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Experimental Studies of the Anomeric Effect. Part V.[1] The Influence of Some Solvents on the Conformational Equilibria in 2-Methoxy- and 2-(2', 2', 2'-Trifluoroethoxy)-Tetrahydropyran.

Harold Booth,* J. Mark Dixon and Simon A. Readshaw

Department of Chemistry, University of Nottingham, Nottingham, NG7 2RD, U.K.

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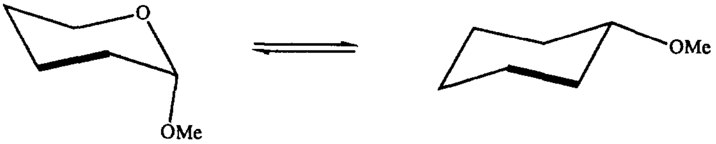
***Abstract*:** The $\Delta H^\circ_{a\to e}$ and $\Delta S^\circ_{a\to e}$ values for conformational equilibria in 2-methoxytetrahydropyran have been determined by variable temperature nmr spectroscopy in solvents CD_2Cl_2, ether/CD_2Cl_2, ether/toluene and ether/methanol, whilst the corresponding values for conformational equilibria in 2-(2',2',2'-trifluoroethoxy)-tetrahydropyran have been determined in ether/toluene and ether/methanol. Replacement of toluene by methanol causes increases in $\Delta H^\circ_{a\to e}$ and $\Delta S^\circ_{a\to e}$. These changes are consistent with a preferential hydrogen bonding of methanol to *axial* alkoxy groups, causing a decrease in both entropy and enthalpy of axial conformations relative to their equatorial counterparts. The enthalpy decrease is probably a result of an enhancement of the stabilising endo-anomeric effect.

There is substantial agreement that the origin of the "anomeric effect" lies in the stabilising overlap of heteroatom lone pair with the antibonding orbital of an anticoplanar carbon-heteroatom bond.[2] The existence of both exo-anomeric[3,4] and endo-anomeric[5,6] effects is also well recognised. It is expected that the conformational enthalpy difference ($\Delta H^\circ_{a\to e}$) between axial and equatorial conformers of 2-methoxytetrahydropyran ($1 \rightleftharpoons 2$) will depend on steric effects, anomeric effects and polar effects. Hitherto, most determinations of the position of equilibrium in ($1 \rightleftharpoons 2$) have involved single temperature measurements, which have inevitably given conformational free energy differences $\Delta G^\circ_{1\to 2}$ and have revealed no insights into conformational enthalpy differences $\Delta H^\circ_{1\to 2}$ and conformational entropy differences $\Delta S^\circ_{1\to 2}$. That conformational entropy differences are rarely zero has been reported in several studies.[1,5,7-10]



(1) (2)

Our approach[7] has involved (i), determinations of equilibrium constants K (=2/1) by integration of several ^{13}C nmr spectra of ($1 \rightleftharpoons 2$) at 140-180K; (ii) line-broadening studies at 165-215K of ^{13}C nmr spectra of ($1 \rightleftharpoons 2$);

and (iii), integration of ^{1}H nmr spectra of the equilibrated mixture of *cis*- and *trans*-4-methyl derivatives of (**1**) and(**2**). Confidence in this approach increased when studies of the equilibria in 4-methylpiperidine[11] and 4-methyltetrahydropyran[7] gave in both cases the anticipated result, namely, a value of $\Delta S^{\circ}_{a\rightarrow e}$ approaching zero. (The data treatment in references 7 and 11 *assumed* a value of zero for ΔS°, but even in the absence of this assumption, the plots of lnK against T^{-1} pass close to the origin).

The carbon-13 chemical shifts for ($1\rightleftharpoons 2$) and for individual conformations (**1**) and (**2**) in 2-methoxytetrahydropyran have already been reported for $CFCl_3/CDCl_3$ (85/15) as solvent,[7] and those for four additional solvents are set out in Table 1.

Table 1 Carbon-13 Chemical Shifts (δ/ppm from Me_4Si) at 62.9MHz for (**1**), (**2**) and ($1\rightleftharpoons 2$).

