

# Absolute Configuration of Chiral Ethanol-1-*d*: Neutron Diffraction Analysis of the (–)-(1*S*)-Camphanate Ester of (+)-(R)-Ethanol-1-*d*

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The absolute configuration of (+)-ethanol-1-*d* has been determined to be *R* by the single-crystal neutron diffraction analysis of its (–)-camphanate ester. The absolute configuration of the (–)-camphanate group, which served as the chiral reference for the neutron study, was in turn established to be 1*S*,4*R* in an X-ray anomalous dispersion study of the complex Cu<sub>2</sub>(camphanate)<sub>4</sub>(ethanol)<sub>2</sub>. These results provide unambiguous confirmation that the optical rotation of (*R*)-ethanol-1-*d* (positive) is opposite to that of its higher homologs, (*R*)-propanol-1-*d*, (*R*)-butanol-1-*d*, and (*R*)-neopentanol-1-*d* (all negative), and demonstrates the usefulness of neutron diffraction in determining the absolute configuration of molecules possessing chiral methylene groups (i.e., molecules of the type CHDRR'). Crystallographic details: for the neutron analysis of (+)-(R)-ethyl-1-*d* (–)-(1*S*)-camphanate: space group *P*2<sub>1</sub>2<sub>1</sub>2 (orthorhombic), *a* = 6.422(1) Å, *b* = 21.004(4) Å, *c* = 9.275(2) Å, *V* = 1251.1(7) Å<sup>3</sup>, *Z* = 4; *R*(*F*<sup>2</sup>) = 0.083, and *wR*(*F*<sup>2</sup>) = 0.075 for 1114 reflections. For the X-ray analysis of Cu<sub>2</sub>(camphanate)<sub>4</sub>(ethanol)<sub>2</sub>: space group *P*1 (triclinic), *a* = 11.086(3), *b* = 11.244(3), *c* = 13.293(4) Å,  $\alpha$  = 111.59(2),  $\beta$  = 107.71(2), and  $\gamma$  = 105.56(3)°, *V* = 1397.6(7) Å<sup>3</sup>, *Z* = 1; *R*(*F*) = 0.054, *wR*(*F*) = 0.058 for 3672 reflections.

## Introduction

The ability of neutron diffraction techniques to distinguish between hydrogen and deuterium<sup>2</sup> has allowed the unambiguous determination of the absolute configurations of several molecules that are chiral by virtue of a stereospecific isotopic substitution. Compounds characterized in this manner have included derivatives of glycolic acid (HOCHDCOOH),<sup>3</sup> malic acid (HOOCCHDCOOH),<sup>4</sup> succinic acid (HOOCCHDCOOH),<sup>5</sup> neopentyl alcohol [(CH<sub>3</sub>)<sub>3</sub>CHDOH],<sup>6</sup> and a steroid derivative bearing a chiral C(CH<sub>3</sub>)(CD<sub>3</sub>) group.<sup>7</sup> In this paper we describe the neutron diffraction determination of the absolute *R* configuration of (+)-ethanol-1-*d*, (+)-CH<sub>3</sub>-CHDOH, as its (–)-camphanate ester.

Optically active ethanol-1-*d* was first obtained by Westheimer, Vennesland, and co-workers in the 1950's.<sup>8ad</sup> At that time these authors tentatively concluded that (–)-ethanol-1-*d* had the *R* configuration; however, several subsequent studies in the 1960's<sup>9–11</sup> concluded that this was in fact the *S* enantiomer. Although the *S* configuration for (–)-ethanol-1-*d* has been universally accepted

in the literature, there is an intriguing difference in the optical rotation of (*S*)-(–)-ethanol-1-*d* versus its higher homologs (RCHDOH): (*S*)-(+)–propanol-1-*d*, (*S*)-(+)–butanol-1-*d*, and (*S*)-(+)–neopentanol-1-*d* about which we have been concerned.<sup>12</sup> Although the opposite rotations of (*S*)-(–)-ethanol-1-*d* and (*S*)-(+)–butanol-1-*d* have been rationalized by Brewster<sup>11</sup> on conformational grounds, the same reasoning would seem to apply to ethanol-1-*d* and neopentanol-1-*d*, where the respective R groups, CH<sub>3</sub> and C(CH<sub>3</sub>)<sub>3</sub>, both have the same *C*<sub>3v</sub> symmetry and would be predicted to have the same sign of rotation, contrary to experimental observation.<sup>12b</sup>

Even though it was almost certain that the assigned configurations of these chiral 1-deuterio primary alcohols were correct, we felt compelled to make absolutely certain of the currently accepted assignment of the ethanol-1-*d* configuration by undertaking a neutron diffraction study of a suitable derivative. Earlier we had reported the neutron diffraction determination of the absolute configuration of (*S*)-(+)–neopentanol-1-*d*,<sup>6</sup> now we report a similar study of (+)-ethanol-1-*d*.

