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Note

Origin of an apparent inequality in the stepwise stability constants of enantiomeric systems

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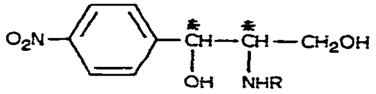
In a recent report, the separation of the two enantiomorphic forms of *threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol as their cupric complexes on a non-asymmetric ion-exchange column was claimed[1]. The phenomenon of stereoselectivity has been defined[2] (in coordination chemistry) as "the difference in properties of molecular diastereoisomers, including transition states". Clearly there can be no selectivity in an enantiomorphic situation and any report of its occurrence under such conditions must be erroneous. The present note explains the origin of the error in the original chromatographic work.



Ia: R=H
Ib: R=COCHCl$_2$

The compound studied (Ia) was 1-*p*-nitrophenyl-2-amino-1,3-propanediol, which contains two asymmetric centres. We are therefore dealing in terms of numbers of possible isomers not with a simple case of a single racemic form but with the pairs of enantiomers of two diastereoisomers. Although the compounds used were supplied as the authentic enantiomeric *threo*-isomers, it now seems clear that they contained some *erythro*-isomer (*i.e.*, the epimeric purity was not absolute).

EXPERIMENTAL

The samples of diols employed were those which had given the original results[1]. These were obtained from a pharmaceutical factory as intermediates in the synthesis of the drug chloramphenicol. The critical Meerwein–Pondorff reduction (by aluminium isopropoxide) is shown:

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The stereoselectivity of this reaction is 96–97%. The *threo*-aminodiol (said to contain 3–4% of contaminant) was purified by a standard method (dissolution in hydrochloric acid, treatment with active charcoal, filtration and precipitation with ammonia), which is said to leave the contaminant in solution. However, as seen from Tables II and III, this "purification" is inadequate, despite the almost identical magnitude of the optical rotations (Table I) of the samples resolved using D-dibenzoyl-tartaric acid (the less soluble diastereoisomeric salt being D-*threo*-aminodiol D-dibenzoyl-tartrate).

Electronic spectra were recorded with a Beckman DK2a spectrophotometer and circular dichroism with a CNRS/Roussel Jouan Dichrographe Mk III. Concentrations of diol were in the region of $1 \cdot 10^{-3}$ moles/dm^3. The latent heat of fusion was measured with a Perkin Elmer DSC 1B differential scanning calorimeter calibrated with benzil.

RESULTS AND DISCUSSION

The infrared and proton magnetic resonance spectra of the D and L diols[*] are identical (as were their pK_a values[1]) and are not reported. Optical activity was considered a more sensitive probe; the molar rotations of the two diols at 546 nm were (within experimental error) identical (Table I). However, when we measured the circular dichroism spectra in the region 440–200 nm, we detected considerable differences between the alleged enantiomers. This is shown in Fig. 1, and is perhaps most strikingly indicated by the extinction coefficients (Table II). Most notably, the g-factor

TABLE I

MOLAR ROTATIONS[*]

Compound	*$[\Phi]_{546\,nm}$*
L-Diol	62.6° (±2.0)
D-Diol	63.7° (±1.0)

[*] Measured as 1% solutions in 0.5 *M* HCl at 20°, using a Bendix-NPL automatic polarimeter.

TABLE II

RESULTS OF CIRCULAR DICHROISM AND ELECTRONIC SPECTRA[*]

Compound	λ_{nm}	ε	$\Delta\varepsilon$	g[**]
L-Diol	325	$3.4 \cdot 10^2$	0.19	$5.59 \cdot 10^{-4}$
D-Diol	325	$3.3 \cdot 10^2$	0.12	$3.64 \cdot 10^{-4}$
L-Diol	275	$1.02 \cdot 10^4$	0.33	$3.24 \cdot 10^{-5}$
D-Diol	275	$1.02 \cdot 10^4$	0.22	$2.16 \cdot 10^{-5}$

[*] Electronic spectra and circular dichroism measured for the same solution within a short period of time.

[**] Kuhn's dissymmetry factor, $\Delta\varepsilon/\varepsilon$, showing clearly that the compounds are not enantiomorphs, and eliminating errors due to concentration.

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[*] D and L are used throughout as in the original work[1]; no comment on absolute configuration or purity is implied.

