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# A Thermodynamic Study of the Reactions of Cyclodextrins with Primary and Secondary Aliphatic Alcohols, with D- and L-Phenylalanine, and with L-Phenylalanineamide

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Equilibrium constants and standard molar enthalpies of reaction have been determined by titration calorimetry for the reactions of 1-propanol, 2-propanol, 1-butanol, (*R*)-(+)-2-butanol, (*S*)-(−)-2-butanol, (±)-butanol, (*R*)-(+)-2-pentanol, (*S*)-(−)-2-pentanol, (*R*)-(+)-2-hexanol, (*S*)-(−)-2-hexanol, (*R*)-(+)-2-heptanol, (*S*)-(−)-2-heptanol, D-phenylalanine, L-phenylalanine, and L-phenylalanineamide with α-cyclodextrin and β-cyclodextrin. The standard molar Gibbs energies, standard molar enthalpies, and standard molar entropies for these reactions correlate well with respect to the number of carbon atoms in the chemical formula of the alcohol and form a series of distinct curves for the different types of alcohols. The results are also discussed in relation to hydrophobic, steric, and charge effects and the exchange reaction for a ligand from α-cyclodextrin to β-cyclodextrin. With the exception of the results for the standard molar enthalpies of reaction of the 2-butanols with α-cyclodextrin, the results obtained in this study show that, within the indicated uncertainties, there are no differences in any of the thermodynamic quantities for the reactions of these ligands with either α- or β-cyclodextrin due to the change in the location of a hydrogen atom on an optically active carbon atom.

## Introduction

Cyclodextrins are known to react with a wide variety of ligands in aqueous solution. These reactions are of considerable interest due to their importance in separation technology,[1−3] drug delivery systems,[4,5] and as models of (enzyme + substrate) interactions.[6] The interactions between the cyclodextrins and the ligands that bind to them are believed to involve primarily hydrophobic interactions, van der Waals forces, and steric effects. Although a general model capable of separating these effects has not yet been developed, a practical approach to some quantitative understanding of these reactions is to perform thermodynamic studies in which the size or nature of the ligands is changed in some systematic way. In this study, we have used titration calorimetry to measure equilibrium constants and standard molar enthalpies for the reactions of a series of primary and secondary alcohols with α- and β-cyclodextrin. These results, when combined with other data from the literature on the reactions of alcohols with cyclodextrins, allow for an examination of the relationships between thermodynamic quantities and the number of carbon atoms in the chemical formula of the alcohol and the location of the hydroxyl group on the alcohol. Since several of these alcohols are stereoisomers, we also performed measurements on the reactions of stereoisomers of the alcohols with the cyclodextrins to see if there were any differences in the thermodynamic quantities due to a change at a chiral center. Measurements were also performed for the reactions of D- and L-phenylalanine and L-phenyalanineamide with α- and β-cyclodextrin as an additional test of possible effects due to a change at a chiral center and to examine the effects of the presence of charges on these ligands.

## Experimental Section

The principal substances used in this study, their respective Chemical Abstracts Services registry numbers, empirical formulas, and molar masses are as follows: 1-butanol, 71-36-3, $C_4H_{10}O$, 0.074 122 8 kg mol$^{-1}$; (*R*)-(−)-2-butanol, 14898-79-4, $C_4H_{10}O$, 0.074 123 kg mol$^{-1}$; (*S*)-(+)-2-butanol, 4221-99-2, $C_4H_{10}O$, 0.074 123 kg mol$^{-1}$; (±)-2-butanol, 15892-23-6, $C_4H_{10}O$, 0.074 123 kg mol$^{-1}$; α-cyclodextrin, 10016-20-3, $C_{36}H_{60}O_{30}$, 0.972 85 kg mol$^{-1}$; β-cyclodextrin, 7585-39-9, $C_{42}H_{70}O_{35}$, 1.1350 kg mol$^{-1}$; (*R*)-(−)-2-heptanol, 6033-24-5, $C_7H_{16}O$, 0.116 20 kg mol$^{-1}$; (*S*)-(+)-2-heptanol, 6033-23-4, $C_7H_{16}O$, 0.116 20 kg mol$^{-1}$; (*R*)-(−)-2-hexanol, 26549-24-6, $C_6H_{14}O$, 0.102 18 kg mol$^{-1}$; (*S*)-(+)-2-hexanol, 52019-78-0, $C_6H_{14}O$, 0.102 18 kg mol$^{-1}$; (*R*)-(−)-2-pentanol, 31087-44-2, $C_5H_{12}O$, 0.088 15 kg mol$^{-1}$; (*S*)-(+)-2-pentanol, 26184-62-3, $C_5H_{12}O$, 0.088 15 kg mol$^{-1}$; D-phenylalanine, 673-06-3, $C_9H_{11}NO_2$, 0.165 19 kg mol$^{-1}$; L-phenylalanine, 63-91-2, $C_9H_{11}NO_2$, 0.165 19 kg mol$^{-1}$; L-phenylalanineamide, 5241-58-7, $C_9H_{12}N_2O$, 0.164 21 kg mol$^{-1}$; 1-propanol, 71-23-8, $C_3H_8O$, 0.060 095 9 kg mol$^{-1}$; 2-propanol, 67-63-0, $C_3H_8O$, 0.060 095 9 kg mol$^{-1}$.

The 1-butanol, (*R*)-(−)-2-butanol, (*S*)-(+)-2-butanol, (±)-2-butanol, (*R*)-(−)-2-heptanol, (*S*)-(+)-2-heptanol, (*R*)-(−)-2-hexanol, (*S*)-(+)-2-hexanol, (*S*)-(+)-2-pentanol, (*R*)-(−)-2-pentanol, and (*S*)-(+)-2-pentanol were obtained from Aldrich;[24] D-phenylalanine, L-phenylalanine, and L-phenylalanineamide were obtained from Sigma; the 1-propanol and 2-propanol were obtained from Mallinckrodt. All substances were used without further purification. The moisture contents given in mass % were determined by Karl−Fischer analysis and found to be 1-butanol (0.08 ± 0.07),[25] (*R*)-(−)-2-butanol (1.25 ± 0.02), (*S*)-(+)-2-butanol (0.49 ± 0.07), (±)-2-butanol (0.25 ± 0.03), (*R*)-(−)-2-heptanol (1.07 ± 0.20), (*S*)-(+)-2-heptanol (0.80 ± 0.10), (*R*)-(−)-2-hexanol (0.77 ± 0.22), (*S*)-(+)-2-hexanol (1.40 ± 0.17), (*R*)-(−)-2-pentanol (1.29 ± 0.09), (*S*)-(+)-2-pentanol (1.20 ± 0.15), D-phenylalanine (0.35 ± 0.01), L-phenylalanine (0.03 ± 0.01), L-phenylalanineamide (5.1 ± 1.0), 1-propanol (0.30 ± 06), and 2-propanol (0.43 ± 02).