## Results

(+)-Ethanol-1-*d* was prepared by the method of Günther, Simon et al.<sup>13</sup> from the equilibration of CH<sub>3</sub>-

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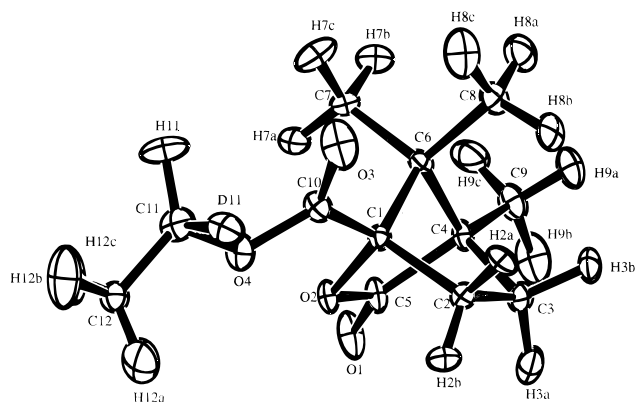
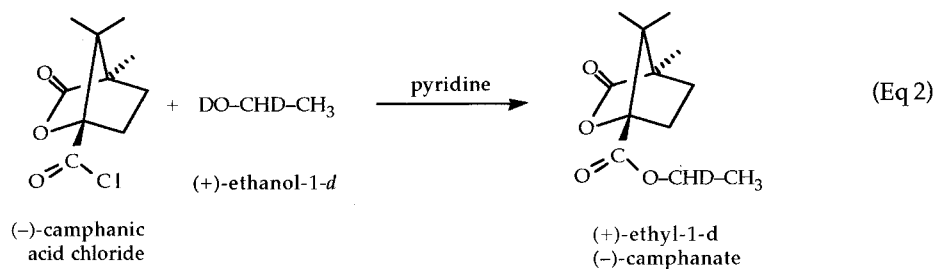
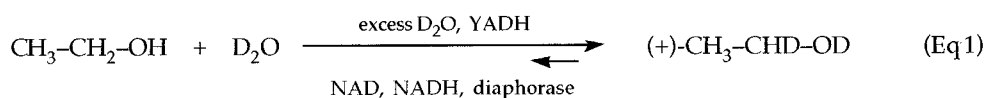
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## Scheme 1



**Figure 1.** ORTEP plot of (+)-ethyl-1-d (-)-camphanate, from the neutron diffraction analysis, showing 40% probability ellipsoids. Note that the CHD group [atom C(11)] has the (*R*) configuration, while C(1) is (*S*) and C(4) is (*R*).

$\text{CH}_2\text{OH}$  in excess  $\text{D}_2\text{O}$  with yeast alcohol dehydrogenase (YADH), diaphorase, and nicotinamide adenine dinucleotide (NAD) (eq 1). Treatment of the resulting (+)-ethanol-1-*d* with (-)-camphanic acid chloride by the method of Gerlach and Zagalak<sup>14</sup> converted the alcohol to the title crystalline ester, (+)-ethyl-1-*d* (-)-camphanate (eq 2).

Colorless crystals of (+)-ethyl-1-*d* (-)-camphanate<sup>14</sup> used in the neutron diffraction analysis were grown by slow cooling of a saturated solution of the compound in cyclopentane. The compound crystallizes in the orthorhombic space group  $P2_12_12$ , with  $a = 6.422(1)$  Å,  $b = 21.004(4)$  Å,  $c = 9.275(2)$  Å,  $V = 1251.1(7)$  Å<sup>3</sup>,  $Z = 4$ . Neutron diffraction data were collected at room temperature at Brookhaven National Laboratory on a crystal with approximate volume 19 mm<sup>3</sup>. Difference maps, phased by the C and O atomic coordinates derived from an earlier X-ray analysis,<sup>15</sup> unambiguously revealed the positions of the D and H atoms in the structure (as one positive and seventeen negative peaks, respectively<sup>16</sup>). Refinement of the structure yielded final agreement factors of  $R(F^2) = 0.083$  and  $wR(F^2) = 0.075$  for a total of 1114 reflections. The structure (Figure 1) shows that the absolute configuration of (+)-ethanol-1-*d* is *R*. Crystal-

**Table 1. Summary of Neutron Diffraction Results for Ethyl-1-*d* Camphanate**

chemical formula	$\text{C}_{12}\text{H}_{12}\text{O}_4$
formula weight	220.20
crystal class	orthorhombic
space group	$P2_12_12$
crystal dimensions	$2.2 \times 3.7 \times 2.4$ mm
crystal color	colorless
$a$ , Å	6.422(1)
$b$ , Å	21.004(4)
$c$ , Å	9.275(2)
$Z$	4
$\rho$ (calcd), $\text{g cm}^{-3}$	1.195
radiation, $\lambda$ (Å)	1.0462(1)
abs coeff ( $\mu_n$ ), $\text{cm}^{-1}$	2.256
abs factor range	1.536–1.968
temperature (K)	298
diffractometer	port H6M, Brookhaven HFBR
scan mode	$\theta/2\theta$ , with $\Delta 2\theta = 2.8^\circ$ for $\sin \theta/\lambda \leq 0.44 \text{ \AA}^{-1}$ and $\Delta 2\theta = 3.0^\circ$ for $0.44 < \sin \theta/\lambda < 0.51 \text{ \AA}^{-1}$
index limits	$h \leq 7, k \leq 23, l \leq 10$
total no. of reflections	1114
no of parameters	309
$R(F^2)^a$	0.083
$R(wF^2)^a$	0.075
$S^a$	1.183

<sup>a</sup> See footnote 29 for definitions of agreement factors.

lographic details, atomic coordinates, and selected distances and angles in the molecule are given in Tables 1–3.

