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Absolute Configuration Determination by Anomalous Scattering of Light Atoms. Have the Limits Been Reached?

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Abstract

The absolute *conformation* determination of the achiral olefin 4,4′-dimethylchalcone (DMC), $C_{17}H_{16}O$, crystallizing in a chiral space group ($P2_12_12_1$), was accomplished from the anomalous scattering of oxygen (Cu $K\alpha$) despite the small O:C ratio (0·059). The symmetry-equivalent intensities of seven enantiomer-sensitive reflections of two crystal specimens were measured with graphite-monochromated Cu $K\alpha$ radiation on a Picker diffractometer. In addition, an extensive data set of one of the specimens was collected on a CAD4 diffractometer with Ni-filtered Cu $K\alpha$ radiation. Bijvoet-difference analysis established that the two specimens were enantiomers. The probability that the absolute *conformation* has been wrongly determined is <0·1% in all three measurements. The results of this study established, for the first time, the correlation between the absolute *conformation*, in the crystal, of an achiral optically inactive molecule and the absolute *configuration* and optical rotation of one of the two possible enantiomers of its dibromide adduct obtained by gas/solid bromination reaction. Statistical analysis of the CAD4 data shows that the use of Friedel pairs tends to minimize the effects of systematic errors and yields a higher statistical confidence in the results.

Introduction

Anomalous scattering of X-rays by heavy atoms has been used as a unique means for the determination of the absolute configurations of crystals and molecules. Indeed, the whole edifice of organic stereochemistry was put on an absolute basis by Bijvoet's determination of the absolute configuration of sodium rubidium tartrate (Bijvoet, Peerdeman & van Bommel, 1951).

Carefully controlled experiments showed that it was possible to determine the absolute configurations of (+)-tartaric acid ($C_4H_6O_6$) by using the oxygen atoms as the heavy scatterers (Hope & de la Camp, 1972). Engel (1972) determined the absolute configurations of seven compounds containing only C, H and O atoms and discussed the factors and parameters involved. His conclusion was that the optimum value of O:C is 0·46, although the absolute configuration of Estron (O:C = 0·16) was also successfully determined in his work. The wrong assignment of absolute configuration to Fecht acid (O:C = 0·44), eventually corrected by using a barium salt (Hulshof, Vos & Wijnberg, 1972, 1973), may be attributed to the procedure adopted (photographic data, visual estimation). Vos (1975) discussed the possible error sources for Bijvoet differences and methods of reducing them. A discussion of the methods needed for high-quality-data acquisition is given by Hope (1975).

In our work on optical induction in chiral crystals (Rabinovich & Shakked, 1974, 1975), it was necessary to determine the absolute *conformation* of the achiral olefin 4,4′-dimethylchalcone (DMC), crystallizing in space group $P2_12_12_1$, in order to correlate it with the absolute *configuration* of its chiral dibromide adducts formed by gas/solid reaction (Rabinovich & Shakked, 1974; Green, Rabinovich, Shakked, Hope & Swanson, 1980). The low O:C ratio (=0·059) in DMC indicated very small anomalous dispersion effects. Indeed, conventional R tests performed on the data used for the structure determination failed to give any significant result.

As we were interested in the absolute *conformation* of DMC in that specific crystal, the introduction of any heavy atom was ruled out. It was therefore decided to try the Bijvoet method, employing all possible precautions.

A preliminary account of the work has already been given (Rabinovich & Hope, 1975). Since then only a single absolute configuration determination of comparable low O:C ratio (0·067) has been reported (Karlsson, 1976).

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Table 1. *Enantiomer-sensitive reflections in* 4,4′*-dimethylchalcone* (*DMC*) *and* (+)*-tartaric acid*

DMC						(+)-tartaric acid*	
$h\,k\,l$	$\sin\theta/\lambda$	F_c	$F_c^2\,\mathrm{Lp}$	$10^2\lvert B_c\rvert$†	D	$h\,k\,l$	$10^2\lvert B_c\rvert$‡
8 1 2	0·2840	5·76	29·1	3·13	3·1	$1\,1\,\bar{7}$	13·2
6 1 6	0·2966	5·30	23·1	2·64	2·3	$5\,4\,\bar{5}$	8·2
1 2 2	0·1855	11·26	196·7	2·13	6·2	1 9 0	7·4
3 4 2	0·3592	7·55	35·6	1·85	2·1	7 3 1	7·2
5 1 4	0·2297	16·74	330·6	0·96	3·6	$5\,1\,\bar{4}$	7·0
3 1 4	0·1885	31·45	1504·9	0·70	5·7	2 6 1	6·8
1 1 4	0·1641	48·18	4177·0	0·50	6·8	2 3 6	6·8
$[\sum B_c^2/7]^{1/2}$				{1·9}			{8·4}

* Hope & de la Camp (1972).

† $f'_{\mathrm{C}} = 0{\cdot}017$, $f''_{\mathrm{C}} = 0{\cdot}009$; $f'_{\mathrm{O}} = 0{\cdot}047$, $f''_{\mathrm{O}} = 0{\cdot}032$ (Cu $K\alpha$).

‡ $f'_{\mathrm{C}} = 0{\cdot}017$, $f''_{\mathrm{C}} = 0{\cdot}010$; $f'_{\mathrm{O}} = 0{\cdot}049$, $f''_{\mathrm{O}} = 0{\cdot}032$ (Cu $K\alpha$).