The vendor provided us with the following information on the optical rotations and respective chemical purities: (*R*)-(−)-2-butanol, −12.9°, 99.3 mol %; (*S*)-(+)-2-butanol, +11.4°, 99.8 mol %; (*R*)-(−)-2-heptanol, −10.2°, 99.7 mol %; (*S*)-(+)-2-heptanol, +10.1°, 99.2 mol %; (*R*)-(−)-2-hexanol, −11.4°, 99.9 mol %; (*S*)-(+)-2-hexanol, +10.8°, 99.2 mol %; (*R*)-

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**TABLE 1: Thermodynamic Quantities $K$, $\Delta_rH°$, $\Delta_rG°$, and $\Delta_rS°$ at $T$ = 298.15 K for the Reaction α-Cyclodextrin(aq) + Ligand(aq) = α-Cyclodextrin·ligand(aq)[a]**

| ligand | $m$ (mol kg$^{-1}$) | pH | $N$ | $K$ | $\Delta_rH°$ (kJ mol$^{-1}$) | $\Delta_rG°$ (kJ mol$^{-1}$) | $\Delta_rS°$ (J K$^{-1}$ mol$^{-1}$) |
|---|---|---|---|---|---|---|---|
| L-phenylalanine$^{\pm}$ | 0.129 | 5.01[b] | 2 | (8 ± 5) | −(12 ± 7) | −(5.2 ± 2.4) | −(23 ± 25) |
| D-phenylalanine$^{\pm}$ | 0.122 | 5.01[b] | 2 | (8 ± 6) | −(15 ± 11) | −(5.2 ± 3.4) | −(33 ± 39) |
| L-phenylalanineamide$^{+}$ | 0.219 | 5.01[b] | 2 | (12.0 ± 1.1) | −(14.3 ± 1.1) | −(6.2 ± 0.3) | −(27 ± 4) |
| L-phenylalanineamide$^{0}$ | 0.219 | 10.02[c] | 2 | (18.6 ± 2.3) | −(18.2 ± 1.9) | −(7.2 ± 0.3) | −(37 ± 7) |
| 2-propanol | 0.624 | 6.90[d] | 2 | (9.7 ± 3.1) | −(1.2 ± 0.3) | −(5.6 ± 1.0) | (15 ± 3) |
| 1-butanol | 0.250 | 6.90[d] | 2 | (79.7 ± 2.5) | −(11.6 ± 0.2) | −(10.9 ± 0.1) | −(3 ± 0.3) |
| (*S*)-(+)-2-butanol | 0.214 | 6.90[d] | 2 | (24.1 ± 2.2) | −(11.1 ± 0.7) | −(7.9 ± 0.3) | −(11 ± 3) |
| (*R*)-(−)-2-butanol | 0.239 | 6.90[d] | 2 | (24.5 ± 1.3) | −(11.0 ± 0.5) | −(7.9 ± 0.2) | −(10.4 ± 1.8) |
| (±)-2-butanol | 0.263 | 6.90[d] | 2 | (27.8 ± 1.5) | −(9.9 ± 0.4) | −(8.2 ± 0.2) | −(5.7 ± 0.5) |
| (*S*)-(+)-2-pentanol | 0.128 | 6.90[d] | 2 | (125 ± 3) | −(15.2 ± 0.2) | −(12.0 ± 0.1) | −(10.7 ± 0.8) |
| (*R*)-(−)-2-pentanol | 0.164 | 6.90[d] | 2 | (126 ± 4) | −(15.4 ± 0.3) | −(12.0 ± 0.1) | −(11.4 ± 1.1) |
| (*S*)-(+)-2-hexanol | 0.052 | 6.90[d] | 3 | (347 ± 11) | −(16.9 ± 0.3) | −(14.5 ± 0.1) | −(8.0 ± 1.1) |
| (*R*)-(−)-2-hexanol | 0.103 | 6.90[d] | 2 | (344 ± 17) | −(17.2 ± 0.4) | −(14.5 ± 0.2) | −(9.0 ± 1.5) |
| (*R*)-(−)-2-hexanol | 0.088 | 6.90[d] | 2 | (359 ± 40) | −(16.4 ± 0.8) | −(14.6 ± 0.3) | −(6 ± 3) |
| (*S*)-(+)-2-heptanol | 0.021 | 6.90[d] | 2 | (763 ± 125) | −(22.0 ± 1.5) | −(16.5 ± 0.4) | −(18 ± 5) |
| (*R*)-(−)-2-heptanol | 0.020 | 6.90[d] | 1 | (758 ± 192) | −(22.1 ± 2.3) | −(16.4 ± 0.7) | −(19 ± 8) |

[a] The molality $m$ of the ligand for which the measurements were performed, the pH, and $N$ the number of sets of titration experiments performed are given in columns 2, 3, and 4, respectively. In all cases the molality of the α-cyclodextrin was (0.0015−0.0035) mol kg$^{-1}$. [b] Acetate (0.1 mol kg$^{-1}$) + acetic acid. [c] Glycine buffer (0.1 mol kg$^{-1}$) + NaOH. [d] Phosphate buffer {($NaH_2PO_4$, 0.025 mol kg$^{-1}$) + ($Na_2HPO_4$, 0.025 mol kg$^{-1}$)}.

**TABLE 2: Thermodyanmic quantities $K$, $\Delta_rH°$, $\Delta_rG°$, and $\Delta_rS°$ at $T$ = 298.15 K for the Reaction β-Cyclodextrin(aq) + Ligand(aq) = β-Cyclodextrin·ligand(aq)[a]**

| ligand | $m$ (mol kg$^{-1}$) | pH | $N$ | $K$ | $\Delta_rH°$ (kJ mol$^{-1}$) | $\Delta_rG°$ (kJ mol$^{-1}$) | $\Delta_rS°$ (J K$^{-1}$ mol$^{-1}$) |
|---|---|---|---|---|---|---|---|
| L-phenylalnine$^{\pm}$ | 0.129 | 5.01[b] | 2 | (3 ± 7) | −(12 ± 22) | −(3 ± 3) | −(30 ± 75) |
| L-phenylalanineamide$^{+}$ | 0.219 | 5.01[b] | 2 | (22 ± 2) | −(9.0 ± 0.5) | −(7.7 ± 0.3) | −(4.4 ± 2) |
| L-phenylalanineamide$^{0}$ | 0.219 | 10.02[c] | 2 | (107 ± 3) | −(11.9 ± 0.2) | −(11.6 ± 0.1) | −(1.0 ± 0.8) |
| 1-propanol | 0.488 | 6.90[d] | 2 | (4.5 ± 1.7) | (6.0 ± 2.0) | −(3.7 ± 1.2) | (33 ± 8) |
| 2-propanol | 0.624 | 6.90[d] | 2 | (2.6 ± 0.5) | 11.1 ± 1.8) | −(2.4 ± 0.5) | (45 ± 6) |
| 1-butanol | 0.361 | 6.90[d] | 4 | (16 ± 2) | (4.3 ± 0.4) | −(6.9 ± 0.5) | (37.5 ± 0.7) |
| (*S*)-(+)-2-butanol | 0.214 | 6.90[d] | 2 | (20 ± 5) | (3.2 ± 0.6) | −(7.4 ± 0.7) | (36 ± 3) |
| (*R*)-(−)-2-butanol | 0.239 | 6.90[d] | 2 | (13 ± 4) | (4.9 ± 1.3) | −(6.4 ± 0.9) | (38 ± 5) |
| (±)-2-butanol | 0.263 | 6.90[d] | 2 | (13 ± 4) | (4.9 ± 1.1) | −(6.4 ± 0.9) | (38 ± 2) |
| (*S*)-(+)-2-pentanol | 0.128 | 6.90[d] | 2 | (32 ± 11) | (4.1 ± 1.1) | −(8.6 ± 1.0) | (43 ± 5) |
| (*R*)-(−)-2-pentanol | 0.164 | 6.90[d] | 2 | (33 ± 12) | (3.7 ± 1.0) | −(8.7 ± 1.1) | (42 ± 5) |
| (*R*)-(−)-2-hexanol | 0.103 | 6.90[d] | 2 | (118 ± 61) | (1.9 ± 0.6) | −(11.8 ± 1.8) | (46 ± 6) |