Species	Solvent	T/K	2-C	3-C	4-C	5-C	6-C	OMe
$1\rightleftharpoons 2$	ether/C_7D_8[a,b]	273	99.49	31.04	19.55	26.27	61.08	54.41
1	"	140	97.38	29.98	18.04	25.65	58.83	53.81
2	"	140	103.01	31.54	22.49	25.65	d	55.40
$1\rightleftharpoons 2$	ether/CD_2Cl_2[c]	294	99.91	31.26	19.82	26.47	61.49	54.58
1	"	152	97.80	30.37	19.38	26.08	59.23	54.19
2	"	152	103.45	31.88	23.00	26.08	d	e
$1\rightleftharpoons 2$	CD_2Cl_2	294	100.38	31.13	19.97	26.10	62.27	54.93
1	"	150	97.90	29.99	18.04	25.58	59.59	54.82
2	"	150	103.32	31.67	22.54	25.58	66.47	56.60
$1\rightleftharpoons 2$	ether/CD_3OD[b]	273	100.04	31.28	19.85	26.44	61.68	54.75
1	"	140	97.92	30.50	18.55	26.22	59.34	54.21
2	"	140	103.61	32.08	23.06	26.22	d	55.83

[a] C_7D_8 = toluene-d_8 [b] 3/1 v/v [c] 85/15 v/v

[d] hidden by CH_2 signal of ether

[e] hidden by CD_2Cl_2 signal

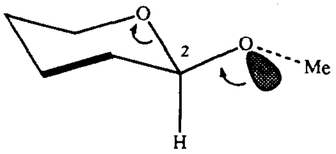
Analyses (see Experimental) of the equilibrium ($1\rightleftharpoons 2$) at 140-160K (4 solvents), of ($1\rightleftharpoons 2$) at 165-190K (2 solvents) and of the equilibrated mixture of *cis*- and *trans*-2-methoxy-4-methyltetrahydropyran at 250-270K (4 solvents) have given thermodynamic parameters which are listed in Table 2; these parameters provide clear examples of the limited value of single temperature ΔG° values. Thus, whilst ΔG° values for ($1\rightleftharpoons 2$) at 300K are similar for solvents CD_2Cl_2 and ether/methanol, the corresponding ΔH° and ΔS° values are substantially different.

Table 2 Thermodynamic Parameters[a] for ($1 \rightleftharpoons 2$)
($\Delta H°$ and $\Delta G°$ in kcal mol^{-1}; $\Delta S°$ in cal K^{-1} mol^{-1})

Solvent	$\Delta H°_{1\rightarrow2}$	$\Delta S°_{1\rightarrow2}$	$\Delta G°_{1\rightarrow2}$(300K)	%(2)(300K)
$CFCl_3/CDCl_3$ (85/15)[b]	0.03	-2.51	0.78	21.1
error	±0.01	±0.09		
CD_2Cl_2[c]	0.04	-1.60	0.50	30.3
error	±0.03	±0.14		
ether/CD_2Cl_2 (85/15)[c]	0.32	-1.47	0.76	21.4
error	±0.06	±0.30		
ether/C_7D_8[d] (3/1)[c]	0.48	-0.90	0.75	22.1
error	±0.04	±0.20		
ether/CD_3OD (3/1)[c]	0.61	0.42	0.48	30.7
error	±0.09	±0.50		

[a] from computer plots of lnK against T^{-1}
[b] reference 7
[c] this work
[d] toluene -d_8

Entries in Table 2 for the first four relatively non-polar solvents show that *either* equatorial and axial conformations have similar enthalpies, *or* that the axial conformation has the lower enthalpy. Since it is the axial conformation which is destabilised by steric repulsions, it follows that anomeric effects must outweigh steric considerations. Further, it is to be noted that the equatorial conformation is stabilised by the exo-anomeric effect, as in (**3**), whereas the axial conformation is subject to opposing exo- and endo-anomeric effects, as in (**4**) and (**5**) respectively.[7] It is reasonable to conclude that, in axial conformations, *the endo-anomeric effect* (**5**) *is inherently stronger than the exo-anomeric effect* (**4**).