Experimental

Selection of enantiomer-sensitive reflections

The calculated Bijvoet differences

$$B_c = [F_c^2(+) - F_c^2(-)]/\tfrac{1}{2}[F_c^2(+) + F_c^2(-)], \qquad (1)$$

where $F_c^2(+) = F_c^2(hkl)$ and $F_c^2(-) = F_c^2(\bar{h}\bar{k}\bar{l})$, are negligible for almost all reflections, except for a very few. The selection of these enantiomer-sensitive reflections was based on observability rather than just the magnitude of the Bijvoet difference. The function

$$D = B_c/\sigma(B_o), \qquad (2)$$

analogous to that used by Hope & de la Camp (1972), was employed as an index of observability. The values of $\sigma(B_o)$ were calculated by

$$B_o = [I(+) - I(-)]/\tfrac{1}{2}[I(+) + I(-)] \qquad (3)$$

or

$$B_o = \Delta I/\bar{I} \qquad (4)$$

and since $B_o \ll 1{\cdot}0$,

$$\sigma(B_o) \simeq \sigma(\Delta I)/\bar{I}, \qquad (5)$$

where

$$\sigma^2(\Delta I) = \sigma^2[I(+)] + \sigma^2[I(-)] \qquad (6)$$

and $I(+)$, $I(-)$ are the expected values of the observed intensities. $I(\pm)$ and $\sigma^2[I(\pm)]$ were calculated as follows:

$$\begin{aligned} I(\pm) &= K^2\,\mathrm{Lp}F_c^2(\pm), \\ \sigma^2[I(\pm)] &= I(\pm) + K^2\,b, \end{aligned} \qquad (7)$$

where Lp is the Lorentz–polarization factor. The scale factor K^2 and the background b were estimated experimentally from a few measured reflections of specimen (II) (see below) using the slowest scan rate of a Picker diffractometer. $F_c^2(\pm)$ values were computed from the published atomic parameters of DMC (Rabinovich & Shakked, 1974). Atomic form factors for O and C are $f = f^0 + f' + if''$, where f^0, f' and f'' are the values given in *International Tables for X-ray Crystallography* (1974); the form factor for H was also taken from the same reference.

A set of seven enantiomer-sensitive reflections with the largest $D(K^2 = 900,\ b = 10)$ values was chosen. Table 1 lists these reflections together with the seven largest B_c values of (+)-tartaric acid (Hope & de la Camp, 1972) for comparison. The minute magnitudes of the anomalous dispersion effects in DMC obviously dictate very careful experimental procedures.

Table 2 gives crystal data and other relevant information pertaining to DMC.

Table 2. *Crystal data, intensity acquisition and discrepancy indices for* 4,4′*-dimethylchalcone*

$C_{17}H_{16}O$, m.p. 405 K.

Orthorhombic, $P2_12_12_1$

MW = 236, $U = 1317{\cdot}2$ Å^3

$a = 15{\cdot}2464$ (3) Å

$b = 5{\cdot}9059$ (5)

$c = 14{\cdot}6283$ (5)

$D_x = 1{\cdot}19$ Mg m^{-3} for $Z = 4$

$D_m = 1{\cdot}20$

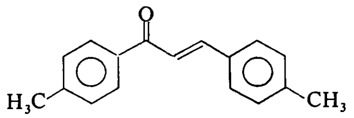
$\mu(\mathrm{Cu}\ K\alpha) = 0{\cdot}6$ mm^{-1}

1500 reflections ($2\theta < 160°$ one octant) measured manually on GE diffractometer with Ni-filtered Cu $K\alpha$ radiation. Data corrected for absorption.

Direct methods.

$R = [\sum|kF_o - |F_c||/\sum kF_o] = 0{\cdot}045.$

$R_w = [w(k^2F_o^2 - |F_c|^2)^2/\sum wk^4F_o^4]^{1/2} = 0{\cdot}010.$



Sample preparation

Large single-crystal boules were grown from the melt by the Bridgman method with an apparatus constructed according to Sherwood & Thomson (1960). Two samples cut from different boules, labeled (I) and (II),*

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* In Rabinovich & Hope (1975) these were labeled (V) and (VII) respectively.

were carefully ground to nearly perfect spheres which were then washed in dioxane to give two clear and immaculate specimens of ~0·25 mm diameter each. The size of the specimens was chosen so as to be smaller than the homogeneous plateau of the monochromated X-ray beam.

Intensity measurements

Three sets of intensities were collected by two different four-circle diffractometers. Specimens (I) and (II) were measured on a Picker diffractometer at the University of California, Davis [experiments (*a*) and (*b*) respectively]; specimen (II) was used to collect the third set of data on a CAD4 diffractometer at the Enraf–Nonius plant in Delft, The Netherlands [experiment (*c*)].

The three experiments were designed and performed in order to ascertain the reliability of the absolute *conformation* determination.

(1) *Picker diffractometer.* The eight symmetry-related intensities $I(\pm h \pm k \pm l)$ of each of the seven selected reflections (Table 1) of specimens (I) and (II) were measured at room temperature with graphite-monochromated Cu $K\alpha$ radiation and the $\theta/2\theta$ mode. The scan rate was 0·125° min^{-1} except for the strongest (114) reflection (0·5° min^{-1}), where the tube current was reduced to avoid counting losses. Accordingly, the set of eight symmetry-related reflections of 114 was measured three times in order to improve counting statistics for this small-Bijvoet-difference reflection (0·5%). The scan range was 2°, backgrounds were counted at fixed points at both ends of the reflection profiles. All measurements were performed at $+\theta$ positions. The symmetry-related reflections were measured in succession and a check reflection was monitored after every set of eight reflections. Counter tests were performed frequently to check the counting-chain stability.