[a] The molality $m$ of the ligand at which the measurements were performed, the pH, and $N$ the number of sets of titration experiments performed are given in columns 2−4, respectively. In all cases the molality of the β-cyclodextrin was (0.0015−0.0035) mol kg$^{-1}$. [b] Acetate (0.1 mol kg$^{-1}$) + acetic acid. [c] Glycine buffer (0.1 mol kg$^{-1}$) + NaOH. [d] Phosphate buffer {($NaH_2PO_4$, 0.025 mol kg$^{-1}$) + ($Na_2HPO_4$, 0.025 mol kg$^{-1}$)}.

(−)-2-pentanol, −12.9°, 99.4 mol %; (*S*)-(+)-2-pentanol, +13.7°, 99.0 mol %; D-phenylalanine, +33.9°, >99 mol %; L-phenylalanine, −32.5°, >99 mol %; and L-phenylalanineamide, +19.3°, >99 mol %. All of these purities were determined by gas chromatography (capillary column with a flame-ionization detector) with the exception of the D-phenylalanine, L-phenylalanine, and L-phenylalanineamide which were determined by thin-layer chromatography. All of the optical rotations were within 2° of the optical rotations given for these substances in the literature. The purities of the (±)-2-butanol, 1-butanol, 1-propanol, and 2-propanol were all ≈99.9 mol % as determined by gas chromatography. The purities of the α- and β-cyclodextrins were determined in an earlier study.[7]

A Microcal MCS Isothermal Titration Calorimeter was used for all of the calorimetry measurements. The procedures and the treatment of the data obtained with the titration calorimeter have been described previously.[7]

## Results and Discussion

All equilibrium constants and standard molar enthalpies of reaction reported in this study are based on the 1:1 binding model:

$$\text{cyclodextrin(aq)} + \text{ligand(aq)} = \text{cyclodextrin·ligand(aq)} \tag{1}$$

Hallén et al.[8] also assumed a 1:1 binding model in their study of the reactions of alcohols with cyclodextrins although they noted that there was some evidence for the formation 1:2 and/or 2:1 complexes for long-chain guest molecules such as 1-heptanol. The equilibrium constant for reaction 1 is

$$K = a(\text{cyclodextrin·ligand})/\{a(\text{cyclodextrin})a(\text{ligand})\} \tag{2}$$

where $a$ is the activity of the indicated substance. The standard state used for the solute is the hypothetical ideal solution of unit molality ($m°$ = 1). Nonideality corrections are assumed to be negligible for both the measured equilibrium constants and the standard molar enthalpies of reaction. This approximation should hold reasonably well even when dealing with a charged ligand (e.g., L-phenylalanineamide$^{+}$) since the reaction is charge symmetric.

Thermodynamic quantities for the reactions of 1-butanol, (*R*)-(−)-2-butanol, (*S*)-(+)-2-butanol, (±)-2-butanol, (*R*)-(−)-2-heptanol, (*S*)-(+)-2-heptanol, (*R*)-(−)-2-hexanol, (*S*)-(+)-2-hexanol, (*S*)-(+)-2-pentanol, (*R*)-(−)-2-pentanol, (*S*)-(+)-2-pentanol, D-phenylalanine, L-phenylalanine, L-phenylalanineamide, 1-propanol, and 2-propanol with α-cyclodextrin and with β-cyclodextrin are presented in Tables 1 and 2, respectively. D- and L-phenylalanine and L-phenylalanineamide exist in different ionic forms at different pHs. From the known acidity constants for these substances[9] it is seen that D- and L-phenylalanine exist predominantly in the zwitterion form at pH = 5.01. Also, L-phenylalanineamide exists predominantly as an ion with a +1 charge at pH = 5.0 and as a neutral species

**TABLE 3: Thermodynamic Quantities $K$, $\Delta_rH°$, $\Delta_rG°$, and $\Delta_rS°$ from the Literature for the Reactions of α-Cyclodextrin and β-Cyclodextrin with Organic Ligands at $T = 298.15$ K**

