$MgSO_4/Na_2CO_3$) and the solvent was removed to give a near quantitative yield of (−)-**9**. An analytical sample was obtained by bulb-to-bulb distillation: bp 80–110 °C (bath temperature) (0.1 mmHg); $[\alpha]^{25}_D$ −22.9° (*c* 2.3, Et_2O); IR (neat film) 2960 (s), 2880 (s), 1465 (m), 1400 (m), 1378 (m), 1312 (m), 1260 (m), 1218 (m), 1100 (m), 1048 (m), 1027 (m), 962 (m), 916 (m), 901 (m), 867 (m), 828 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.57 (2 H, 2-OCH, d, J_{AB} = 11.5 Hz), 3.42 (2 H, 2-OCH, d, J_{AB} = 11.5 Hz), 2.65 (2 H, epoxide H, m), 1.71 (2 H, CH_2, m), 1.55 (4 H, 2-CH_2, m), 1.37 (3 H, CH_3, s), 1.02 (3 H, CH_3, s), 0.98 (3 H, CH_3, t, *J* = 7 Hz), 0.86 (3 H, CH_3, s); mass spectrum, *m/e* (relative intensity) 227 (12, $M^+ - CH_3$), 129 (100), 99 (15), 97 (10), 95 (13), 81 (15), 71 (17), 70 (10), 69 (55), 57 (15), 55 (13), 43 (38); CI (isobutane) 243 (53, $M^+ + 1$), 225 (14), 157 (62), 141 (18), 140 (10), 139 (100), 129 (35), 123 (12). Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.64; H, 11.01.

A similar reaction of (+)-**8** with $LiCuMe_2$ yielded (+)-**9**: $[\alpha]^{25}_D$ +21.0° (*c* 2.2, Et_2O).

(+)-*endo*-Brevicomin (1). A solution of (−)-**9** (17.2 g, 71.1 mmol) in pentane (250 mL) was stirred with 2 N HCl (60 mL) for 16 h at room temperature. The organic phase was washed with saturated $NaHCO_3$ solution (50 mL) and saturated NaCl solution (50 mL). After drying (anhydrous $MgSO_4$) and removal of solvent on a rotary evaporator without heating, the residue was distilled to yield (+)-**1** (7.73 g, 69%): $[\alpha]^{25}_D$ +64.2° (*c* 2.3, Et_2O), lit.[5b] $[\alpha]^{21}_D$ +78.8° (*c* 0.5, Et_2O), lit.[5c] $[\alpha]^{25}_D$ −65.4° (*c* 2.1, Et_2O).

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On the Deuterium Thermodynamic Isotope Effect on the Equilibration of 2-Cyclohexenol-α-*d* and 2-Cyclohexenol-γ-*d*

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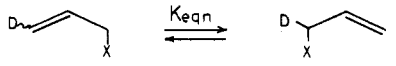
In connection with other work we needed to know the equilibrium distribution of a deuterium label for equilibration of allylic-α-*d* and -γ-*d* derivatives (eq 1) in systems

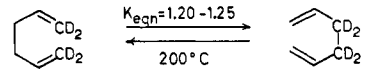


(1)

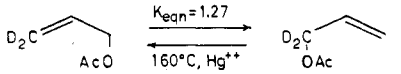
in which the rearrangement is degenerate except for the deuterium label. In such systems the equilibrium constant is the so-called[1] deuterium thermodynamic isotope effect (TIE) as shown by eq 2.

$$K_{eqn} = sp^3\alpha\text{-}d/sp^2\gamma\text{-}d = \text{TIE} \quad (2)$$

Deuterium isotope effects have been reported for equilibration of 1,1,6,6- and 3,3,4,4-tetradeuterio-1,5-hexadiene (eq 3)[1] and 1,1- and 3,3-dideuterioallyl acetate (eq 4).[2] However, these thermal equilibrations require higher temperatures than the range of interest to us, and isotope effects are complicated by the presence of more than one deuterium.