(2) *CAD*4 *diffractometer.* In view of the importance of an unequivocal determination of the absolute *conformation* of DMC and owing to the minute anomalous dispersion effects involved, it was felt desirable to collect an independent intensity data set on another diffractometer to check the results obtained with the Picker diffractometer. An additional purpose of this experiment was to collect a statistically large set of data in order to enable an analysis of possible sources of systematic errors, typical of this kind of investigation. Consequently, each set of the symmetry-related intensities of the seven reflections was measured four times, twice at $+\theta$ and twice at $-\theta$, on a CAD4 automatic diffractometer with Ni-filtered Cu $K\alpha$ radiation. This experiment was also performed at room temperature. The $\omega/2\theta$ scan mode was employed with a speed ratio of 2:3; scan rates varied from 0·25 to 6·7° min^{-1} according to the intensity of the reflection measured. The procedure seeks to yield a constant $\sigma(I)/I$ (= 0·005) value provided a maximum scan time (600 s) is not exceeded; this is achieved by a fast prescan. The ω range was determined by

$$\Delta\omega = a + b \tan \theta.$$

The counter aperture $= A + B \tan \theta$, where $a = 2{\cdot}4$, $b = 0{\cdot}14$, $A = 2{\cdot}0$ and $B = 2{\cdot}0°$.

Backgrounds were measured at 16 points at both ends of the profile. Friedel pairs $I(hkl)$ and $I(\bar{h}\bar{k}\bar{l})$ were measured successively, first at $+\theta$ and then at $-\theta$. The 004 reflection, used as a monitor, was counted at $\pm\theta$ at intervals of eight intensity measurements.

Determination of the absolute conformation

Results

Results of the Bijvoet measurements of the three experiments are summarized in Table 3. The observed averaged Bijvoet differences, $\bar{B}_o$, were calculated for each *hkl* according to (3) where $\bar{I}(\pm)$ are the two means, each of n measurements $I_i(\pm)$, of Bijvoet reflections of the same parity (*hkl*, $h\bar{k}\bar{l}$, *etc*.). $\sigma(\bar{B}_o)$ is defined as in (5) and (6), with

$$\sigma^2[\bar{I}(\pm)] = \sum_n \sigma^2[I_i(\pm)]/n^2, \tag{8}$$

where $\sigma^2[I_i(\pm)]$ are based on counting statistics only. An experimental estimate of the error, $s^2(\bar{B}_o)$, is obtained by replacing $\sigma^2[\bar{I}(\pm)]$ in (8) by the sample mean variance

$$s^2[\bar{I}(\pm)] = \sum_n [\bar{I}(\pm) - I_i(\pm)]^2/n(n-1). \tag{9}$$

χ^2_{2n-2}, used in variance tests, is calculated from

$$\chi^2(\pm)_{n-1} = (n-1)\, s^2[\bar{I}(\pm)]/\sigma^2[\bar{I}(\pm)] \tag{10}$$

by

$$\chi^2_{2n-2} = \chi^2(+)_{n-1} + \chi^2(-)_{n-1}.$$

Table 3 shows that the quality of the data fulfilled our expectations. The values of w agree with the corresponding values of D (equation 2) and show that the values of B_o in the three experiments were determined highly significantly with respect to errors based on counting statistics only. Since, however, the sample sizes are small (particularly in experiments *a* and *b*) and, moreover, there is no guarantee that the values of $\sigma(\bar{B}_o)$ are indeed realistic estimates of the random errors in the $\bar{B}_o$'s, we use Student's t distribution (*International Tables for X-ray Crystallography*, 1959) as applied to the difference of two means to assess the statistical significance of the

Table 3. *Summary of the results of the Bijvoet measurements*

$\bar{I}$, $\bar{B}_o$, $\sigma(\bar{B}_o)$, $s(\bar{B}_o)$ and χ^2_{2n-2} are defined in (3)–(10); $Q=\bar{B}_o/B_c$; $w=\bar{B}_o/\sigma(\bar{B}_o)$ and $t=\bar{B}_o/s(\bar{B}_o)$ are the standard normal and Student's t variates, respectively, of the difference of two means. α is the significance level of t_{2n-2}.

	hkl	n	$\bar{I}$	$\bar{B}_o$*	B_c*	Q	$\sigma(\bar{B}_o)$*	$s(\bar{B}_o)$*	w	t_{2n-2}	$<\alpha$%	χ^2_{2n-2}
(*a*)	8 1 2	4	17041	+3·97	+3·13	1·27	0·70	0·95	5·67	4·18	1·0	11·21
	6 1 6	4	13932	−3·09	−2·64	1·17	0·79	0·75	3·91	3·91	1·0	5·43
	1 2 2	4	29423	+2·57	+2·13	1·21	0·47	0·56	5·47	4·59	0·5	8·35
	3 4 2	4	20279	+1·41	+1·85	0·76	0·61	0·72	2·31	1·96	5·0	8·44
	5 1 4	4	190684	+0·61	+0·96	0·64	0·17	0·39	3·59	1·56	10·0	30·95
	3 1 4	4	819349	−0·73	−0·70	1·04	0·08	0·35	9·13	2·09	5·0	119·50
	1 1 4	12	212384	+1·06	+0·50	2·12	0·09	0·26	11·78	4·08	1·0	180·84
												364·72
(*b*)	8 1 2	4	26795	−2·78	+3·13	−0·89	0·49	0·94	−5·67	−2·96	5·0	22·20
	6 1 6	4	22126	+2·97	−2·64	−1·13	0·55	1·16	−5·40	−2·56	5·0	26·64
	1 2 2	4	46143	−2·84	+2·13	−1·34	0·36	0·58	−7·89	−4·90	0·5	15·34
	3 4 2	4	32085	−2·02	+1·85	−1·09	0·44	0·63	−4·59	−3·21	2·5	12·53
	5 1 4	4	302753	−0·64	+0·96	−0·67	0·13	0·42	−4·92	−1·52	20·0	59·25
	3 1 4	4	1288361	+1·00	−0·70	−1·43	0·06	0·25	−16·67	−4·00	1·0	93·81
	1 1 4	12	327262	−0·41	+0·50	−0·82	0·07	0·12	−5·86	−3·42	2·5	63·37
												293·14
(*c*)	8 1 2	16	3489	−2·03	+3·13	−0·65	0·71	0·73	−2·86	−2·78	1·0	31·66
	6 1 6	16	2898	+3·46	−2·64	−1·31	0·81	0·83	−4·27	−4·17	0·1	31·09
	1 2 2	16	24125	−1·44	+2·13	−0·68	0·23	0·28	−6·26	−5·14	0·1	46·05
	3 4 2	16	4328	−2·09	+1·85	−1·13	0·61	1·65	−3·43	−1·27	25·0	221·38
	5 1 4	16	31922	−1·16	+0·96	−1·21	0·19	0·35	−6·11	−3·31	0·5	99·28
	3 1 4	16	27648	0·60	−0·70	−0·86	0·20	0·34	−3·00	−1·76	10·0	89·55
	1 1 4	16	25692	−0·61	+0·50	−1·22	0·20	0·42	−3·05	−1·45	25·0	132·68
												651·69