| ligand | conditions | $K$ | $\Delta_rH°$ (kJ mol$^{-1}$) | $\Delta_rG°$ (kJ mol$^{-1}$) | $\Delta_rS°$ (J K$^{-1}$ mol$^{-1}$) | reference |
|---|---|---|---|---|---|---|
| α-Cyclodextrin(aq) + Ligand(aq) = α-Cyclodextrin·ligand(aq) | | | | | | |
| D-phenylalanine$^-$ | phosphate buffer (0.1 M), pH = 11.0 | $(18.1 \pm 2.8)^{a,b}$ | $(16.3 \pm 1.7)$ | $-(7.18 \pm 0.42)$ | $(79 \pm 10)$ | Cooper and MacNicol[10] |
| L-phenylalanine$^\pm$ | phosphate buffer (0.1 M), pH = 11.0 | $(15.5 \pm 0.5)^a$ | $(15.5 \pm 0.84)$ | $-(6.79 \pm 0.08)$ | $(75 \pm 3)$ | Cooper and MacNicol[10] |
| L-phenylalanine$^\pm$ | phosphate buffer (0.1 M), pH = 7.4 | 42.3 | −1.2 | −9.28 | 27.1 | Matsuyama et al.[11] |
| L-phenylalanine$^\pm$ | water | $(13.6 \pm 1.0)$ | −7.7 | $-(6.5 \pm 0.2)$ | $-(4 \pm 3)$ | Paduano et al.[12] |
| (L-phenylalanine$^\pm$ + L-phenylalanine$^-$) | Tris buffer pH = 9.0, $I_c = 0.10$ M | $(12 \pm 6)$ | | $-(6.2 \pm 1.7)$ | | Chokchainarong et al.[13] |
| 2-propanol | water | $(8 \pm 1)$ | | $-(5.2 \pm 0.3)$ | | Rymdén et al.[14] |
| 1-butanol | $H_2SO_4$ (0.1 + M) + $Na_2SO_4$ $I_c = 0.50$ M | 89 | −12 | −11.1 | −3 | Matsui and Mochida[15] |
| 1-butanol | water | $(46 \pm 15)$ | | $-(9.5 \pm 1.0)$ | | Rymdén et al.[14] |
| 1-butanol | water | 99.9 | −9.9 | −11.41 | 5.1 | Barone et al.[16] |
| 1-butanol | water | 80 | −10.2 | −10.9 | 2.2 | Fujiwara et al.[17] |
| 1-butanol | water | $9.1 \times 10^3$ | −7.9 | −22.6 | 49 | Fujisawa et al.[18] |
| 1-butanol | water | $(82.9 \pm 1.0)$ | $-(10.70 \pm 0.05)$ | $-(10.95 \pm 0.03)$ | $(0.8 \pm 0.3)$ | Hallén et al.[8] |
| 2-butanol | water | $(22 \pm 0.5)$ | | $-(7.66 \pm 0.06)$ | | Rymdén et al.[14] |
| 2-butanol | water | 28.4 | −9.0 | −8.3 | −2.3 | Barone et al.[16] |
| 2-butanol | $H_2SO_4$ (0.1 M) + $Na_2SO_4$ $I_c = 0.50$ M | 26.3 | | −8.1 | | Matsui and Mochida[15] |
| 2-pentanol | water | $(105 \pm 9)$ | | $-(11.5 \pm 0.2)$ | | Rymdén et al.[14] |
| 2-pentanol | water | $(101 \pm 16)$ | $-(13.4 \pm 0.8)$ | $-(11.4 \pm 0.4)$ | $-(7 \pm 3)$ | Andini et al.[19] |
| 2-pentanol | $H_2SO_4$ (0.1 M) + $Na_2SO_4$ $I_c = 0.50$ M | 135 | | −12.2 | | Matsui and Mochida[15] |
| 2-hexanol | water | $(285 \pm 26)$ | $-(15.5 \pm 0.4)$ | $-(14.0 \pm 0.2)$ | $-(5.0 \pm 1.5)$ | Andini et al.[19] |
| 2-hexanol | $H_2SO_4$ (0.1 M) + $Na_2SO_4$ $I_c = 0.50$ M | 355 | | −14.6 | | Matsui and Mochida[15] |
| β-Cyclodextrin(aq) + Ligand(aq) = β-Cyclodextrin·ligand(aq) | | | | | | |
| 1-propanol | water | $(13 \pm 7)$ | | $-(6.4 \pm 1.9)$ | | Rymdén et al.[14] |
| 2-propanol | water | $(14 \pm 1)$ | | $-(6.5 \pm 0.2)$ | | Rymdén et al.[14] |
| 1-butanol | citrate + phosphate buffer pH = 6.4, $I_c = 0.05$ M | 17 | 2.9 | −7.0 | 33 | Matsui and Mochida[15] |
| 1-butanol | water | $(19 \pm 4)$ | | $-(7.3 \pm 0.6)$ | | Rymdén et al.[14] |
| 1-butanol | sodium carbonate (≈0.004 M) | 17 | | −7.0 | | Sasaki et al.[20] |
| 1-butanol | water | $1.4 \times 10^3$ | 3.0 | −18.0 | 70 | Fujisawa et al.[18] |
| 2-butanol | citrate + phosphate buffer pH = 6.4, $I_c = 0.05$ M | 15.5 | | −6.8 | | Matsui and Mochida[15] |
| 2-butanol | water | $(22 \pm 5)$ | | $-(7.7 \pm 0.6)$ | | Rymdén et al.[14] |
| 2-pentanol | citrate + phosphate buffer pH = 6.4, $I_c = 0.05$ M | 30.9 | | −8.5 | | Matsui and Mochida[15] |
| 2-pentanol | water | $(59 \pm 10)$ | | $-(10.1 \pm 0.5)$ | | Rymdén et al.[14] |
| 2-hexanol | citrate + phosphate buffer pH = 6.4, $I_c = 0.05$ M | 95.5 | | −11.3 | | Matsui and Mochida[15] |

[a] Cooper and MacNicol[10] also obtained $K = (20.6 \pm 1.2)$ and $K = (15.9 \pm 2.7)$ for the respective reactions of D- and L-phenylalanine using the method of spectral inhibition titrations. [b] The uncertainties in this table are equal to two standard deviations except for the results of Rymdén et al.[14] who reported 80% confidence limits and possibly the results of Paduano et al.[12] who did not specify the basis of their assignment of error.

at pH = 10.0. The standard molar Gibbs energies of reaction $\Delta_rG°$ and standard molar entropies of reaction $\Delta_rS°$ given in Tables 1 and 2 were calculated from the measured equilibrium constants and standard molar enthalpies of reaction. It is seen that the reactions involving α-cyclodextrin are "enthalpy driven" at $T = 298.15$ K with the exception of the reaction involving 2-propanol. The reactions of L-phenylalanine$^\pm$, L-phenylalanineamide$^+$, and L-phenylalanineamide$^0$ with β-cyclodextrin are also enthalpy driven at $T = 298.15$ K. However, the reactions of 1-propanol, 2-propanol, 1-butanol, 2-butanol, 2-pentanol, and 2-hexanol with β-cyclodextrin are seen to be "entropy driven" at $T = 298.15$ K. Hallén et al.[8] have pointed out that, since the heat-capacity changes are large for these reactions, the sign of the standard molar entropy of reaction can change with temperature and therefore some degree of caution must be used in characterizing reactions such as the ones studied herein as either enthalpy or entropy driven.

With only one exception, the results obtained in Tables 1 and 2 show that, within the indicated uncertainties, there are no differences in any of the thermodynamic quantities for the reactions of these ligands with either α- or β-cyclodextrin due to the change in the location of a hydrogen atom on an optically active carbon atom. The exceptions are the standard molar enthalpies of reaction of the 2-butanols with α-cyclodextrin. Here the difference between the result for (±)-2-butanol and the results obtained for (*S*)-(+)-2-butanol and (*R*)-(−)-2-butanol is only (0.1−0.2) kJ mol$^{-1}$ outside the indicated uncertainty intervals. The results obtained for the *R* and *S* optical isomers of 2-butanol are the same within the indicated uncertainties. Since, in this series of measurements, the change made at the optically active carbon atom involved only a hydrogen atom, it is not surprising that the effects were too small to measure. Berthod et al.[2] have reported substantial differences (up to ≈12 kJ mol$^{-1}$) in standard molar enthalpies of reaction when larger changes are made at chiral centers. Their results were based upon gas chromatography measurements performed at several temperatures and involved some assumptions about the relationship of the equilibrium constant of the reaction to the retention time. It would be useful to have some direct calorimetric measurements on these reactions for purposes of comparison.