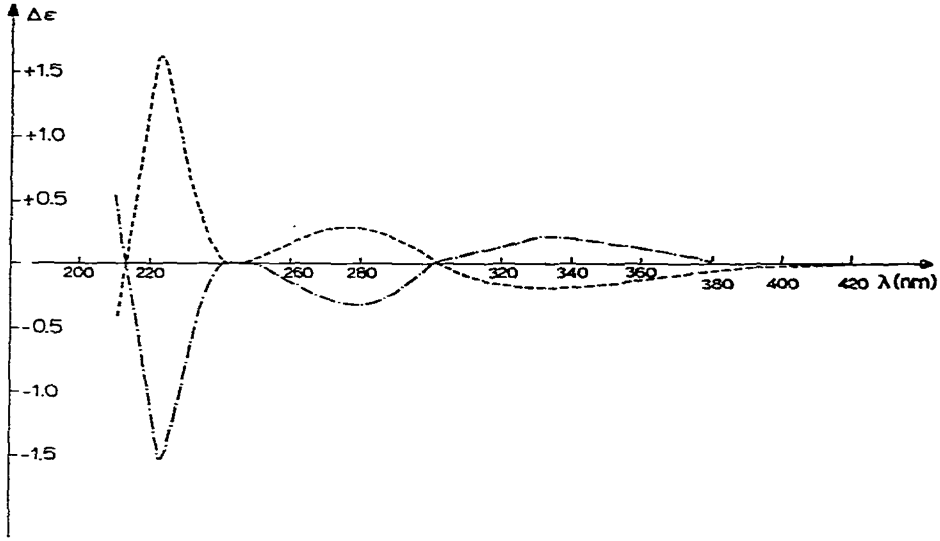

Fig. 1. Molar circular dichroism spectra for the diols, at wavelengths greater than 210 nm (———, D-diol; –·–·–, L-diol). Note that, despite minor changes in band maxima (around 275 and 325 nm), the non-enantiomeric nature of these samples emerges most clearly from the g-factors given in Table II.

of Kuhn[3] (effectively independent of concentration errors) is markedly different for the two samples.

We have further measured the melting points and latent heats of fusion of the D and L forms and recorded small but reproducible differences (Table III).

These differences correspond to the differences in values of stability constants with copper(II) for the enantiomeric systems recorded earlier (the differences recorded were 0.32 for $\Delta K_{1(\mathrm{D-L})}$ and, for $\Delta\beta_{2(\mathrm{D-L})}$, 1.06).

Clearly, one or both "*threo*-enantiomers" in fact contained some *erythro*-isomer, so that the equilibria being studied were not those assumed, but more complicated. For K_1, the possible equilibria are:

$$\begin{array}{lll} \mathrm{Cu}^{2+} & + \text{L-}\textit{threo} & \rightleftharpoons \mathrm{Cu(L{-}T)} \\ & + \text{L-}\textit{erythro} & \rightleftharpoons \mathrm{Cu(L{-}E)} \\ & + \text{D-}\textit{erythro} & \rightleftharpoons \mathrm{Cu(D{-}E)} \\ & + \text{D-}\textit{threo} & \rightleftharpoons \mathrm{Cu(D{-}T)} \end{array}$$

The values of the stability constants K_{LT} and K_{DT} are equal, and those of K_{LE} and K_{DE} are also equal. However, $K_{\mathrm{LT}} \neq K_{\mathrm{LE}}$, and, in general[4], for conformational reasons, *erythro*-isomers give less stable chelate rings than *threo*-isomers, so it seems likely that the more contaminated sample is the L-isomer (since it had the lower value for the measured first stepwise stability constant, denoted ΣK_1). This would also agree with the resolution method used: since the less soluble diastereoisomer contains the D-*threo*-aminodiol, the epimeric impurities will tend to concentrate in the L-diol.

TABLE III

MELTING POINTS AND LATENT HEAT

The other solid state properties measured in comparing the two original "enantiomers" were the infrared spectra (in KBr discs) which both agreed exactly with the Sadtler Standard Spectrum (also in KBr), and the X-ray powder photographs. Here, the lines for the L-diol were much wider than for the D-diol, but no other contrasts were apparent. Both had strong lines at d-spacings of: 5.30, 4.38 and 3.89.

Compound	*ΔH(kJ mole^{-1})*	*M.p. (°C)*[*]
L-Diol	30.9 (±0.6)	166–173
D-Diol	32.4 (±0.5)	171–174

[*] In both samples the major change occurs at 172°: however, they may easily be distinguished by the onset of change. The literature m.p. for the pure *threo*-isomer, D(−), is 161–162°.

CONCLUSION

In conclusion, the results of the previous work are explained in terms of the D- and L-diols being unequally contaminated with diastereoisomers. The results previously presented are clearly in error when considered in the light of the present work and indeed are also precluded by classical thermodynamic considerations.

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