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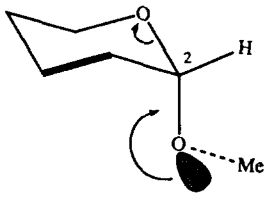

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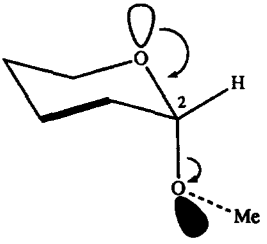


(5)

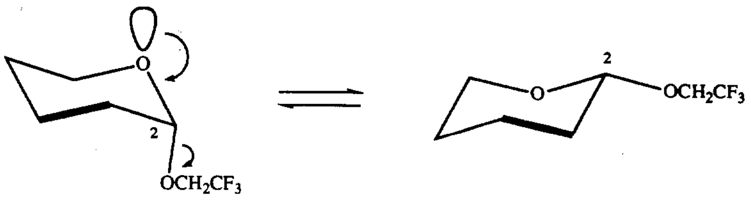
Superficially, this conclusion appears to be supported by ^{17}O chemical shifts,[12] measured at 100° in concentrated solution in toluene. Thus, the most shielded, and therefore the most electron rich, oxygen in conformationally biased 2-methoxytetrahydropyrans is the exo-oxygen of axial methoxy groups. However, despite the strong exo-anomeric effect in biased 2-methoxytetrahydropyrans with equatorial methoxy, it is the exo-oxygen which appears to be more shielded than the ring oxygen. Evidently correlations of perceived anomeric effects with chemical shifts have to be made with caution.

The entries in Table 2 also reveal a trend in conformational entropy differences $\Delta S^{o}_{a \to e}$. If the ether/toluene mixture is taken as a "standard" non-polar solvent, the change to halogenated solvents causes a decrease in $\Delta S^{o}_{a \to e}$ values, possibly due to preferential complexation to the equatorial conformations. The marked reduction in $\Delta S^{o}_{a \to e}$ which accompanies the replacement of CD_2Cl_2 by $CFCl_3/CDCl_3$ is in line with previous observations on four 2-alkoxytetrahydropyrans.[1]

Table 3 Carbon-13 Chemical Shifts (δ/ppm from Me_4Si) at 62.9MHz for (6), (7) and (6⇌7).

Species	Solvent	T/K	2-C	3-C	4-C	5-C	6-C	1'-C	2'-C
6⇌7	ether/C_7D_8[a]	270	98.55	30.29	18.83	25.84	61.42	64.15[d]	125.16[e]
6	"	140	96.94	29.51	17.85	25.53	59.80	63.18[d]	f
7	"	140	102.28	31.21	b	25.53	c	c	f
6⇌7	ether/CD_3OD[a]	296	99.35	30.77	19.36	26.17	62.21	64.7	125.5
6	"	147	97.25	29.83	18.13	25.87	60.05	63.41[g]	125.5[h]
7	"	147	102.52	31.59	22.74	25.87	c	c	i

[a] 75/25 v/v
[b] hidden by CD_3 (toluene -d_8)
[c] hidden by CH_2 (ether)
[d] quartet $^2J_{CF}$ 34.22Hz
[e] quarter $^1J_{CF}$ 278.27Hz
[f] hidden by solvent (toluene -d_8)
[g] quartet $^2J_{CF}$ 33.23Hz
[h] quartet $^1J_{CF}$ 276.58Hz
[i] not clear



(6) (7)

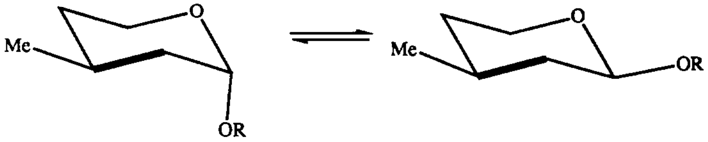
One of the purposes of the present study was to assess the effect of a polar, protic solvent (methanol) on equilibria such as (1⇌2). The positions of conformational equilibria in (1⇌2) and in the 2-trifluoroethoxy analogue ($6 \rightleftharpoons 7$) were studied in ether/toluene (3/1) and in ether/methanol (3/1) by methods previously described,[7] namely, (a) direct integration of ^{13}C nmr spectra at 140K to 150K; (b) analysis of ^{13}C nmr spectra in the region 165K to 190K by a line-broadening technique; and (c) integration of the ^{1}H nmr spectra of the equilibrated mixture ($8 \rightleftharpoons 9$) and of the equilibrated mixture ($10 \rightleftharpoons 11$), both carried out at 270K and 250K. Method (c) was only applicable in the case of ether/toluene as solvent, as use of ether/methanol would inevitably have led to appreciable replacement of OCH_2CF_3 by OCH_3 under the conditions of acid catalysis. The derived thermodynamic parameters are collected in Table 4, whilst the observed ^{13}C nmr chemical shifts are reported in Tables 1 and 3.