Results from the literature on these reactions are summarized in Table 3. Calorimetry was the method used in all of the studies with the exception of the studies of Chokchainarong et al.,[13] Matsui and Mochida,[15] and Sasaki et al.[20] who used spectrophotometry and the study of Rymdén et al.[14] who used NMR. Cooper and MacNicol[10] used both calorimetry and spectrophotometry. No specification of the stereoisomer form of a ligand is given in Table 3 when the workers made no clear statement as to whether an optical isomer or a racemic mixture was used. Nevertheless, direct comparisons of our results, obtained in most cases with optically active substances, with the results given in Table 3 are made possible because of the above finding that the differences in thermodynamic quantities due to a change made at the optically active carbon atom were generally within the experimental uncertainties of the measurements. In several cases comparisons with results from the literature are complicated by the absence of specified uncertainties in the published results.

Our approximate results for the equilibrium constant and the standard molar enthalpy of reaction of L-phenylalanine$^{\pm}$ with α-cyclodextrin are in agreement with the results obtained by Paduano et al.[12] Both our results and those of Paduano et al.[12] differ from the results obtained by Matsuyama et al.[11] Our result for the equilibrium constant for the reaction of L-phenylalanine$^{\pm}$ with α-cyclodextrin cannot be compared with the values obtained by Cooper and MacNicol[10] and of Chokchainarong et al.[13] since the reactions they studied pertain respectively to D- and L-phenylalanine$^{-}$ and to the mixture (L-phenylalanine$^{\pm}$ + L-phenylalanine$^{-}$). The values of the equilibrium constants and standard molar enthalpies of reaction obtained in this study are either in agreement or near agreement with all of the results obtained by Matsui and Mochida[15] who used a spectrophotometric method. Our result for the equilibrium constant for the reaction of 2-butanol with α-cyclodextrin is in agreement with the result of Barone et al.[16] Their[16] value of the standard molar enthalpy for this reaction may also be in agreement with our result. The equilibrium constants reported by Fujisawa et al.[18] are judged to be in error since they are substantially out of the range of values obtained in this study and in the rest of the literature. Rymdén et al.[14] used NMR to obtain equilibrium constants for the reactions of a wide variety of alcohols with both α- and β-cyclodextrin. We find that our results are in agreement with the values they[14] reported for the reactions of 2-propanol with α-cyclodextrin and for the reactions of 1-propanol, 1-butanol, and 2-butanol with β-cyclodextrin. In the several other cases seen in Table 3, the differences between the results of our measurements and theirs[14] are outside the indicated limits of error.

Our result for the equilibrium constant for the reaction of 1-butanol with α-cyclodextrin is in good agreement with the results reported by Fujiwara et al.[17] and by Hallén et al.[8] The value of the standard molar enthalpy of this reaction obtained in this study is seen to be ≈(1−2) kJ mol$^{-1}$ more exothermic than the results obtained by Barone et al.,[16] by Fujiwara et al.,[17] and by Hallén et al.[8] However, it is very close to the result obtained by Matsui and Mochida.[15] A comparison with the results of Andini et al.[19] shows systematic differences in the results for the equilibrium constants and standard molar enthalpies for the reactions of 2-pentanol and 2-hexanol. It does not seem possible to arrive at a definitive explanation for these and the other differences seen in Table 3. However, the results obtained[7] on test reactions such as the hydrolysis of sucrose and the reactions of cyclohexanol and 1-hexanol with α-cyclodextrin and the careful characterization of the substances used in this study lend some confidence in the accuracy of our results. This is reinforced by the excellent agreement found between our results for several alcohols and the results of the very careful spectrophotometric study of Matsui and Mochida.[15]

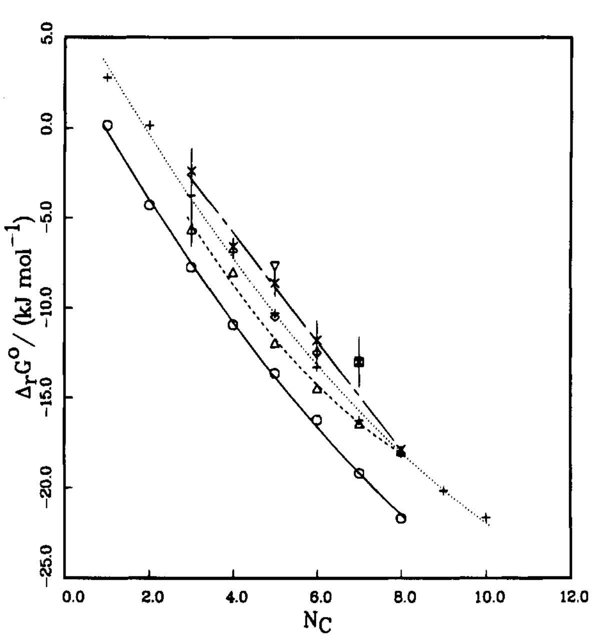

**Figure 1.** Standard molar Gibbs energies $\Delta_rG^{\circ}$ for the reactions of the primary and secondary aliphatic alcohols with both α- and β-cyclodextrin as a function of the number of carbon atoms $N_C$ in the chemical formula of the alcohol. The symbols and their significance are ○, the reactions of the 1-alkanols with α-cyclodextrin; △, the reactions of the 2-alkanols with α-cyclodextrin; +, the reactions of the 1-alkanols with β-cyclodextrin; ×, the reaction of the 2-alkanols with β-cyclodextrin; ◇, the reactions of 3-pentanol and 3-hexanol with α-cyclodextrin; ▽, the reaction of 3-pentanol with β-cyclodextrin; and □, the reaction of 4-heptanol with α-cyclodextrin. The lines are (—) the fit for the reactions of the 1-alkanols with α-cyclodextrin; (- - -) the fit for the reactions of the 2-alkanols with α-cyclodextrin; (•••) the fit for the reactions of the 1-alkanols with β-cyclodextrin; and (— — —) the fit for the reactions of the 2-alkanols with β-cyclodextrin.