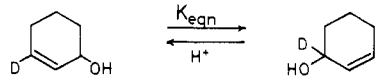


(3)



(4)

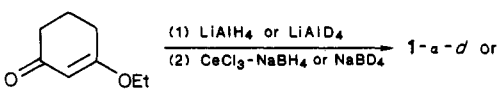
In this work we determined the equilibrium deuterium distribution for the acid-catalyzed ($HClO_4$) equilibration of 2-cyclohexenol-α-*d* and -γ-*d* (*1*) in aqueous acetone (eq 5). This equilibration was selected because from earlier



1-γ-*d* 1-α-*d* (5)

studies[3] it was known that the pseudo-first-order rates for such equilibrations are directly proportional to the acid concentration. Thus convenient rates can be arranged by adjusting acid concentration. Moreover, the equilibrium distribution can easily be determined for different temperatures because equilibration is quenched instantly by neutralization of the acid. Also, in this system the 1-α-*d*/1-γ-*d* ratio can readily be determined directly by ^2H NMR spectroscopy.[4]

The labeled alcohols 1-α-*d* and 1-γ-*d* were prepared from 3-ethoxy-2-cyclohexenone by a method similar to that reported earlier.[4] These preparations involve two hydride reductions (eq 6). The first gives 2-cyclohexenone (or



(6)

2-cyclohexenone-3-*d* and this is converted to 1-α-*d* or 1-γ-*d* by the second reduction. In this work we used sodium borohydride with cerium chloride[5] instead of lithium aluminum hydride for the second reduction. With lithium aluminum hydride the product contain 3–7% cyclohexanol (or deuteriated cyclohexanol) that results from conjugate addition to the enone. Conjugate addition is lowered to ~2% with the $CeCl_3$–$NaBH_4$ (or $NaHD_4$) reduction. Thus 1-α-*d* contained ~2% 1,3-dideuteriocyclohexanol. This saturated contaminant is inert under the conditions of the

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Table I. Equilibrium Studies of the Acid-Catalyzed Equilibrium of 2-Cyclohexenol-α-*d* and -γ-*d*

compd	% acetone[a]	temp °C	10^2-[$HClO_4$], M	k_{eqn},[b] h^{-1}	K_{eqn}[c]
1-α-*d*	35	30.2	9.51	0.298	1.17 ± 0.02
1-γ-*d*	35	30.2	9.51	0.310	1.17 ± 0.02
1-α-*d*	35	50.68	3.04	1.00	1.14 ± 0.02
1-γ-*d*	35	50.65	3.04	1.14	1.17 ± 0.02
1-γ-*d*	60	50.00	6.40	0.60	1.18 ± 0.02
1-γ-*d*	60	90.02	0.64	0.61	1.14 ± 0.02

[a] Solvent composition refers to volumes of pure components at room temperature prior to mixing. [b] Observed pseudo-first-order rate constants for equilibration. [c] Average and average deviation of three independent determinations of the equilibrium ratio of 1-α-*d*/1-γ-*d*.

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equilibration experiments. However, the 1-deuterium ^2H NMR signal overlapped with that for 1-α-*d*. Thus data for experiments with 1-α-*d* were corrected for the presence of the saturated contaminant. The exact amount of the contaminant was determined by capillary GC. Similarly, 1-γ-*D* contained ~2% 3-deuteriocyclohexanol. In this case the ^2H NMR signal is completely resolved from those for 1-α-*d* and 1-γ-*d* and thus this inert contaminant does not interfere with the equilibration measurements.

Results of the equilibrium studies are presented in Table I. Pseudo-first-order rate constants for equilibration (k_{eqn}) were obtained by quenching samples of reaction mixture with base at appropriate times and determining the deuterium distribution (amount of equilibration) by planimeter measurements of the ^2H NMR signals for 1-α-*d* and 1-γ-*d*. Reactions were followed from about 20% to 80% completion, and good first-order behavior was observed.

The equilibrium 1-α-*d*/1-γ-*d* ratios (K_{eqn}) were determined after 10 half-lives for equilibration. The equilibrium constants in Table I are average values (and average deviations) of three independent determinations. As would be expected, K_{eqn} is insensitive to change in solvent. This constant is also relatively insensitive to change in temperature; values for 30 and 90 °C are within combined experimental uncertainties.

The data in Table I show that for the temperature range investigated the equilibrium deuterium distribution is about 53.6% 1-α-*d* and 46.4% 1-γ-*d*. The equilibrium constant corresponds to a standard free-energy difference of ~90 cal/mol favoring the isomer with a sp^3 α-deuterium and a sp^2 γ-hydrogen over that with a sp^3 α-hydrogen and a sp^2 γ-deuterium. The magnitude of this thermodynamic deuterium isotope effect is similar to that estimated from the earlier data[1,2] by correcting for temperature differences and multiple deuterium atoms.