* These values are multiplied by 10^2.

determination of the $\bar{B}_o$'s. We test therefore the hypothesis

$$H_0:\bar{B}_o=0,\ i.e.\ \bar{I}(+)=\bar{I}(-)$$

against the alternative hypothesis

$$H_1:\bar{B}_o\neq 0,\ i.e.\ \bar{I}(+)\neq\bar{I}(-)$$

for $v=2n-2$ degrees of freedom (Hamilton, 1964).

The listed values of t and of the significance levels α show that for most measurements of $\bar{B}_o$ the null hypothesis can be rejected at $\alpha=0{\cdot}05$ significance level or less. The exceptions will be discussed later.

These tests which do not depend on any unknown population parameters and hence require no use of questionable sample estimates indicate that anomalous dispersion effects can be reliably assessed, notwithstanding their minute magnitudes.

It remains only to see how well the experimental determination of the B_o's agrees with the calculated, both in magnitudes and signs.

The determination of the enantiomeric indication

The signs of $Q=\bar{B}_o/B_c$ yield the enantiomeric indication of the specimens, their magnitudes provide information on the agreement between the values of the effective f'' terms and those used in the calculation of B_c (Parthasarathy, 1962).

Examination of the Q entries indicates that the experiments have been successfully accomplished. Specimen (I) (experiment *a*) has the absolute *conformation* of the published structure of DMC with correct signs for all Q's; specimen (II) (experiments *b* and *c*) is the enantiomer of (I) with all Q signs inverted.

Quantitative indices for the enantiomer determination are given by the statistics $R(+)$, $R(-)$, R, $\{\sigma\}$ and $\{s\}$ listed in Table 4 and defined as follows:

$$R(+)=[\textstyle\sum(|\bar{B}_o|+|B_c|)^2/7]^{1/2},$$

$$R(-)=[\textstyle\sum(|\bar{B}_o|-|B_c|)^2/7]^{1/2},$$

$$\mathsf{R}=R(+)/R(-),$$

$$\{\sigma\}=[\textstyle\sum\sigma^2(\bar{B}_o)/7]^{1/2},$$

$$\{s\}=[\textstyle\sum s^2(\bar{B}_o)/7]^{1/2}.$$

The values of R show very high significance in the determination of the absolute *conformation*, despite the small O:C ratio. In comparison, the largest R in Engel's (1972) work is 6·6 for Rhodom with O:C = 0·35.

Table 4. *Statistical significance of the absolute conformation determination*

R (+), R (−), R, $\{\sigma\}$ and $\{s\}$ are defined in the text; $\bar{Q}$ is the mean value for the seven reflections in each experiment; $s(\bar{Q})$ is calculated according to (9); $t = \bar{Q}/s(\bar{Q})$; α is the probability of error in the determination; $\nu = n - 1$.

	(+) (*a*)	(+) (*a**)	(−) (*b*)	(−) (*c*)	[(−) (*b*) + (−) (*c*)]
R (+)	4·190		4·006	3·771	
R (−)	0·497		0·371	0·595	
R	8·4		10·8	6·3	
$\{\sigma\}$	0·498		0·357	0·493	
$\{s\}$	0·669		0·678	0·796	
$\bar{Q}$	1·173	1·015	−1·053	−1·009	−1·031
$s(\bar{Q})$	0·181	0·105	0·105	0·103	0·071
t	6·47	9·63	−10·03	−9·75	−14·53
ν	6	5	6	6	13
α	<0·001	≪0·001	≪0·001	≪0·001	≪ 0·001
Confidence limits (95%)	±0·44	±0·27	±0·25	±0·25	±0·15

* Rejecting $Q(114)$.

The means of the Q values, $\bar{Q}$, in experiments (*b*) and (*c*) are very close (numerically) to unity (Table 4). In experiment (*a*), the deviation is larger due to $Q(114)$. Rejection of this value yields excellent agreement for $\bar{Q}$ in all three experiments. In any case, the deviation from unity is smaller than one $s(\bar{Q})$. Thus the agreement between the effective and theoretical f'' is excellent.