Plots of the standard molar Gibbs energies, standard molar enthalpies, and standard molar entropies of reaction of the primary and secondary aliphatic alcohols with both α- and β-cyclodextrin as a function of the number of carbon atoms $N_C$ in the chemical formulas of the alcohols are shown in Figures 1, 2, and 3, respectively. In the construction of these plots, the values of the standard Gibbs energies and standard molar enthalpies for the reactions of 1-propanol, 1-pentanol, and 1-hexanol with α-cyclodextrin and the standard molar enthalpy for the reaction of 1-heptanol with α-cyclodextrin were taken from Hallén et al.[8] The values of the standard molar Gibbs energies for the reactions of methanol, ethanol, 1-heptanol, 1-octanol, and 2-octanol with α-cyclodextrin and for the reactions of methanol, ethanol, 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol, 2-octanol, and 3-pentanol with β-cyclodextrin were taken from Matsui and Mochida.[15] We also used their[15] standard molar enthalpies for the reactions of 1-pentanol and 1-hexanol with β-cyclodextrin. Sasaki et al.[20] report equilibrium constants for the reactions of the 1-alkanols ($N_C$ = 4−10) with β-cyclodextrin. Their[20] results are close to those reported by Matsui and Mochida[15] for $N_C$ = 4−8. We have used the results of Sasaki et al.[20] for $N_C$ = 9 and 10 in Figure 1. The values of the standard molar Gibbs energies and standard molar enthalpies of reaction of 3-pentanol, 3-hexanol, and 4-heptanol with α-cyclodextrin are from Andini et al.[19] The remainder of the values of the standard molar Gibbs energies and standard molar enthalpies of reaction are from this study. Since Matsui and

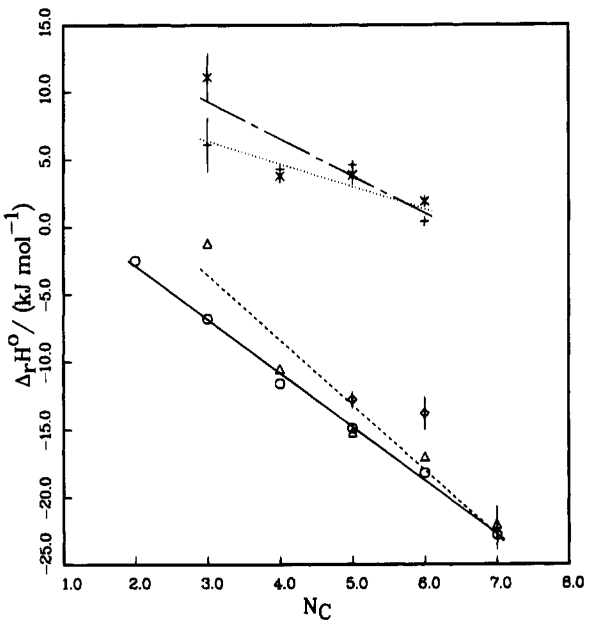

**Figure 2.** Standard molar enthalpies $\Delta_rH°$ for the reactions of the primary and secondary aliphatic alcohols with both α- and β-cyclodextrin as a function of the number of carbon atoms $N_C$ in the chemical formula of the alcohol. The symbols and their significance are ○, the reactions of the 1-alkanols with α-cyclodextrin; △, the reactions of the 2-alkanols with α-cyclodextrin; +, the reactions of the 1-alkanols with β-cyclodextrin; ×, the reaction of the 2-alkanols with β-cyclodextrin; and ◇, the reactions of 3-pentanol and 3-hexanol with α-cyclodextrin. The lines are (—) the fit for the reactions of the 1-alkanols with α-cyclodextrin; (- - -) the fit for the reactions of the 2-alkanols with α-cyclodextrin; (• • •) the fit for the reactions of the 1-alkanols with β-cyclodextrin; and (— — —) the fit for the reactions of the 2-alkanols with β-cyclodextrin.

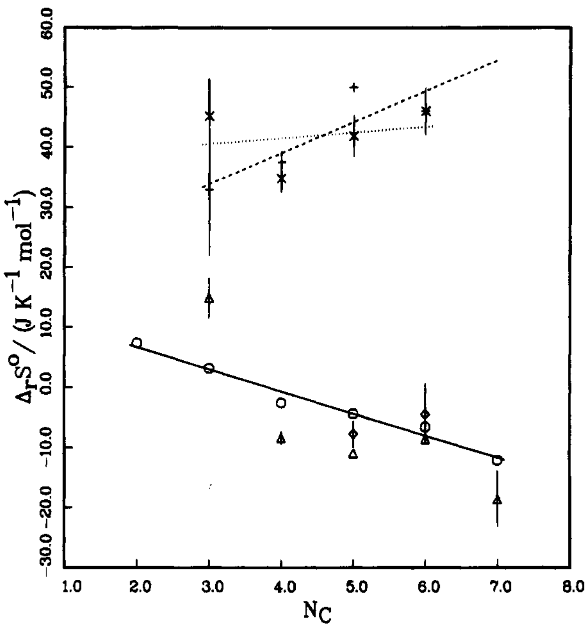

**Figure 3.** Standard molar enthalpies $\Delta_rS°$ for the reactions of the primary and secondary aliphatic alcohols with both α- and β-cyclodextrin as a function of the number of carbon atoms $N_C$ in the chemical formula of the alcohol. The symbols and their significance are ○, the reactions of the primary alcohols with α-cyclodextrin; △, the reactions of the secondary alcohols with α-cyclodextrin; +, the reactions of the 1-alkanols with β-cyclodextrin; ×, the reaction of the secondary alcohols with β-cyclodextrin; and ◇, the reactions of 3-pentanol and 3-hexanol with α-cyclodextrin. The lines are (—) the fit for the reactions of the 1-alkanols with α-cyclodextrin; (- - -) the fit for the reactions of the 1-alkanols with β-cyclodextrin; and (• • •) the fit for the reactions of the 2-alkanols with β-cyclodextrin. There is no satisfactory linear or simple polynomial fit to the results for the reactions of the 2-alkanols with α-cyclodextrin.

Mochida,[15] Barone et al.,[16] and Sasaki et al.[20] did not report any uncertainties, no error bars are attached to their results. In the remainder of the cases, when an error bar is not shown in these figures, the error bar is less than the size of the symbol used in the figure.

Inspection of Figures 1–3 shows a series of essentially monotonic relationships between the thermodynamic quantities and $N_C$ the number of carbon atoms in the chemical formula of the alcohol. Previously, Hallén et al.[8] found that a plot of the standard molar heat-capacity changes as a function of $N_C$ for the reactions of the 1-alkanols with α-cyclodextrin also showed a monotonic and almost linear relationship from $N_C = 3$ to 7. Table 4 contains the results of fits to the thermodynamic quantities as a function of $N_C$. The quality of the fits is particularly good for the standard molar Gibbs energies of reaction. The results for the standard molar enthalpies and standard molar entropies of reaction do not indicate a need for anything more than a simple linear fit, although it was found that no simple linear or polynomial fit would work for the standard molar entropies of reaction of the 2-alkanols with α-cyclodextrin. Clearly, there is no physical reason why these fits must be smooth; sufficiently precise and accurate measurements might reveal some fine structure in these relationships such as was found by Bastos et al.[21] for the reactions of alkane-α,ω-diols with α-cyclodextrin. The approximate slope of the four curves in Figure 1 is $-2.8$ kJ mol$^{-1}$. Several workers[8,14,21] have noted that a slope (i.e., a $CH_2$ increment) of $\approx -3$ kJ mol$^{-1}$ is typical for the transfer of a $CH_2$ group in a hydrocarbon chain from water to the interior of a micelle and not too far from the $CH_2$ increment for the transfer of an alkane from water to a liquid hydrocarbon phase. While this is consistent with the presence of hydrophobic interactions between the alcohols and the cyclodextrin cavities, the characteristic differences in the standard molar entropies and enthalpies (see Figures 2 and 3) for the reactions of the different forms of the alcohols with α- and β-cyclodextrin indicate the existence of additional effects which we are unable to explain rigorously. However, the existence of steric effects is clearly demonstrated by a comparison of the equilibrium constants for the reactions of 1-butanol, 2-butanol, 2-methyl-1-propanol, and 2-methyl-2-propanol with α-cyclodextrin. The equilibrium constants for these respective reactions are (79.7 ± 2.5), (25.5 ± 0.9), 27.5, and 4.4. The first two values are from this study and the last two are from Matsui and Mochida[15] who obtained results for the reactions of other branched alcohols with α- and β-cyclodextrin that also demonstrate steric effects for these reactions.