Experimental Section

General Methods. Proton-decoupled ^2H NMR spectra were determined with a JEOLCO FX-200 spectrometer operating at 30.6 MHz. Deuterium chemical shifts are relative to $CDCl_3$ set to 7.24 ppm. Fourier transform was used with a 2.40-s acquisition time and 2.0-s relaxation delay. Proton spectra were determined with a Brucker WP-200SY instrument. $LiAlD_4$ and $NaBD_4$ (98 atom % D) were obtained from Aldrich. Acetone was stored over $KMnO_4$, dried over $CaSO_4$, and fractionated. Conductivity water was obtained from a Millipore Super-Q filtration system. Aqueous acetone compositions are based on volumes of pure components at ambient temperature prior to mixing.

2-Cyclohexenol-α-*d* (1-α-*d*). Reduction of 2-cyclohexenone[4] by a cerium chloride catalyzed borodeuteride reduction[5] gave a 76% yield of 1-α-*d*, bp 78 °C (22 mm). Capillary GC (147 ft, UCON LB550, 80 °C) showed that this product contained ~2% 1,3-dideuteriocyclohexanol. This product had the following: ^1H NMR ($CDCl_3$) δ 5.84 (dt, 1 H, J = 10.1, 3.5 Hz), 5.79 (d, 1 H, J = 10.1 Hz), 3.48 (br s, 1 H (OH)), 1.5-2.1 (m, 6 H); ^2H NMR (acetone) δ 3.33 (98.5%), 1.3 (1.5%). The latter signal results from 1,3-dideuteriocyclohexanol.

2-Cyclohexenol-γ-*d* (1-γ-*d*). This compound was prepared in a similar manner by $CeCl_3$-$NaBH_4$ reduction of 3-deuterio-2-cyclohexenone.[4] This product had the following: ^1H NMR ($CDCl_3$) δ 5.75 (s, 1 H), 4.20 (br, d, 1 H, J = 3 Hz), 3.70 (s, 1 H (OH)), 1.4-2.0 (m, 6 H); ^2H NMR (acetone) δ 4.98.

Rates of Acid-Catalyzed Equilibration of 1-α-*d* and 1-γ-*d*. In typical experiments 15 mmol of labeled **1** was rapidly mixed with 100 mL of thermostated aqueous acetone containing the indicated concentration of $HClO_4$ (Table I). Aliquots of the thermostated reaction mixture were withdrawn at appropriate times and delivered into excess aqueous NaOH to quench the reaction. The quenched samples were saturated with salt, extracted with ether, dried, and distilled. Three aliquots were quenched after 10 half-lives for equilibration to determine the equilibrium deuterium distribution. Deuterium distributions were determined from relative peak areas (planimeter) for α-*d*- and γ-*d* signals. Pseudo-first-order rate constants were determined from slopes of ln (X-X_e) vs. time plots, in which X is the fraction of deuterium in the α position at various times and X_e is the fraction of deuterium in the α position after equilibration (10 half-lives). Data for the kinetic and equilibration experiments are presented in Table I.

Acknowledgment. This work was supported by the National Science Foundation (Grant CHE-8406480).

Registry No. 1-γ-*d*, 73741-72-7; 1-α-*d*, 55282-88-7.

A Convenient, General Synthesis of α-Trichloromethyl Carbinols

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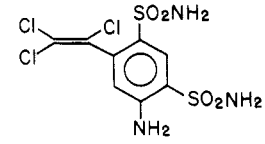
The condensation of chloroform with aldehydes and ketones under basic conditions is a standard method for the preparation of α-trichloromethyl carbinols, which serve as key intermediates in a variety of synthetic applications.[1] With highly reactive aldehydes such as nitrobenzaldehydes, the competing Cannizzaro reaction is often a serious problem resulting in low yields or exclusively Cannizzaro products.[2] This problem was overcome in the simple, high-yielding preparation of α-(trichloromethyl)-3-nitrobenzyl alcohol (**3**) described in this paper. We required **3** in our synthesis of clorsulon (**1**), used in the treatment of liver flukes in animals.[3]



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Several reports describe the condensation of substituted benzaldehyde derivatives with chloroform in the presence of various bases to produce the corresponding α-(trichloromethyl)benzyl alcohols.[2a,4] With solid potassium hydroxide without solvent only Cannizzaro reaction products were obtained in the condensation of *m*-nitrobenzaldehyde (**2**) and chloroform.[2a] Phase-transfer conditions[4a] produced a mixture of nitrobenzoic acid, nitrobenzyl alcohol, and modest yields of α-(trichloromethyl)-nitrobenzyl alcohol. Potassium *tert*-butoxide in liquid ammonia at −75 °C has been reported to effect the desired condensation to form α-(trichloromethyl)-3-nitrobenzyl

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