This result, which is gratifying *per se*, is important in the context of our chemical studies of the gas/solid bromination of DMC, discussed briefly below, as it implies that the three specimens are essentially devoid of heterochirality. By heterochirality we mean the presence of the two enantiometric structures in one specimen as a result of micro- and/or macro-twinning. In DMC this possibility cannot be ruled out *a priori*, since twinning by reflecting the structure in one of the unit-cell faces would result in a racemic crystal. Such twinning is undetectable by standard X-ray diffraction techniques.

Statistical significance of the determination

The statistical significance of the absolute *conformation* determination is the same as that determined for the sign of the $\bar{Q}$ value obtained in each case. Two alternative methods are available, Student's t distribution of the mean and Hamilton's R-factor ratio. The former, being independent of any population parameter, is calculated by

$$t = |\bar{Q} - m|/s(\bar{Q}),$$

where m is the unknown true value. By putting $m = 0$ we test the hypothesis that the specimens are completely racemic. Table 4 shows that this hypothesis is rejected for all three experiments at 0·1% significance level. The probabilities that the absolute *conformations* have been wrongly determined ($m = -\bar{Q}$) are much smaller. The last column of Table 4 lists the pooled estimates pertaining to the t distribution for experiments (*b*) and (*c*). This procedure is justified as the statistics are based on the intensity measurements of the same specimen. These pooled values emphasize the excellent statistical reliability of our results.

The t distribution yields confidence limits (Table 4). These have a bearing on the question of heterochirality; thus, we can deduce that in experiments (*a**) [rejecting $Q(114)$], (*b*) and (*c*), the probability that the enantiomeric dilution exceeds 0·27/2, 0·25/2 and 0·25/2, respectively, is <5%; the (*b*) + (*c*) pooled value is 0·15/2. Indeed, somewhat lower values may be quoted since heterochirality always diminishes the values of $\bar{Q}$, so we may use the one-tailed t distribution at 5% significance level and obtain the following limits for the enantiomer dilution: 18, 11, 10, 10 and 6% for (*a*), (*a**), (*b*), (*c*) and [(*b*) + (*c*)] respectively.

For Hamilton's R-factor test it can be shown that the listed R values (Table 4) may be used as estimates for R_1/R_0 and be compared with theoretical $\mathsf{R}_{b,N,\alpha}$ values with $b = 1$, $N = 6$. Since all R values in Table 4 exceed $\mathsf{R}_{1,6,0\cdot001} = 2\cdot63$, the result of this test, as that of t, is highly significant.

Chemical significance of the absolute conformation determination

The chemical significance of this work rests on the fact that it provides a basis for correlating the absolute *conformation* of the DMC molecule in the crystal with the absolute *configuration* of its dibromide adduct obtained in a gas/solid reaction.

A full account of this correlation is given in a separate paper (Green, Rabinovich, Shakked, Hope & Swanson, 1980). A brief sketch is outlined below.

Penzien & Schmidt (1969) have shown that when single crystals of DMC are exposed to bromine vapour an excess of one of the two possible enantiomeric dibromides (DMCDB) is formed in rather small optical yields (6–20%). This solid-state reaction was the first example of asymmetric synthesis where crystal chirality was the sole agent of optical induction. In solution, molecules of DMC undergo rapid racemization and show no optical rotation.

In order to study the stereocourse of the reaction and analyze it in terms of crystal structure *versus* molecular conformation, the structure of DMC (Rabinovich & Shakked, 1974) was determined as well as the structure and absolute configuration of DMCDB. The latter was established straightforwardly by Hamilton's *R*-factor ratio test, aided by the presence of two Br atoms (Green, Rabinovich, Shakked, Hope & Swanson, 1980). The missing link in this study, namely the determination of the absolute *conformation* in a given single crystal of DMC, was provided by the successful accomplishment of the present analysis.

It is thus very satisfying that the enantiomeric indication determined by X-ray analysis is in complete accord with the chemical data. Bromination of samples from boule (I) yield laevorotatory (−)-DMCDB, while samples from (II) afford (+)-DMCDB. Not only are these results consistent with the X-ray analysis but they allow, for the first time, a correlation between the absolute *conformation* of a species whose chirality is detectable only in the solid with the absolute configuration of a stable reaction product; *i.e.* we can state that a molecule of DMC (boule I) having the absolute *conformation* of the published structure yields the (−)-DMCDB (αS, βR) enantiomer in excess. This correlation is crucial to the elucidation of the stereochemical course of the reaction.

Heterochirality has been invoked as a possible cause for the rather low optical yields. The statistical analysis of the previous section rules out this explanation.

Analysis of the CAD4 data

In this work an attempt has been made to push to its limits the method of absolute configuration determination by anomalous scattering of light atoms. The results of experiments (*a*) and (*b*) suffice to show that this attempt has been successful. It was deemed appropriate, however, to try to analyze the causes of this success and, in addition, to obtain an independent check on the quantitative results of experiments (*a*) and (*b*). To this end, we have collected an extensive set of data (experiment *c*), comprising 224 sample points (intensity measurements) compared to 72 in (*a*) or (*b*). We felt that this set, measured at both $+\theta$ and $-\theta$, would enable the sorting out of the various sources of systematic errors and allow a more reliable statistical analysis. The following analysis will therefore be mainly based on these data.

