] However, the fact that nearly 17 000 crystals of quartz had to be analyzed, gives an indication of the tedium involved in experimental tests of theories that propose crystallisation based amplification. Reported herein is a novel strategy to circumvent this problem, by which statistically significant results may be obtained relatively easily.

The basis of the present strategy is a spontaneous optical resolution, first observed by Schlenk Jr.,[3] that occurs in the formation of urea inclusion compounds of certain *n*-alkyl esters of α-methyl-*n*-alkanoic acids. These channel compounds possess a hexagonal crystalline lattice which is chiral by virtue of its helicity. Also, the enantiomers of the above alkanoate esters (‘guests’) are accommodated in enantiomorphic lattices of the urea (‘host’). When the crystallisation of the inclusion compound is interrupted, it is observed that the supernatant liquid phase is faintly optically active. Apparently, the enantiomeric host–guest lattices have formed to differing extents, so that the liquid phase is enriched in the guest enantiomer which is included relatively slowly.

The origin of this optical resolution, however, is intriguing, but may involve the electroweak force discussed above. Note that the crystalline inclusion compounds are chiral, but essentially form from an achiral precursor (the guest is in racemate form and cannot *per se* introduce chiral bias). Note also that the optical enrichment in the liquid phase mirrors the chiral bias in the crystalline phase (thus, there is no need to examine the crystals themselves to determine their ee). On these bases, the above resolution phenomenon could well be an opportunity to detect the electroweak force.

On the other hand, the observation that the liquid phase is enriched in either enantiomer of guest seemingly randomly in a series of trials,[3a] suggests the operation of a ‘chance factor’, *e.g.* accidental nucleation. Of course, it is possible that both chance and determinate effects (the latter in the guise of the electroweak effect) are in play. If so, a relatively large number of trials could detect the determinate effect as a persistent chiral bias, throwing it into relief against the background chance effect (as it were). The studies described below are based on this premise.

Essentially, the execution of the above strategy involves the crystallisation of a *n*-alkyl α-methylalkanoate in the presence of urea, and then measuring the optical activity of the supernatant liquid phase in a polarimeter. The overall objective would be to conduct a statistically significant number of such runs. Three esters of α-methylcaproic acid were thus studied, the *n*-hexyl, *n*-heptyl and *n*-octyl derivatives, by crystallising them (~0.1 M) from 5 M urea in methanol at 0–5 °C. A total of over 150 trials were performed (in batches of 5–10 at a time), and the results are shown in Table 1.

Initially, a dramatic chiral bias was observed in the case of *n*-hexyl α-methylcaproate, the levorotatory isomer being preferentially included in 32 out of 45 trials. However, this bias practically disappeared when care was taken to filter the solution prior to crystallisation. The most likely explanation is the involvement of dust particles of biological origin (*e.g.* pollen), as is also indicated in reported work.[3a] (These results are significant *vis-a-vis* the theory that optical activity could have originated from extraterrestrial dust.) In the case of the heptyl and octyl esters, again a very mild bias towards inclusion of the levorotatory isomer was observed (although in unfiltered solutions). Studies were not continued as the overall bias was too small to rule out alternative explanations, in all of the present cases.

The specific rotations for the compounds under study are unknown, but are expected to be relatively small on the basis of those reported for the decyl,[3a] ethyl[6a] and methyl[6b] esters of 2-methylhexanoic acid (0.36, 5.97 and 21.9° respectively). Thus, despite the small rotations observed, the ee values are far from negligible. (The relationship between rotational sign and configuration is believed to be the same in all the three compounds studied herein,[3a] and this indicates a consistent preference for one of the enantiomeric crystalline lattices.)