The above conclusion, however, is based on the accepted *1S* absolute configuration of the (-)-camphanate group. As shown in Scheme 2, the absolute configuration of (-)-(*1S*)-camphanic acid, from which ethyl-1-*d* camphanate was prepared, is tied to that of (+)-(*1R*)-camphor, which in turn has been established via its 3-bromo derivative by X-ray anomalous dispersion.<sup>17</sup> It has also been interrelated to several other terpenes whose absolute configurations are known.<sup>18</sup> (Note that C-3 in camphor becomes the COOH group in camphanic acid with a change in camphor's C-4 stereochemistry in the transformation). Nevertheless, the absolute configuration of camphanic acid itself has never been confirmed directly by X-ray methods, so we felt that such a study would be useful to be certain that there were no loose ends.

Consequently, a Cu(II) complex of (-)-camphanic acid was prepared for an X-ray anomalous dispersion analysis, in which Cu served as the anomalous scattering center

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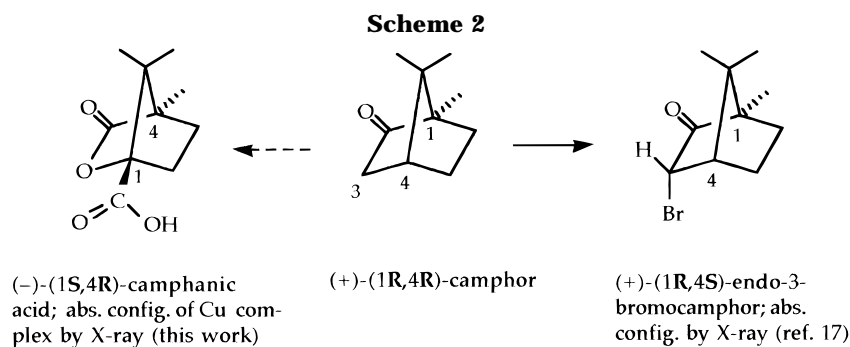
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**Table 2. Fractional Atomic Coordinates ( $\times 10^4$ ) and Equivalent Isotropic Thermal Factors ( $\text{\AA}^2 \times 10^3$ ) for Ethyl-1-*d* Camphanate (neutron results)**

atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq) <sup>a</sup>
C(1)	1433(7)	3898(2)	6570(5)	67(2)
C(2)	2925(12)	4442(4)	6929(8)	94(3)
C(3)	3424(10)	4277(3)	8530(10)	94(3)
C(4)	2236(7)	3646(2)	8809(6)	73(2)
C(5)	-17(8)	3870(3)	8750(6)	88(2)
C(6)	2347(7)	3315(2)	7331(5)	70(2)
C(7)	913(15)	2740(4)	7223(12)	104(4)
C(8)	4558(14)	3129(5)	6904(12)	101(4)
C(9)	2873(17)	3278(6)	10128(10)	121(4)
C(10)	960(10)	3844(3)	4972(6)	92(2)
C(11)	-1418(22)	3995(6)	3102(9)	135(5)
C(12)	-3072(24)	4407(10)	2825(12)	200(9)
O(1)	-1265(11)	3907(6)	9687(8)	146(5)
O(2)	-440(8)	4031(3)	7386(6)	80(3)
O(3)	2172(16)	3625(6)	4126(9)	180(6)
O(4)	-876(13)	4038(4)	4640(7)	109(3)
H(2a)	4311(21)	4414(7)	6276(17)	125(6)
H(2b)	2263(24)	4871(6)	6766(17)	127(6)
H(3a)	2974(25)	4640(6)	9243(16)	136(7)
H(3b)	5085(18)	4187(6)	8709(16)	123(6)
H(7a)	-577(24)	2821(7)	7528(23)	140(7)
H(7b)	1474(29)	2368(7)	7897(21)	152(8)
H(7c)	1008(34)	2536(8)	6144(20)	177(10)
H(8a)	5073(25)	2760(10)	7496(26)	153(9)
H(8b)	5630(19)	3477(8)	7042(24)	155(10)
H(8c)	4581(27)	2953(11)	5791(19)	180(10)
H(9a)	4380(26)	3179(9)	10103(19)	144(8)
H(9b)	2615(32)	3540(12)	11063(15)	191(12)
H(9c)	2050(37)	2829(9)	10230(23)	193(12)
D(11)	-28(25)	4261(7)	2491(15)	138(6)
H(11)	-1219(20)	3502(20)	2770(46)	147(39)
H(12a)	-2889(56)	4872(10)	3070(36)	238(17)
H(12b)	-3567(39)	4370(14)	1679(23)	282(16)
H(12c)	-4272(26)	4034(16)	3399(22)	259(19)

<sup>a</sup> See footnote 32 for definition of *U*(eq).

(for Mo  $K\alpha$  X-rays). (-)-Camphanic acid was converted to sodium camphanate via treatment with  $\text{Na}_2\text{CO}_3$ , and subsequent reaction with  $\text{Cu}(\text{NO}_3)_2$  in ethanol yielded green crystals of a new compound,  $\text{Cu}_2(\text{camphanate})_4(\text{EtOH})_2$ . The dimeric compound crystallizes in the triclinic space group *P1*, with  $a = 11.086(3)$ ,  $b = 11.244(3)$ ,  $c = 13.293(4)$   $\text{\AA}$ ,  $\alpha = 111.59(2)$ ,  $\beta = 107.71(2)$ , and  $\gamma = 105.56(3)^\circ$ ,  $V = 1397.6(7)$   $\text{\AA}^3$ , and  $Z = 1$ . X-ray diffraction data were collected on a Siemens P4 diffractometer at room temperature, and the structure (Figure 2) was solved by direct methods. Refinement of the structure with the camphanate ligands in a 1*S*, 4*R* configuration (see Scheme 2) yielded an agreement factor of  $R_w = 0.058$ , whereas refinement in the enantiomeric 1*R*, 4*S* configuration yielded a significantly inferior agreement factor of  $R_w = 0.065$ . This difference<sup>19</sup> conclusively validates the previously established configuration of (-)-camphanate to be 1*S*, 4*R* (Figure 3 and