Evaluation of $\sigma(B_o)$ *and* $s(B_o)$

Table 4 reveals that $\{s(\bar{B}_o)\} > \{\sigma(B_o)\}$ in all three experiments; the individual values of χ^2 increase, in general, with $\bar{I}(hkl)$, as is evident from Table 3. Since the random variate $\nu s^2/\sigma^2$ based on a sample size n in a normal population is distributed as χ^2 with $\nu = n - 1$ degrees of freedom, we shall use the χ^2 values of experiment (*c*) to perform hypothesis tests for $\sigma^2(\bar{B}_o)$ as follows:

$$H_0 : \sigma^2 = \sigma^2(\bar{B}_0)$$

against the alternative

$$H_1 : \sigma^2 > \sigma^2(\bar{B}_o)$$

for $\nu = 7 \times (32 - 2) = 210$ degrees of freedom, using the additive property of the χ^2 distribution, namely, $\chi^2_{\nu_1+\nu_2} = \chi^2_{\nu_1} + \chi^2_{\nu_2}$.

Table 5. *Results of CAD*4 *data analysis*

χ^2_{15} and χ^2_{30} are defined in (10) with $n = 16$; $s_F(\bar{B}_o)$ in (13); $t_{15} = \bar{B}_o/s_F(\bar{B}_o)$; $\sigma_c(\bar{B}_o)$ in (5, 6) with $\sigma_c[I_l(\pm)]$ in (11); m_1, m_2, *etc.* are the first four moments of the distribution δb_{lJ} defined in (14) where $m_k = \sum(\delta b_{lJ})^k/n$; { } denotes root-mean-square values.

	θ set				$\pm\,\theta$ set					
$h\ k\ l$	χ^2_{15}	$s_F(\bar{B}_o)$	t_{15}	<α%	χ^2_{15}	$s_F(\bar{B}_o)$	t_{15}	<α%	χ^2_{30}	$\sigma_e(\bar{B}_o)$
8 1 2	10·8	0·62	−3·30	0·5	7·7	0·52	−3·91	0·5	30·5	0·73
6 1 6	12·2	0·75	4·62	0·1	15·9	0·85	4·05	0·1	30·2	0·83
1 2 2	9·3	0·21	−6·81	0·1	13·5	0·25	−5·67	0·1	33·2	0·27
3 4 2	30·6	0·89	−2·34	5·0	19·6	0·71	−2·92	1·0	210·0	0·62
5 1 4	31·4	0·35	−3·33	0·5	23·4	0·30	−3·85	0·5	64·9	0·24
3 1 4	21·2	0·29	2·27	5·0	40·4	0·40	1·50	20·0	59·1	0·24
1 1 4	18·7	0·27	−2·25	5·0	21·4	0·29	−2·11	10·0	88·2	0·24
	134·2	{0·54}			142·0	{0·52}			516·1	{0·51}
m_1	0·00				−0·03					
m_2	0·98				1·09					
m_3	0·03				0·12					
m_4	3·10				3·37					
n	110				109					

Comparing the summed $\chi'_{210} = 651{\cdot}7$ with the theoretical value of $\chi^2_{210,0{\cdot}95} = 244{\cdot}5$, we can safely reject the null hypothesis. The rejection is still valid when we omit the abnormally high $\chi^2(342)$ reflection ($\chi^2_{180} = 430{\cdot}3$, $\chi^2_{180,0{\cdot}95} = 212{\cdot}0$).

The results of these tests indicate that either $\sigma^2(\bar{B}_o)$ is underestimated or that $s^2(\bar{B}_0)$ is too large because of systematic errors in the data or, which is more likely, that the large χ^2 values are due to a combination of both effects.

That counting statistics do not solely account for the observed variations in intensity measurements of strong reflections is well known. It is customary to add a term, proportional to I^2, to the counting-statistics variance

$$\sigma_c^2(I) = \sigma^2(I) + c^2 I^2, \qquad (11)$$

where c [= 0·004 in experiment (c)] corresponds to the intensity variations in the monitor reflections. New $\sigma_c(\bar{B}_o)$ and χ^2 values calculated from the modified intensity variances are in the last two columns of Table 5. The drop in χ^2_{210} and χ^2_{180} is, however, of no avail as the null hypothesis must be rejected again.

Rather than doctor the value of c in order to reduce χ^2, a search for systematic-error effects, possibly responsible for the high $s(\bar{B}_0)$, seemed more rewarding.

Systematic errors

Additional evidence for systematic errors is the observation that $R(-)$, the discrepancy index between $\bar{B}_o$ and B_c which is significantly smaller than $\{s(\bar{B}_o)\}$, agrees reasonably well with $\{\sigma(B_o)\}$. This indicates that while the $\bar{B}_o$ values may be regarded as good estimates of the true values, the scatter of the $I_i(\pm)$'s is too large, possibly due to systematic errors. Apparently, these errors are intrinsically systematic in the sense that they affect certain Bijvoet partners to approximately the same extent. Thus, they have only slight influence on the magnitudes of $\bar{B}_o$, whereas they are fully reflected in $s(\bar{B}_o)$.

In trying to pinpoint these errors we have followed the check-list given by Vos (1975) for possible error sources for Bijvoet differences and methods for reducing them.

(i) Good counting statistics, judging by w (Table 3), were obtained through repetitive measurements of symmetry-related reflections on a reliable four-circle diffractometer, taking care of all necessary precautions, such as scanning range, counter aperture, electronic and mechanical stability of the apparatus.

(ii) Bijvoet-related reflections were measured in succession to minimize long-term instability effects.

(iii) Small spherical specimens were used to minimize absorption effects.

(iv) Error due to thermal diffuse scattering, multiple diffraction and possible crystal imperfections (also anisotropic extinction) are best reduced by using equivalent geometrical conditions.

Since (i), (ii) and (iii) were checked, it seems that the errors are due to (iv). The best equivalent geometrical condition occurs with Friedel pairs, so that variations in intensity of the partners tend to be strongly correlated. Hence, the scatters of the Friedel-pair differences about their means are likely to be smaller than in any other pairing arrangement, and obviously also smaller than $s(\bar{B}_0)$.