Table 1 Optical enrichment of *n*-$C_4H_9CH(Me)CO_2R$ during inclusion into urea channels[a]

R	N_t	N_l	$10^{-3}\,\bar{\alpha}_\mathrm{l}/°$	N_d	$10^{-3}\,\bar{\alpha}_\mathrm{d}/°$
n-hexyl	45	8	4 (2.5)	32	5 (3)
n-hexyl[b]	29	14	6 (3)	15	7 (6)
n-heptyl	41	19	18 (28)	22	4 (3)
n-octyl	37	15	6 (10)	20	7 (7)

[a] R refers to the ester alkyl residue; N_t refers to the total number of trials; N_l and N_d refer respectively to numbers of levo- and dextro-rotatory readings obtained, and $\bar{\alpha}_\mathrm{l}$ and $\bar{\alpha}_\mathrm{d}$ to the corresponding mean values of the rotations with standard deviations (from a hand-held calculator in parentheses). Note that in two cases $N_\mathrm{t} > N_\mathrm{l} + N_\mathrm{d}$, as some trials gave zero rotations.
[b] Filtration prior to crystallisation.

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The above studies describe a strategy, essentially practicable under normal laboratory conditions, to test for the electroweak effect, although conclusive evidence has not so far been obtained. It is entirely likely that the sought after effect, being infinitesimal in magnitude, would be evident only after an even larger number of trials (than reported herein) is performed. Also, it would be interesting to extend these studies to other systems wherein inclusion compound formation is accompanied by a spontaneous resolution, a well known example being that of tri-*o*-thymotide.[4]

Experimental

General.—*n*-Hexyl, *n*-heptyl and *n*-octyl α-methylcaproate[3a] were prepared *via* α-methylation[5] of the relevant caproate esters (see below). Instruments used: JEOL FX-90Q (NMR at 90 MHz); Perkin-Elmer 781 (IR); and JASCO DIP-370 digital polarimeter [path length 0.1 dm; light source, Na lamp at 589 nm; accuracy ±0.002° (up to ±1°), ±0.2% (±1° or more)].

n-Hexyl α-Methylcaproate.—A stirred solution of lithium diisopropylamide in THF (5 ml), prepared from diisopropylamine (1.1 mmol) and Bu^nLi (1.1 mmol) at 0 °C, was cooled to −78 °C, under N_2. *n*-Hexyl caproate (1 mmol) in THF (20 ml) was added, and after 1 h methyl iodide (1.5 mmol), all at −78 °C. The mixture was allowed to warm to ambient temperature over 2 h, and quenched with water (10 ml). Concentration *in vacuo*, followed by extraction ($CHCl_3$), work-up, and distillation *in vacuo* afforded the α-methylcaproate (1.0 mmol, 90%); ν_{max}/cm^{-1} (neat) 2930, 1735 and 1465; δ_H ($CDCl_3$) 4.10 (2 H, unsymmetrical t, diastereotopic —OCH), 2.38 (1 H, m, α MeC*H*), 1.75–0.75 (m, 25 H, C*H*).

The heptyl and octyl esters were similarly prepared, and had nearly identical spectral characteristics.

Crystallisations.—The ester (0.1 ml) was added to a solution of urea (1.50 g) in reagent grade MeOH (5.0 ml) with stirring in an Erlenmeyer flask, and the resulting solution maintained at 0–5 °C for 24 h, when the crystallisation was interrupted. The supernatant was pipetted out and directly introduced into the polarimeter cell to obtain the rotation at 25 °C. The solution was recovered from the cell and reintroduced into the crystallisation flask; the solids were redissolved in the mother liquors, care being taken to ensure that a homogeneous solution was obtained. The above crystallisation procedure was repeated to obtain the next polarimetric reading. These studies were performed in batches of 5–10 at a time.

Errors obtaining from the above transfers seem to be insignificant, as both levo- and dextro-rotation were observed in subsequent trials. Also, in a typical trial, 50% of the hexyl ester remained unincluded, with $[\alpha]_D^{25} = 3.3$; this indicates a very substantial ee, as the derivatives under study probably possess $[\alpha] < 5°$.

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