**Table 3. Selected Distances and Angles for Ethyl-1-*d* Camphanate (neutron results)**

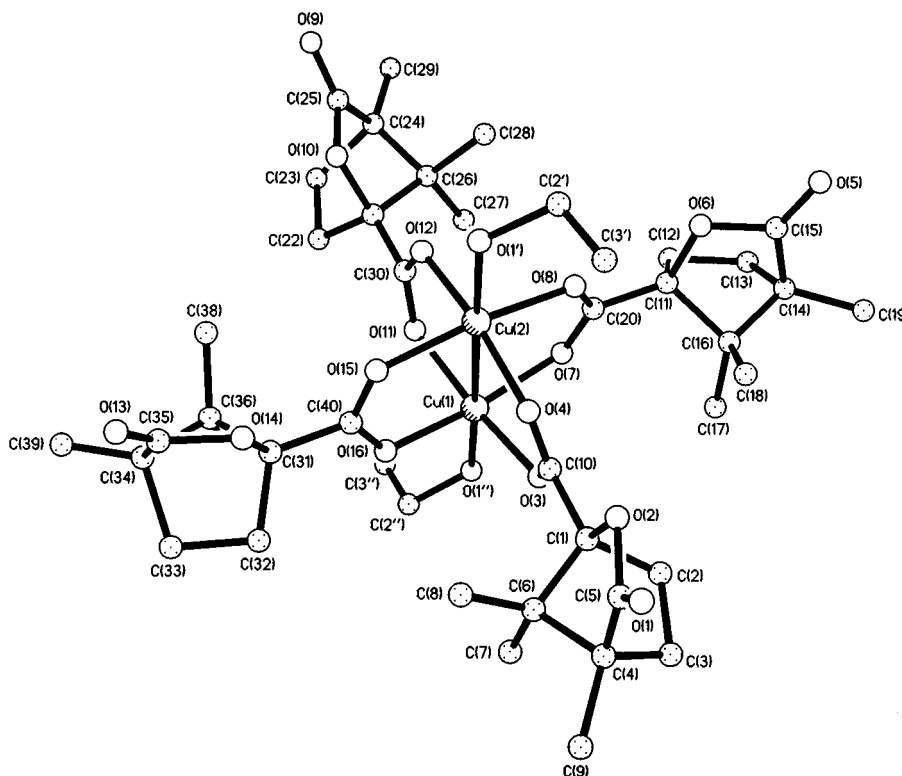
(a) Distances ( $\text{\AA}$ )			
C(1)-C(2)	1.527(8)	C(2)-H(2a)	1.079(20)
C(1)-C(10)	1.518(7)	C(3)-H(3a)	1.050(18)
C(1)-O(2)	1.448(7)	C(3)-H(3b)	1.096(15)
C(1)-C(6)	1.531(6)	C(7)-H(7a)	1.012(23)
C(2)-C(3)	1.558(8)	C(7)-H(7b)	1.064(24)
C(3)-C(4)	1.552(8)	C(7)-H(7c)	1.090(24)
C(4)-C(5)	1.523(7)	C(8)-H(8a)	1.005(28)
C(4)-C(6)	1.539(7)	C(8)-H(8b)	1.013(24)
C(4)-C(9)	1.503(10)	C(8)-H(8c)	1.096(24)
C5)-O(1)	1.185(8)	C(9)-H(9a)	0.990(24)
C(5)-O(2)	1.337(7)	C(9)-H(9b)	1.041(25)
C(6)-C(7)	1.522(9)	C(9)-H(9c)	1.086(27)
C(6)-C(8)	1.525(9)	C(11)-H(11)	1.088(49)
C(10)-O(3)	1.198(9)	C(11)-D(11)	1.195(13)
C(10)-O(4)	1.284(9)	C(12)-H(12a)	1.009(36)
O(4)-C(11)	1.472(10)	C(12)-H(12b)	1.112(23)
C(11)-C(12)	1.394(14)	C(12)-H(12c)	1.221(33)
C(2)-H(2b)	1.007(21)		
(b) Angles (deg)			
C(1)-C(2)-C(3)	99.8(5)	O(4)-C(11)-D(11)	108.7(9)
C(1)-C(6)-C(4)	91.8(3)	H(2b)-C(2)-H(2a)	108.2(11)
C(1)-O(2)-C(5)	106.1(4)	H(3a)-C(3)-H(3b)	107.4(11)
C(2)-C(3)-C(4)	104.3(4)	H(7a)-C(7)-H(7b)	106.3(13)
C(2)-C(1)-C(6)	104.9(4)	H(7a)-C(7)-H(7c)	112.1(15)
C(2)-C(1)-C(10)	113.2(5)	H(7b)-C(7)-H(7c)	103.4(14)
C(2)-C(1)-O(2)	105.3(5)	H(8a)-C(8)-H(8b)	105.3(14)
C(3)-C(4)-C(5)	101.3(5)	H(8a)-C(8)-H(8c)	104.5(16)
C(3)-C(4)-C(6)	102.4(4)	H(8b)-C(8)-H(8c)	110.7(17)
C(3)-C(4)-C(9)	116.1(6)	H(9a)-C(9)-H(9b)	106.6(13)
C(4)-C(5)-O(1)	129.5(6)	H(9a)-C(9)-H(9c)	107.1(16)
C(4)-C(5)-O(2)	107.8(5)	H(9b)-C(9)-H(9c)	108.0(17)
C(7)-C(6)-C(8)	110.1(7)	H(11)-C(11)-D(11)	102.9(34)
C(1)-C(10)-O(3)	122.6(7)	H(12a)-C(12)-H(12b)	108.4(20)
C(1)-C(10)-O(4)	113.3(6)	H(12a)-C(12)-H(12c)	126.6(22)
C(10)-O(4)-C(11)	115.5(9)	H(12b)-C(12)-H(12c)	101.1(19)