The literature survey of Inoue et al.[22] shows that, as a rule, the presence of a charge on a ligand correlates with a smaller equilibrium constant for the reaction of that ligand with either α- or β-cyclodextrin than for the corresponding reaction of the uncharged ligand. The equilibrium constants for the reactions of D- and L-phenylalanine$^{\pm}$, L-phenylalanineamide$^{+}$, and L-phenylalanineamide$^{0}$ with α-cyclodextrin and β-cyclodextrin are seen to be consistent with this general rule when it is recognized that the charges on the zwitterions D- and L-phenylalanine$^{\pm}$ are located on separate parts of the molecule. The differences due to the effects of charge are seen to be much larger for the reactions of these ligands with β-cyclodextrin than for the corresponding reactions with α-cyclodextrin. Additional, systematic studies of this effect would be useful.

Some additional trends and relationships are also seen in Figures 1–3. For example, the standard molar enthalpies of reaction of the 1-alkanols and 2-alkanols with α-cyclodextrin

**TABLE 4: Results of Least-Squares Fits to the Results Shown in Figures 1−3 for the Reactions of Primary and Secondary Aliphatic Alcohols with α-Cyclodextrin (α-CD) and with *β*-Cyclodextrin (*β*-CD)[a]**

$$\Delta_r G^\circ = A + BN_c + CN_c^2$$

| reaction | $A$ (kJ mol$^{-1}$) | $s$ ($A$) (kJ mol$^{-1}$) | $B$ (kJ mol$^{-1}$) | $s$ ($B$) (kJ mol$^{-1}$) | $C$ (kJ mol$^{-1}$) | $s$ ($C$) (kJ mol$^{-1}$) | rsd (kJ mol$^{-1}$) |
|---|---|---|---|---|---|---|---|
| 1-alkanol + α-CD = α-CD•1-alkanol | 3.865 | 0.46 | −4.161 | 0.23 | 0.1240 | 0.025 | 0.33 |
| 2-alkanol + α-CD = α-CD•2-alkanol | 7.537 | 2.3 | −4.926 | 0.87 | 0.22 | 0.078 | 0.48 |
| 1-alkanol + *β*-CD = *β*-CD•1-alkanol | 7.488 | 0.50 | −4.182 | 0.21 | 0.1239 | 0.019 | 0.43 |
| 2-alkanol + *β*-CD = *β*-CD•2-alkanol | 6.216 | 0.76 | −3.014 | 0.14 | | | 0.53 |

$$\Delta_r H^\circ = A + BN_c$$

| reaction | $A$ (kJ mol$^{-1}$) | $s$ ($A$) (kJ mol$^{-1}$) | $B$ (kJ mol$^{-1}$) | $s$ ($B$) (kJ mol$^{-1}$) | rsd (kJ mol$^{-1}$) |
|---|---|---|---|---|---|
| 1-alkanol + α-CD = α-CD•1-alkanol | 5.071 | 0.60 | −3.972 | 0.12 | 0.52 |
| 2-alkanol + α-CD = α-CD•2-alkanol | 10.87 | 3.8 | −4.810 | 0.73 | 2.3 |
| 1-alkanol + *β*-CD = *β*-CD•1-alkanol | 11.41 | 2.8 | −1.680 | 0.60 | 1.3 |
| 2-alkanol + *β*-CD = *β*-CD•2-alkanol | 17.56 | 5.0 | −2.755 | 1.1 | 2.4 |

$$\Delta_r S^\circ = A + BN_c$$

| reaction | $A$ (J K$^{-1}$ mol$^{-1}$) | $s$ ($A$) (J K$^{-1}$ mol$^{-1}$) | $B$ (J K$^{-1}$ mol$^{-1}$) | $s$ ($B$) (J K$^{-1}$ mol$^{-1}$) | rsd (J K$^{-1}$ mol$^{-1}$) |
|---|---|---|---|---|---|
| 1-alkanol + α-CD = α-CD•1-alkanol | 14.04 | 1.5 | −3.669 | 0.30 | 1.3 |
| 2-alkanol + α-CD = α-CD•2-alkanol[b] | | | | | |
| 1-alkanol + *β*-CD = *β*-CD•1-alkanol | 18.52 | 10 | 5.140 | 2.2 | 4.9 |
| 2-alkanol + *β*-CD = *β*-CD•2-alkanol | 37.77 | 13 | 0.9400 | 2.7 | 6.0 |

[a] $N_C$ is the number of carbon atoms in the chemical formula of the alcohol. The standard deviations *s* of the parameters and the residual standard deviations rsd are also given. [b] There is no satisfactory linear or simple polynomial fit to these results.

**TABLE 5: Thermodynamic Quantities $\Delta_r G^\circ$, $\Delta_r H^\circ$, and $\Delta_r S^\circ$ for the Exchange Reactions of Primary (Reaction 3) and Secondary (Reaction 4) Aliphatic Alcohols with α- and *β*-Cyclodextrin at $T$ = 298.15 K[a]**

| $N_C$ | $\Delta_r G^\circ$(3) (kJ mol$^{-1}$) | $\Delta_r G^\circ$(4) (kJ mol$^{-1}$) | $\Delta_r H^\circ$ (3) (kJ mol$^{-1}$) | $\Delta_r H^\circ$(4) (kJ mol$^{-1}$) | $\Delta_r S^\circ$(3) (J K$^{-1}$ mol$^{-1}$) | $\Delta_r S^\circ$(4) (J K$^{-1}$ mol$^{-1}$) |
|---|---|---|---|---|---|---|
| 3 | (4.0 ± 2.6) | (3.3 ± 1.1) | (12.9 ± 2.0) | (12.3 ± 1.8) | (30 ± 11) | (30 ± 7) |
| 4 | (4.0 ± 0.4) | (1.4 ± 0.5) | (15.9 ± 0.5) | (14.3 ± 0.6) | (40.1 ± 1.9) | (43.2 ± 2.5) |
| 5 | 3.3 | (3.3 ± 0.7) | 19.5 | 19.1 ± 0.8 | 54.3 | (52.8 ± 3.5) |
| 6 | 2.95 | (2.66 ± 1.1) | 18.6 | 18.9 ± 0.5 | 52.5 | (54.5 ± 4.0) |
| 7 | 2.9 | | | | | |
| 8 | 3.6 | 0.11 | | | | |