Analysis of Friedel-paired data

In view of the foregoing discussion, $\bar{B}_0$ and $s_F(\bar{B}_o)$ were recalculated according to

$$\bar{B}_o = \sum_{16} B^i_o/16, \qquad (12)$$

$$B^i_o = [I_i(+) - I_i(-)]/\tfrac{1}{2}[I_i(+) + I_i(-)],$$

where $I_i(\pm)$ are the intensity of the Friedel partners.

$$s^2_F(\bar{B}_o) = \sum_{16} (\bar{B}_o - B^i_o)^2/15 \times 16. \qquad (13)$$

Obviously, the changes in the new $\bar{B}_o$ compared to those calculated previously are negligible.

The results from two sets of calculations, *i.e.* one with $I_i(\pm)$ measured at the same θ positions (θ set) the second at $+\theta$ and $-\theta$ ($\pm\theta$ set), are in Table 5. For most reflections in the two sets the $s_F(\bar{B}_o)$ are considerably smaller than $s(\bar{B}_o)$; for 342 the change is dramatic. The agreement among $\{s_F(\bar{B}_o)\}$, $\{\sigma_c(\bar{B}_o)\}$ and $R(-)$ is now good. The t-distribution statistics show significant improvement for 342, 314 and 114 in the two sets (except for 314 in the $\pm\theta$ set).

χ^2 tests show that the H_0 hypothesis would not be rejected at 0·01 significance level ($\chi^2_{105,0{\cdot}99} = 140{\cdot}9$) for the θ set; it would be rejected, however, for the $\pm\theta$ set. Both would be rejected at 0·05 significance level ($\chi^2_{105,0{\cdot}95} = 129{\cdot}6$). Nevertheless, the χ^2 values have approached considerably the region of acceptance.

A close examination of the variate δb_{ij} in the two sets

$$\delta b_{ij} = (\bar{B}^j_o - B^{ij}_o)/\sigma_c(B^{ij}_o), \quad i = 1,\ldots,16, j = 1,\ldots,7, \qquad (14)$$

shows that in the θ set, two out of the 112 δb_{ij}'s are outstandingly large, $|\delta b_{ij}| > 3{\cdot}2$; in the $\pm\theta$ set there are three with $|\delta b_{ij}| > 2{\cdot}8$. Rejection of the corresponding Friedel pairs improves considerably the χ^2 statistics:

$$\theta \text{ set} \quad \chi^2 = 106{\cdot}8, \quad \chi^2_{103,0{\cdot}90} = 121{\cdot}6;$$

$$\pm\theta \text{ set} \quad \chi^2 = 119{\cdot}4, \quad \chi^2_{102,0{\cdot}90} = 120{\cdot}6;$$

i.e. the null hypothesis is not rejected even at 10% significance level.

In other words, the δb_{ij} are nearly normally distributed with zero mean and unit variance. The small departure from normality is indicated by the first four moments given in Table 5; the theoretical values are 0, 1, 0, 3.

As a check for the validity of the Friedel-pairing method we analyzed similarly all six other pairing combinations, *e.g.* $I(hkl)$ and $I(\bar{h}kl)$. The statistics in all were much inferior to that of the Friedel pairing. When the rejection criterion $|\delta b_{ij}| > 2{\cdot}8$ was applied, many reflections were excluded with no apparent improvement.

The large $s(\bar{B}_o)$ of the 342 reflection is due to a 5% increase in the intensities of the Friedel pairs $3\bar{4}\bar{2}$, $\bar{3}42$ and $\bar{3}4\bar{2}$, $3\bar{4}2$ with respect to the remaining pairs. As no azimuthal sweep was performed it is not clear whether the former were strengthened as a result of multiple diffraction or whether the latter were weakened by some geometrical cause. The relevant point here is that the variations in the intensities affected the Friedel partners to the same extent and were repeated in all four measurements of the same *hkl*. The value of $\bar{B}_o$ is obviously not affected, the scatter $s(\bar{B}_o)$ does reflect the 5% difference.

Conclusions

The main conclusion of this study is that the absolute configuration determination of compounds comprising C, H and O atoms only can be successfully achieved by the Bijvoet-difference method, even in extreme cases, with high statistical reliability.

The success of this investigation is attributed to three factors: the excellent quality of the crystal specimens, the nearly perfect performance of the diffractometers and the data-acquisition procedure adopted. The first two factors are self-evident, the last, collecting a complete set of Friedel pairs, is of crucial importance. The conventional way of applying the Bijvoet-difference method, undoubtedly dictated by the limitations of three-circle diffractometers, is to measure a non-Friedel pair long enough to obtain good counting statistics. However, rather than spend hours, in this way, on one reflection trying to assign high statistical significance to, most probably, a biased observation, it seems more profitable to sample repeatedly all reciprocal-lattice points related by symmetry and obtain a set of data that, in principle, can yield $\bar{B}_o$ values free of systematic errors.

As our experiments have demonstrated, the procedure advocated here tends to cancel out the effects of all systematic errors, not merely those due to absorption, and thus avoids data doctoring which is frequently of a dubious nature. It should be noted here that not only spheres but also regular-crystal specimens (needles, plates, laths, *etc.*) show similar absorption effects when Friedel, but not general Bijvoet pairs, are compared.

The detailed CAD4 data analysis has demonstrated that the Friedel-paired procedure yields $\bar{B}_o$ estimates practically devoid of the effects of any systematic error. The analysis of the variance carried out accordingly has yielded excellent agreement between theoretical and experimental error estimates.