Scheme 2) and unambiguously reconfirms the earlier neutron diffraction result on ethyl camphanate (Figure 1). It thus establishes beyond any doubt the *R* absolute configuration of (+)-ethanol-1-*d*.

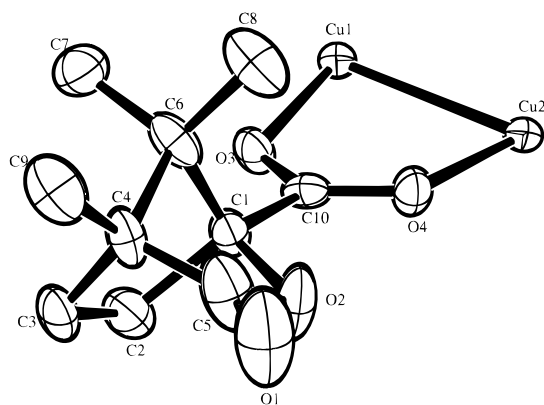
The structure of  $\text{Cu}_2(\text{camphanate})_4(\text{ethanol})_2$  is shown in Figure 2. The four camphanate ligands bridge the two Cu-centers via their deprotonated carboxylate groups, to form the familiar  $\text{M}_2(\text{carboxylate})_4$  core.<sup>20</sup> The dimeric complex has noncrystallographic  $C_4$  symmetry, with all four camphanate ligands oriented in the same rotational direction (Figure 2, for example, shows all four bridgehead  $\text{C}(\text{CH}_3)_2$  groups oriented in a clockwise direction). Thus, despite the centrosymmetric nature of the  $\text{Cu}_2(\text{CO}_2)_4(\text{ethanol})_2$  core, the complex as a whole is decidedly noncentrosymmetric, reflecting the chiral nature of the ligands. Average distances and angles in  $\text{Cu}_2(\text{camphanate})_4(\text{ethanol})_2$  are listed in Table 4. All Cu-Cu-O angles involving the equatorial (carboxylate) oxygens are

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**Figure 2.** Molecular plot of  $\text{Cu}_2(-)\text{-camphanate}]_4(\text{ethanol})_2$  from the X-ray analysis. Note that the central  $\text{Cu}_2(\text{carboxylate})_4(\text{ethanol})_2$  core is approximately centrosymmetric, in contrast to the arrangement of the four bicyclic groups, which are chiral. The dimeric structure as a whole has noncrystallographic  $C_4$  symmetry: note how the four bridgehead  $\text{CMe}_2$  groups [C(6,7,8), C(16,17,18), etc.] all are oriented in a clockwise fashion, and the four  $-\text{O}-\text{CO}-$  lactone groups [O(2)C(5)O(1), O(6)C(15)O(5), etc.] all are situated above the plane of the paper.



**Figure 3.** ORTEP plot of one of the four  $(-)\text{-camphanate}$  ligands in  $\text{Cu}_2(-)\text{-camphanate}]_4(\text{ethanol})_2$ , showing its absolute configuration. Atoms are plotted as 40%-probability ellipsoids. C(1) has the  $(S)$  configuration while C(4) is  $(R)$  (cf. Scheme 2).

less than  $90^\circ$ , a distortion caused by the "bite angle" of the carboxylate group. The intermetallic Cu–Cu distance, 2.667(2) Å, as well as the equatorial Cu–O distances [average 1.980(7) Å], are in agreement with those found in related Cu dimers,<sup>21</sup> while the axial Cu–O distances [average 2.148(8) Å] are significantly longer than the equatorial ones, as expected.