Table 4 Thermodynamic Parameters[a] for ($1 \rightleftharpoons 2$) and ($6 \rightleftharpoons 7$)
($\Delta H°$ in kcal mol^{-1}; $\Delta S°$ in cal K^{-1} mol^{-1}) in ether/toluene and ether/methanol.

	($1 \rightleftharpoons 2$)		($6 \rightleftharpoons 7$)	
Solvent	$\Delta H^{o}_{a \to e}$	$\Delta S^{o}_{a \to e}$	$\Delta H^{o}_{a \to e}$	$\Delta S^{o}_{a \to e}$
ether/C_7D_8[b] (3:1)	0.48	-0.90	0.50	-1.39
error	±0.04	±0.20	±0.07	±0.26
ether/CD_3OD (3:1)	0.61	0.42	0.72	0.34
error	±0.09	±0.50	±0.13	±0.80

[a] from computer plots of lnK against T^{-1}

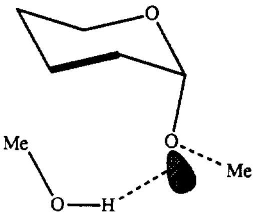
[b] toluene -d_8



(8; R=Me)
(10; R=CH_2CF_3)

(9; R=Me)
(11; R=CH_2CF_3)

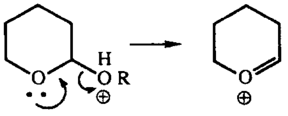
A comparison of entries in Table 4 reveals the changes in $\Delta H^{o}_{a \to e}$ and $\Delta S^{o}_{a \to e}$ which result from the replacement of the relatively non-polar solvent ether/toluene by the polar hydrogen-donating solvent ether/methanol. These changes are surprising and occur in the same direction for both systems (1⇌2) and (6⇌7). An increase in solvent polarity was expected to lower the enthalpy of the relatively more polar equatorial conformation, causing $\Delta H^{o}_{a\rightarrow e}$ to *decrease*. On the contrary, $\Delta H^{o}_{a\rightarrow e}$ values are seen to *increase* for both (1⇌2) and (6⇌7). We propose that the strong endo-anomeric effect in conformations (**1**) and (**6**) stimulates the selective hydrogen bonding of methanol to the oxygen of the axial methoxy group in (**1**) and (**6**) - see (**12**) for example.



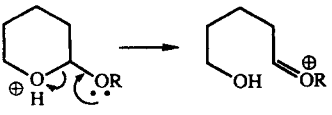
(12)

Some hydrogen bonding must also occur, of course, between methanol and the remaining oxygen atoms of systems (1⇌2) and (6⇌7), but this is considered to be relatively weaker. The strong involvement in hydrogen bonding of the exo-cyclic oxygens of (**1**) and (**6**) renders such atoms more positive, thus strengthening already dominant endo-anomeric effects, and causing a reduction in the enthalpies of (**1**) and (**6**). The observed increases in $\Delta H^{o}_{1\rightarrow 2}$ and $\Delta H^{o}_{6\rightarrow 7}$ for ether/methanol, over those for ether/toluene, are therefore intelligible. At the same time, the stronger bonding of methanol to (**1**) and (**6**) will inevitably reduce the entropies of (**1**) and (**6**), leading to significant increases in $\Delta S^{o}_{a\rightarrow e}$ for ether/methanol over those for ether/toluene, as indeed is observed for both (1⇌2) and (6⇌7).

Lemieux and Praly[6] have also studied the effect of solvent changes on the equilibrium in 2-methoxytetrahydropyran (1⇌2). However, the measured effects on $\Delta H^{o}_{1\rightarrow 2}$ and $\Delta S^{o}_{1\rightarrow 2}$ values for a non-polar solvent (CCl_4/C_6D_6) caused by change to D_2O, were *opposite* to those recorded in the present investigation. Such differences are difficult to understand except perhaps on the assumption that water is unique in its hydrogen bonding behaviour.