[a] $N_C$ is the number of carbon atoms in the chemical formula of the alcohol.

and with *β*-cyclodextrin at $T$ = 298.15 K are seen to be either equal within experimental error or nearly equal for a given value of $N_C$ with the exception of the results for $N_C$ = 3. The standard molar enthalpies of reaction of the alcohols with α-cyclodextrin are seen to be always more exothermic than the corresponding standard molar enthalpies for the reactions with *β*-cyclodextrin. Also, as seen from Figure 1, the following general order of the standard Gibbs energies of reaction with respect to the reactants is $\Delta_r G^\circ$(1-alkanol + α-cyclodextrin) < $\Delta_r G^\circ$(2-alkanol + α-cyclodextrin) < $\Delta_r G^\circ$(1-alkanol + *β*-cyclodextrin) < $\Delta_r G^\circ$(2-alkanol + *β*-cyclodextrin). For either α- or *β*-cyclodextrin, the order of the standard Gibbs energies of reaction with respect to the position of the hydroxy group on the carbon chain is $\Delta_r G^\circ$(1-alkanol + cyclodextrin) < $\Delta_r G^\circ$(2-alkanol + cyclodextrin) < $\Delta_r G^\circ$(3-alkanol + cyclodextrin) < $\Delta_r G^\circ$(4-alkanol + cyclodextrin). The last two inequalities involving the 3-alkanols and 4-heptanol are based on a very limited set of results.

Empirical observations such as these can be useful in estimating values of thermodynamic quantities. For example, with the fits given in Table 4 and the results shown in Figures 1−3, we estimate that at $T$ = 298.15 K: $\Delta_r G^\circ = -14.9$ kJ mol$^{-1}$ and $K$ = 408 for the reaction of 2-heptanol with *β*-cyclodextrin; $\Delta_r H^\circ = -0.4$ kJ mol$^{-1}$ for the reaction of 1-heptanol with *β*-cyclodextrin; and $\Delta_r H^\circ = -1.8$ kJ mol$^{-1}$ for the reaction of 2-heptanol with *β*-cyclodextrin. Barone et al.[16] report that $\Delta_r H^\circ$ for the reaction of methanol with α-cyclodextrin is approximately zero. This result[16] is consistent with the extrapolated value of $\Delta_r H^\circ = 1.1$ kJ mol$^{-1}$ obtained from Figure 2 and Table 4.

We have also compared the differences in thermodynamic quantities obtained for the exchange reactions

$$\text{α-cyclodextrin·primary alcohol(aq)} + \beta\text{-cyclodextrin(aq)} = \text{α-cyclodextrin(aq)} + \beta\text{-cyclodextrin·primary alcohol(aq)} \quad (3)$$

$$\text{α-cyclodextrin·secondary alcohol(aq)} + \beta\text{-cyclodextrin(aq)} = \text{α-cyclodextrin(aq)} + \beta\text{-cyclodextrin·secondary alcohol(aq)} \quad (4)$$

These quantities are obtained by combination of the appropriate thermodynamic quantities for the reactions (see reaction 1 above) of the primary and secondary aliphatic alcohols with α- and *β*-cyclodextrin. These comparisons are shown in Table 5. The sources of the results are the same as those used in the construction of Figures 1−3. Where possible, uncertainties have been attached to the calculated values of these standard molar enthalpies and entropies for these exchange reactions. It is seen that, within the indicated uncertainties, in all cases $\Delta_r S^\circ(3) = \Delta_r S^\circ(4)$ and that, with the exception of $N_C$ = 4, $\Delta_r H^\circ(3) = \Delta_r H^\circ(4)$. The lack of agreement here is 0.5 kJ mol$^{-1}$ outside the indicated uncertainties. The most serious lack of agreement (2.6 kJ mol$^{-1}$) is seen in the case of the standard Gibbs energies of reaction when $N_C$ = 4. Although uncertainties are not attached to $\Delta_r G^\circ$(3) and $\Delta_r G^\circ$(4) for $N_C$ = 6 and 8, it is likely there is agreement in these standard Gibbs energies of reaction when $N_C$ = 6 and a lack of agreement when $N_C$ = 8.

A plot of $\Delta_r H^\circ$(3) and $\Delta_r H^\circ$(4) as respective functions of $\Delta_r S^\circ$(3) and $\Delta_r S^\circ$(4) is shown in Figure 4. A least-squares fit to these results yields an intercept of (4.21 ± 2.8) kJ mol$^{-1}$

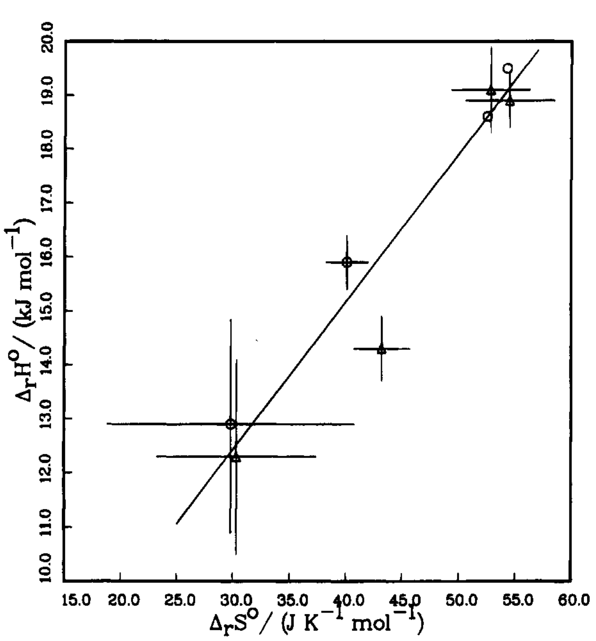

**Figure 4.** Standard molar enthalpies $\Delta_r H^\circ$ for the exchange reactions 3 (○) and 4 (△) as respective functions of the standard molar entropies $\Delta_r S^\circ$ for these reactions. The straight line is the least-squares fit to the results.

and a slope of (274 ± 60) K. The residual standard deviation of the fit is 0.84 kJ mol$^{-1}$. The slope is comparable with the slope of (334 ± 70) K found in a previous study[7] of the reactions of cyclohexane derivatives with cyclodextrins and with the slope of 360 K found by Bertrand et al.[23] in their study of the reactions of substituted phenols with cyclodextrins.

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(24) Certain commercial materials and products are identified in this paper to specify adequately the experimental procedure. Such identification does not imply recommendation or endorsement by the National Institute of Standards and Technology.

(25) All uncertainties given in this paper are, unless indicated otherwise, based on two estimated standard deviations of the mean.