**Table 4. Selected Distances and Angles in  $\text{Cu}_2(\text{camphanate})_4(\text{ethanol})_2$  (X-ray results)**

(a) Distances (Å)			
Cu(1)–Cu(2)	2.667 (2)	Cu(2)–O(15)	1.971 (8)
Cu(1)–O(16)	1.973 (8)	Cu(2)–O(8)	2.014 (8)
Cu(1)–O(7)	1.968 (8)	Cu(2)–O(12)	1.989 (5)
Cu(1)–O(11)	1.970 (6)	Cu(2)–O(4)	1.964 (6)
Cu(1)–O(3)	1.994 (6)	Cu(2)–O(1')	2.143 (8)
Cu(1)–O(1'')	2.152 (8)		
(b) Angles (deg)			
Cu(2)–Cu(1)–O(16)	82.5(2)	Cu(1)–Cu(2)–O(15)	85.1(2)
Cu(2)–Cu(1)–O(7)	84.1(2)	Cu(1)–Cu(2)–O(8)	83.0(2)
O(16)–Cu(1)–O(7)	166.5(3)	O(15)–Cu(2)–O(8)	168.1(3)
Cu(2)–Cu(1)–O(11)	83.6(2)	Cu(1)–Cu(2)–O(12)	83.9(2)
O(16)–Cu(1)–O(11)	89.8(3)	O(15)–Cu(2)–O(12)	89.0(3)
O(7)–Cu(1)–O(11)	89.4(3)	O(8)–Cu(2)–O(12)	89.4(3)
Cu(2)–Cu(1)–O(3)	84.4(2)	Cu(1)–Cu(2)–O(4)	82.9(2)
O(16)–Cu(1)–O(3)	89.3(3)	O(15)–Cu(2)–O(4)	87.4(3)
O(7)–Cu(1)–O(3)	88.7(3)	O(8)–Cu(2)–O(4)	91.5(3)
O(11)–Cu(1)–O(3)	168.0(3)	O(12)–Cu(2)–O(4)	166.6(3)
Cu(2)–Cu(1)–O(1')	178.9(2)	Cu(1)–Cu(2)–O(1')	177.6(2)
O(16)–Cu(1)–O(1')	97.1(3)	O(15)–Cu(2)–O(1')	96.4(3)
O(7)–Cu(1)–O(1')	96.4(3)	O(8)–Cu(2)–O(1')	95.4(3)
O(11)–Cu(1)–O(1')	95.4(3)	O(12)–Cu(2)–O(1')	94.2(3)
O(3)–Cu(1)–O(1')	96.6(3)	O(4)–Cu(2)–O(1')	99.0(3)
Cu(1)–O(3)–C(10)	121.0(6)	Cu(2)–O(4)–C(10)	125.3(5)
Cu(1)–O(7)–C(20)	121.9(6)	Cu(2)–O(8)–C(20)	122.1(7)
Cu(1)–O(11)–C(30)	121.5(5)	Cu(2)–O(12)–C(30)	121.2(6)
Cu(1)–O(16)–C(40)	123.8(7)	Cu(2)–O(15)–C(40)	122.1(6)
C(1)–O(2)–C(5)	99.9(7)	C(11)–O(6)–C(15)	106.2(7)
C(21)–O(10)–C(25)	104.2(6)	C(31)–O(14)–C(35)	105.8(7)

## Discussion

The classical enzyme experiments by Westheimer, Vennesland, and co-workers<sup>8a–c</sup> established that the transfer of hydrogen in the reduction of acetaldehyde-1-*d* by reduced nicotinamide adenine dinucleotide (NADH) in the presence of yeast alcohol dehydrogenase (YADH)

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gave enantiomerically pure ethanol-1-*d*. The reverse reaction selectively removed hydrogen from the chiral ethanol-1-*d* giving back acetaldehyde-1-*d* without loss of deuterium. However, the amount of chiral ethanol-1-*d* that was produced by the purified enzyme system was insufficient for determination of the optical rotation of the ethanol-1-*d*; but by coupling this reduction of CH<sub>3</sub>-CDO to the glucose/ $\delta$ -gluconolactone/glucose dehydrogenase/NAD system (to maintain the NAD in its reduced form), sufficient ethanol-1-*d* was obtained so that it could be rigorously purified and its optical rotation could be determined, i.e.,  $[\alpha]^{28}_D$  (-)0.27° (neat). Stereospecific enzymatic transformations of this product proved that it had the same stereochemistry as that prepared by the uncoupled purified YADH/NADH system, thereby proving the (-) rotation of the product of the purified NADH/ADH system. Our neutron and X-ray diffraction studies have now confirmed the (*R*)-(+)-, (*S*)-(-)-configuration for ethanol-1-*d*, in complete accord with earlier chemical and biochemical studies.<sup>9-11,22</sup>

This paper demonstrates the usefulness of single-crystal neutron diffraction techniques to determine the absolute configuration of molecules possessing chiral methylene groups (molecules of the type CHDRR'). The markedly different neutron-scattering behavior between hydrogen and deuterium means that, in a neutron-scattering experiment, H and D effectively behave as though they were different elements. In this piece of work we have unequivocally shown, via the neutron analysis of its (-)-(1*S*)-camphanate ester, that the absolute configuration of (+)-ethanol-1-*d* is indeed *R*. This result reconfirms the fact that (*R*)-(+)-ethanol-1-*d* has an optical rotation opposite to that of (*R*)-(-)-propanol-1-*d*, (*R*)-(-)-butanol-1-*d*, and (*R*)-(-)-neopentyl-1-*d* alcohol [(*R*)-2,2-dimethylpropanol-1-*d*].<sup>12b,c</sup> Most importantly, our neutron and X-ray diffraction studies unequivocally confirm the (*S*)-(-)-ethanol-1-*d* configuration and supply final proof for the validity of the stereochemistry of the many prior related biochemical studies.