The absolute configurations were determined with high statistical significance from seven reflections only. Three of these have $\bar{B}_o$ values $<1\%$. Nevertheless, in experiment (*c*), they all have been significantly determined and their values agree well with the theoretical ones. In fact, the probability of wrong enantiomer indication is still exceedingly small even when only these $\bar{B}_o$'s are considered.

In view of these arguments it appears that the limits of the method have not yet been reached. Employing the Friedel-pairing method with a good specimen, a well-tuned four-circle diffractometer and good counting statistics would render feasible the determination of absolute configuration of organic compounds with an O:C ratio as low as 0·02. This conclusion is also qualitatively valid for compounds containing N atoms.

The O:C ratio of 0·02 is about 4% of the optimum quoted by Engel (1972). The optimum quoted for H:C is 36; the values usually encountered are 2–5% of this optimum. Since the effective $f''_{\mathrm{C:H}}$ value is not substantially different from that of $f''_{\mathrm{O:C}}$ our predictions about organic compounds with light heteroatoms may well be valid for hydrocarbons. The importance of both in stereochemical studies cannot be overemphasized.

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References

Bijvoet, J. M., Peerdeman, A. F. & van Bommel, A. J. (1951). *Nature (London)*, **168**, 271–272.

Engel, D. W. (1972). *Acta Cryst.* B**28**, 1496–1509.

Green, B. S., Rabinovich, D., Shakked, Z., Hope, H. & Swanson, K. (1980). *Acta Cryst.* Submitted.

Hamilton, W. C. (1964). *Statistics in Physical Science.* New York: The Ronald Press Company.

Hope, H. (1975). In *Anomalous Scattering*, edited by S. Ramaseshan & S. C. Abrahams, pp. 293–305. Copenhagen: Munksgaard.

Hope, H. & de la Camp, U. (1972). *Acta Cryst.* A**28**, 201–207.

Hulshof, L. A., Vos, A. & Wijnberg, H. (1972). *J. Org. Chem.* **37**, 1767–1770.

Hulshof, L. A., Vos, A. & Wijnberg, H. (1973). *J. Org. Chem.* **38**, 4217.

International Tables for X-ray Crystallography (1959). Vol. II. Birmingham: Kynoch Press.
International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press.
KARLSSON, R. (1976). *Acta Cryst.* B**32**, 2609–2614.
PARTHASARATHY, R. (1962). *Acta Cryst.* **15**, 41–46.
PENZIEN, K. & SCHMIDT, G. M. J. (1969). *Angew. Chem. Int. Ed. Engl.* **8**, 608–609.
RABINOVICH, D. & HOPE, H. (1975). *Acta Cryst.* A**31**, S128.
RABINOVICH, D. & SHAKKED, Z. (1974). *Acta Cryst.* B**30**, 2829–2834.
RABINOVICH, D. & SHAKKED, Z. (1975). *Acta Cryst.* B**31**, 819–825.
SHERWOOD, J. N. & THOMSON, S. T. (1960). *J. Sci. Instrum.* **37**, 242–245.
VOS, A. (1975). In *Anomalous Scattering*, edited by S. RAMASESHAN & S. C. ABRAHAMS, pp. 307–339. Copenhagen: Munksgaard.

Acta Cryst. (1980). A**36**, 678–682

Oxidation Reactions in Natural Fe–Ti Oxide Spinels

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Abstract

Defects and oxidation reactions in naturally occurring Fe–Ti oxide spinels have been investigated by a combination of *in situ* environmental-cell high-voltage electron microscopy (HVEM) and high-resolution lattice-imaging electron microscopy (HREM) methods. The experiments conducted on the magnetite–ulvöspinel (Fe_3O_4–Fe_2TiO_4) system show that partial oxidation to cation-deficient cubic spinels sometimes occurs before the oxidation of the system to the rhombohedral hematite–ilmenite oxides (Fe_2O_3–$FeTiO_3$).

Introduction

The possible compositions of naturally occurring mineral spinels have been reviewed by Lindsley (1976). Industrial applications have caused considerable interest in Fe–Ti oxides in recent years. However, experimental work on these systems is limited at temperatures below ~1273 K and is mostly done on simple synthetic minerals. It is, therefore, felt that with natural minerals as starting materials a clearer understanding of oxidation reactions in specific environments may be obtained. The development of an environmental cell in the HVEM (Swann & Tighe, 1971) has allowed such reactions to be observed directly under controlled atmospheres. Flowers, Tighe & Swann (1974) for example were able to perform controlled reduction experiments on hematite–magnetite and Thoeni, Gai & Hirsch (1977) on oxide catalyst systems. The present experiments were designed to observe oxidation reactions in complex magnetite–ulvöspinel systems.

Experimental

Samples from an ore vein in a ferrogabbro from a middle zone of Skaergaard intrusion (East Greenland) rich in these minerals were used. They were cut with a diamond saw, polished, and thinned with an ion beam. The sample compositions were determined with an electron-microscope microanalyser and crystal structures were determined by X-ray and electron diffracton. For HREM work, a recently installed JEOL JEM 200CX electron microscope fitted with a LaB_6 gun and operating at 200 kV was used. The performance characteristics of the JEM 200CX electron microscope have been described by Boyes *et al.* (1980). Thinned samples were examined at magnifications up to a million and micrographs were recorded between about −700 and −900 A defocus in steps of ~90 Å with an objective aperture to include diffracted beams out to about 0·6 $Å^{-1}$. Many-beam-contrast calculations were carried out where necessary to interpret the images. The oxidation reactions on the samples were conducted in an environmental cell fitted to an

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