(13)



(14)

The selective hydrogen bonding of methanol to the oxygen atom of an axial alkoxy group [as in (**12**)] has implications for acid-catalysed glycosidic cleavage, the mechanism of which may be related to the preferred site of protonation. Indeed, recent experiments by Fraser-Reid *et al.*[13] have demonstrated that acetolysis of methyl α-D-glucopyranoside (*axial* OMe) occurs almost exclusively through the cyclic cation (**13**), whereas the isomeric β-glycopyranoside (*equatorial* OMe) reacts through both cyclic (**13**) and acyclic (**14**) cations. These results are consistent with our proposal, based on the experiments herein described, that methanol bonds preferentially to the oxygen atom of an axial alkoxy group in a simple 2-alkoxytetrahydropyran.

Experimental

General - See Part 1,[7]
cis- and *trans*-2-(2',2',2'-Trifluoroethoxy)-4-methyltetrahydropyran. - The ^{1}H nmr spectrum of the *cis*-isomer was reported in Part IV.[1] The ^{1}H nmr spectrum (250MHz, $CDCl_3$) of the *trans*-isomer showed signals at δ4.89 (apparent doublet, width 6.5Hz; 2-H), 3.97 (dq, $^2J_{H(A)H(B)}$ 12.28Hz, $^3J_{H(A)F}$ 9.04Hz; H_A of OCH_AH_B), 3.84 (dq, $^2J_{H(A)H(B)}$ 12.28Hz, $^3J_{H(B)F}$ 8.75Hz; H_B of OCH_AH_B), 3.75 (td, $^3J_{6a5e}$ 2.37Hz, $^2J_{6a6e}$ + $^3J_{6a5a}$ 23.7Hz; 6-H_a), 3.63 (ddd, $^2J_{6a6e}$ 11.18Hz, $^3J_{6e5a}$ 4.98Hz, $^3J_{6e5e}$ 1.70Hz; 6-H_e), 2.05-1.90 (m; 4-H), 1.81 (dm, $^2J_{3e3a}$ 13.53Hz; 3-H_e), 1.57 (dm, $^2J_{5e5a}$ 13.13Hz; 5-H_e), 1.30 (td, $^3J_{3a2e}$ 3.45Hz, $^2J_{3a3e}$ + $^3J_{3a4a}$ 25.83Hz; 3-H_a), 1.29 (qd, $^3J_{5a6e}$ 4.73Hz, $^2J_{5a5e}$ + $^3J_{5a6a}$ + $^3J_{5a4a}$ 38.08Hz; 5-H_a) and 0.90 (d, ^3J 6.60Hz; 4-Me).Syntheses of the required tetrahydropyrans were reported in Parts I[7] and IV.[1]

Determination of Thermodynamic Parameters

See Part I.[7]

Data Treatment

Data treatment employed computer drawn plots of lnK (K = e/a) against T^{-1} (method B of Part I).

1. The equilibrium in 2-methoxytetrahydropyran ($1 \rightleftharpoons 2$)

(a) 2-methoxytetrahydropyran ($1 \rightleftharpoons 2$)
equilibrium constant K = 2/1 = e/a

Solvent:	CD_2Cl_2		ether/CD_2Cl_2 (85/15)	
T/K	150	155	152	156
K	0.393	0.387	0.163	0.173
± error	0.012	0.017	0.005	0.005

Solvent:	ether/C_7D_8 (3/1)		ether/CD_3OD (3/1)	
T/K	140	150	140	146
K	0.099	0.134	0.126	0.143
± error	0.013	0.005	0.005	0.006

(b) A line broadening study[14] of the carbon-13 nmr spectrum of ($1 \rightleftharpoons 2$) in the range 165-190K gave w, the maximum line widths (corrected for TMS line widths) for selected signals, the temperatures at which the maxima were observed, and the equilibrium constant K derived by using the accurate equation of reference 14.