## Experimental Section

**Preparation of (+)-Ethyl-1-*d* (-)-Camphanate.** Rigorously purified (+)-ethanol-1-*d* was made by the method of Gunther, Simon et al.<sup>13</sup> by equilibration of CH<sub>3</sub>CH<sub>2</sub>OH in excess D<sub>2</sub>O with yeast alcohol dehydrogenase, DPN, and diaphorase.<sup>12b,c</sup> This was converted to the camphanate ester.<sup>12b,14</sup> by adding (-)-camphanic acid chloride<sup>14</sup> (2.17 g) to a stirred mixture of pyridine (5 mL) and anhydrous (+)-ethanol-1-*d*: 0.72 g,  $\alpha^{20}_D + 0.188$ ,  $\alpha^{25}_D + 0.1 \pm 0.002^\circ$  (neat,  $l = 1$ ), 93  $\pm$  1% CH<sub>3</sub>CHDOH (enantiomerically pure), 7  $\pm$  1% CH<sub>3</sub>CH<sub>2</sub>OH; specific rotation  $[\alpha]^{20}_D + 0.25^\circ \pm 0.01^\circ$  (neat, corrected for dilution). There was immediate warming, and the reaction mixture became semisolid. The crude product, after being washed with ice-water several times, was air-dried (wgt 1.33 g), crystallized, and recrystallized from 6 mL of warm cyclopentane to which a few drops of methanol were added. The solution was allowed to cool slowly, finally to -10 °C, to give crystals (mp 61 °C), which were recrystallized from cyclopentane at room temperature. These well-formed crystals [wgt 0.47 g, mp 61.5–62.0 °C (microscope hot stage), lit.<sup>14</sup> mp 59–60 °C,  $[\alpha]^{20}_D - 8.8^\circ \pm 0.1^\circ$  ( $c = 1$ , acetone)] were stored in a vacuum desiccator over P<sub>2</sub>O<sub>5</sub>.

**Preparation of Cu<sub>2</sub>(camphanate)<sub>4</sub>(ethanol)<sub>2</sub>.** A concentrated mixture of (-)-camphanic acid (5 mmol, 99 mg) and Na<sub>2</sub>CO<sub>3</sub> (2.5 mmol, 268 mg) was heated under reflux conditions until CO<sub>2</sub> evolution stopped. Subsequently a solution of Cu(NO<sub>3</sub>)<sub>2</sub> (2.5 mmol, 469 mg) in 16 mL of EtOH was added.

The resulting green solution was filtered and the filtrate allowed to slowly evaporate at room temperature to give green prismatic crystals of Cu<sub>2</sub>(camphanate)<sub>4</sub>(ethanol)<sub>2</sub>·2EtOH.

**Neutron Diffraction Analysis of (+)-Ethyl-1-*d* (-)-Camphanate.** Large crystals of (+)-ethyl-1-*d* (-)-camphanate were obtained from a cyclopentane solution by slowly evaporating the solvent over a period of 4 days. The low-melting crystals, which were soft and waxy, were cut very gently with a slightly-warmed knife to get crystals of suitable size. Data collection at 15 K was attempted following procedures described elsewhere.<sup>23</sup> Cooling to 270 K produced an abrupt decrease in the intensity of a monitored reflection (060):  $\omega$  scans at 15 K showed profiles splitting into two peaks with separations as large as 1°. Subsequent warming to 295 K showed that the effect was irreversible, since the original profiles were not recovered. Consequently, it was decided to collect data at room temperature on another crystal.

The crystal fragment chosen for data collection had faces approximating the forms {100}, {010}, {001} and had dimensions 2.2  $\times$  3.7  $\times$  2.4 mm, where the longest dimension was coincident with the *b* axis. The data were collected with the four-circle diffractometer at port H6M of the Brookhaven High Flux Beam Reactor. The neutron beam, monochromated by reflection from Be(002) planes, was of wavelength 1.0462(1) Å as determined by calibration with a KBr crystal ( $a_0 = 6.6000$  Å at 295 K). Lattice parameters were determined by a least-squares fit of  $\sin^2 \theta$  values for 30 reflections within the range 49° <  $2\theta$  < 53°. One octant of data ( $h \leq 7$ ,  $k \leq 23$ ,  $l \leq 10$ ; 1219 reflections) was measured by the  $\theta/2\theta$  scan method using scan widths of  $\Delta 2\theta = 2.8^\circ$  for  $\sin \theta/\lambda \leq 0.44$  Å<sup>-1</sup>, and  $\Delta 2\theta = 3.0^\circ$  for  $0.44 < \sin \theta/\lambda < 0.51$  Å<sup>-1</sup>. The intensities of two reflections [(5 -3 1); (4 8 4)], monitored at regular intervals, showed no systematic variations. Integrated intensities  $I_0$  and variances  $\sigma^2(I_0)$  were derived from the scan profiles as previously described.<sup>23</sup> Absorption corrections<sup>24</sup> were applied using  $\mu_n = 2.256$  cm<sup>-1</sup> evaluated from  $\mu/\rho = 24.8$  cm<sup>2</sup> g<sup>-1</sup> for hydrogen at  $\lambda = 1.0462$  Å.<sup>25</sup> Minimum and maximum calculated absorption factors were 1.536 and 1.968. Of 1114 independent observations, 418 were less than  $3\sigma(F_0^2)$  and 21 were less than  $1\sigma(F_0^2)$ .