Solvent	Carbon Signal	T/K	w(Hz)	K	±error
ether/C_7D_8	C3	175	15.1	0.163	0.001
ether/C_7D_8	OCH_3	175	16.1	0.171	0.001
ether/CD_3OD	C3	175	19.9	0.216	0.001
ether/CD_3OD	OCH_3	175	25.6	0.275	0.001

(c) *cis*- and *trans*-2-methoxy-4-methyltetrahydropyran ($8 \rightleftharpoons 9$)
equilibrium constant K = 9/8 = e/a

Solvent:	CD_2Cl_2		ether/CD_2Cl_2 (85/15)	
T/K	255	270	255	270
K	0.398	0.428	0.235	0.282
± error	0.008	0.011	0.010	0.012

Solvent:	ether C_7D_8 (3/1)		ether/CD_3OD (3/1)	
T/K	250	270	250	270
K	0.250	0.244	0.352	0.365
± error	0.008	0.015	0.006	0.008

Data Treatment

Solvent CD_2Cl_2
Plot of lnK against T^{-1} (4 points) gave

$$\Delta H^{\circ}_{a\rightarrow e} = 0.04 \pm 0.05 \text{ kcal mol}^{-1} \text{ and}$$
$$\Delta S^{\circ}_{a\rightarrow e} = -1.60 \pm 0.14 \text{ cal K}^{-1} \text{ mol}^{-1}$$

Solvent ether/CD_2Cl_2 (85/15)
Plot of lnK against T^{-1} (4 points) gave

$$\Delta H^{\circ}_{a\rightarrow e} = 0.32 \pm 0.06 \text{ kcal mol}^{-1} \text{ and}$$
$$\Delta S^{\circ}_{a\rightarrow e} = -1.47 \pm 0.30 \text{ cal K}^{-1}\text{mol}^{-1}$$

Solvent ether/C_7D_8 (3/1)
Plot of lnK against T^{-1} (6 points) gave

$$\Delta H^{\circ}_{a\rightarrow e} = 0.48 \pm 0.04 \text{ kcal mol}^{-1} \text{ and}$$
$$\Delta S^{\circ}_{a\rightarrow e} = -0.90 \pm 0.20 \text{ cal K}^{-1} \text{ mol}^{-1}$$

Solvent ether/CD_3OD (3/1)
Plot lnK against T^{-1} (6 points) gave

$$\Delta H^{\circ}_{a\rightarrow e} = 0.61 \pm 0.09 \text{ kcal mol}^{-1} \text{ and}$$
$$\Delta S^{\circ}_{a\rightarrow e} = 0.42 \pm 0.51 \text{ cal K}^{-1} \text{ mol}^{-1}$$

2. The equilibrium in 2-(2',2',2'-trifluoroethoxy)tetrahydropyran (6⇌7)

(a) 2-(2',2',2'-trifluoroethoxy)tetrahydropyran (6⇌7)
equilibrium constant K = 7/6 = e/a

Solvent:	ether/C_7D_8 (3/1)		ether/CD_3OD (3/1)
T/K	140	147	147
K	0.092	0.075	0.098
± error	0.007	0.009	0.004

(b) A line broadening study of the carbon-13 nmr spectrum of (6⇌7) in the range 165-190K gave the following results:

Solvent	Carbon Signal	T/K	w(Hz)	K	±error
ether/C_7D_8	C2	181	37.2	0.116	0.001
ether/C_7D_8	C3	172	13.5	0.133	0.001
ether/CD_3OD	C2	180	47.3	0.155	0.001
ether/CD_3OD	C3	170	15.9	0.152	0.009
ether/CD_3OD	C4	180	44.9	0.151	0.003

(c) *cis*- and *trans*-2-(2',2',2'-trifluoroethoxy)-4-methyltetrahydropyran (10⇌11)
equilibrium constant K = 11/10 = e/a

Solvent:	ether/C_7D_8 (3/1)
T/K	280
K	0.200
± error	0.010

Data Treatment

Solvent ether/C_7D_8 (3/1)
Plot of lnK against T^{-1} (5 points) gave

$$\Delta H^{\circ}_{a\rightarrow e} = 0.50 \pm 0.07 \text{ kcal mol}^{-1} \text{ and}$$
$$\Delta S^{\circ}_{a\rightarrow e} = -1.39 \pm 0.26 \text{ cal K}^{-1} \text{ mol}^{-1}$$

Solvent ether/CD_3OD (3/1)
Plot lnK against T^{-1} (4 points) gave

$$\Delta H^{o}_{a\rightarrow e} = 0.72 \pm 0.13 \text{ kcal mol}^{-1} \text{ and}$$
$$\Delta S^{o}_{a\rightarrow e} = 0.34 \pm 0.80 \text{ cal K}^{-1} \text{ mol}^{-1}$$

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