The initial atomic parameters were taken from a previously performed X-ray analysis.<sup>15</sup> Coherent neutron-scattering lengths (fm) for H(-3.7409), D(6.674), C(6.6484), and O(5.803) were taken from the tabulation by Koester.<sup>26</sup> A series of difference maps unambiguously showed the existence of 17 negative peaks (hydrogen) and one positive peak (deuterium). Refinement was carried out by full-matrix least-squares using the program UPALS.<sup>27</sup> The residual  $\sum w|F_0^2 - F_c^2|^2$  was minimized with weights  $w = [\sigma(F_0^2) + (0.02F_0^2)^2]^{-1}$ , summing initially over the 1093 independent observations with  $F_0^2 > 1\sigma(F_0^2)$ . A total of 309 parameters were varied, including (a) an overall scale factor, (b) the atomic coordinates, (c) the anisotropic thermal factors, (d) the scattering lengths of atoms D(11) and H(11) (*vide infra*), and (e) an isotropic secondary extinction parameter for a type I crystal.<sup>28</sup> The data were affected by extinction, the largest corrections ( $\times F_0^2$ ) being 1.39 for reflection (0 4 0) and 1.22 for reflection (1 1 0), which were omitted from the final refinement. The refinement converged with agreement indices  $R(F^2) = 0.083$ ,  $wR(F^2) = 0.075$ , and  $S$

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= 1.183.<sup>29</sup> Damping factors of 0.1–0.5 were applied to the coordinates and thermal factors of the two H(D) sites, which otherwise displayed oscillatory behavior. In the final  $\Delta F$  map, the largest  $|\Delta\rho|$  errors were  $\sim 3.8\%$  of the peak maximum for carbon in the  $\rho_o$  map; these residuals occurred near the ester group and are attributed to pronounced thermal motion or static disorder that is unresolved by the present data set obtained at room temperature.

During the neutron analysis, the scattering lengths of the two atoms comprising the chiral CHD group, D(11) and H(11), were refined as variables. They converged to values of +4.35(15) fm and  $-1.05(14)$  fm for D(11) and H(11), respectively, as compared with standard values of +6.67 fm for D and  $-3.74$  fm for H. This corresponds to 78(2)% occupancy of deuterium at the D(11) site and a 74(2)% occupancy of hydrogen at the H(11) site, whereas NMR integration yielded a total deuterium incorporation of  $93 \pm 1\%$  at the CHD site (vide supra). However, this minor discrepancy (which incidentally was not observed in our other neutron diffraction analyses of chiral CHD groups<sup>4–6</sup>) does not affect the validity of the overall conclusion.

**X-ray Analysis of  $\text{Cu}_2(\text{camphanate})_4(\text{ethanol})_2$ .** A crystal of dimensions  $0.8 \times 0.6 \times 0.4$  mm was used for data collection. This crystal was mounted in a glass capillary with the mother liquor to prevent its desolvation. Intensity data were collected with  $\omega$ -scans of variable scan-speed,  $6.0\text{--}60.0^\circ \text{ min}^{-1}$  in  $\omega$ , and with a scan width of  $2.0^\circ$ . A Siemens P4 diffractometer with graphite-monochromated Mo  $K\alpha$  radiation was used for preliminary examination and data collection. The lattice parameters were determined from a constrained least-squares fit of the angular settings of 25 reflections having a  $2\theta_{\text{max}}$  of  $45.5^\circ$ . Three standard reflection intensities were recorded at 100-reflection intervals, and only random deviations were detected during the time of data collection. Two hemispheres of data (3678 reflections) with  $2.0 \leq 2\theta \leq 45.5^\circ$ , ( $-10 \leq h \leq 11$ ,  $-10 \leq k \leq 10$ ,  $-13 \leq l \leq 13$ ) were measured. The data were reduced and corrected for Lorentz-polarization and absorption effects (via empirical  $\psi$ -scans) yielding 3672 unique reflections, 3184 of which had  $F \geq 4.0 \sigma(F)$ . The

(29) For the neutron analysis,  $R(F^2) = \Sigma\Delta/\Sigma F_o^2$ ;  $wR(F^2) = [\Sigma w\Delta^2/\Sigma (wF_o^2)^2]^{1/2}$ ;  $S = [\Sigma w\Delta^2/\Sigma(n-p)]^{1/2}$ , where  $\Delta = |F_o^2 - F_c^2|$ , and  $n$  and  $p$  are the numbers of observations and parameters, respectively. For the X-ray analysis,  $R(F) = \Sigma|F_o - F_c|/\Sigma F_o$  and  $wR(F) = [\Sigma w(|F_o - F_c|)^2/\Sigma wF_o^2]^{1/2}$ .

structure was solved in space group  $P1$  via direct methods.<sup>30</sup> It was refined (on  $F$ ) using full-matrix least-squares with anisotropic thermal factors for all non-H atoms and a common isotropic thermal factor for the H-atoms, which were placed in calculated positions. A total of 610 parameters were refined<sup>31</sup> to agreement factors<sup>29</sup> of  $R(F) = 0.054$  and  $wR(F) = 0.058$  with  $(\Delta/\sigma)_{\text{max}} = 0.06$ .

For the anomalous dispersion analysis, models corresponding to the two enantiomeric isomers were refined separately. The  $1S,4R$  isomer gave an  $R_w$  value of 0.058, whereas the inverted  $1R,4S$  isomer could be refined under analogous conditions only to  $R_w = 0.065$ . This significant difference in  $R$ -values proves<sup>19</sup> the absolute configuration of camphanic acid to be  $1S,4R$ .

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**Supporting Information Available:** Supplementary tables for the X-ray analysis of  $\text{Cu}_2(\text{camphanate})_4(\text{ethanol})_2$  (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(31) Sheldrick, G. M. *SHELX-76 System for Crystallographic Programs*; University of Cambridge, England, 1976.

(32)  $U(\text{eq})$ , the equivalent isotropic temperature factor, is defined as one-third of the trace of the orthogonalized  $U(ij)$  tensor.