

The Configurations of Isomeric 2,2,4,6-Tetramethyl-1,3-dioxanes

KALEVI PIHLAJA and JUSSI HEIKKILÄ

Department of Chemistry, University of Turku, Turku, Finland

This paper describes the synthesis of isomeric 2,2,4,6-tetramethyl-1,3-dioxanes and the clarification of their structures on the basis of calorimetric data.

The title compound was previously prepared by Pihlaja¹ and Maroni *et al.*² The former author reported that 2,2,4,6-tetramethyl-1,3-dioxane has two isomeric forms and he solved their configurations and conformations on the basis of synthetic and kinetic data, whereas Maroni *et al.* concluded that this compound has only one configuration. Therefore it is very interesting to reinvestigate the problem with the aid of synthetic approach and calorimetric measurements.

EXPERIMENTAL

Synthesis of isomeric 2,2,4,6-tetramethyl-1,3-dioxanes. The *cis* and *trans* isomers of 2,2,4,6-tetramethyl-1,3-dioxane were synthesized by the method of Pihlaja¹ from acetone and a mixture of *meso*- and *DL*-2,4-pentanediols (weight ratio about 2:3) that had been prepared by hydrogenating acetylacetone. The less volatile isomer II was isolated in fairly high purity from the reaction mixture in the early stages of the reaction (after about 2–4 h); this may have been the reason why Maroni *et al.*² reported that 2,2,4,6-tetramethyl-1,3-dioxane exists only in one configurational form. The more volatile isomer I was isolated in the later stages of the reaction; this compound was distilled several times from sodium metal before it was employed in calorimetric experiments. The isomer II was purified by careful distillation in a Todd Precise Fractionation Assembly; the final isolated sample contained less than 0.2% of isomer I. The weight ratio of the yields of the isomers I and II was 1.5. From these synthetic results and from the rates of acid-catalyzed hydrolysis of the isomers Pihlaja¹ has recently concluded that the more volatile isomer I has the *trans* configuration and the less volatile isomer II the *cis* configuration; this is in contrast to the volatilities and configurations of the isomers of 1,1,3,5-tetramethylcyclohexane.³ The isomers were found to have the following physical constants:

Isomer I: b.p. 131.8–132.5°C/760 mm Hg; $n_D^{20} = 1.4126$; $d_4^{20} = 0.8939$; $(R_D)_{obs.}$ 40.19 (calc. 40.15).

Isomer II (sample D): b.p. 137.9°/719 mm Hg; $n_D^{20} = 1.4175$; $d_4^{20} = 0.9014$; $(R_D)_{obs.}$ 40.27 (calc. 40.15).

Preparation of 2,2,4-trimethyl-1,3-dioxane. This compound was prepared from acetone and 1,3-butanediol in the presence of *p*-toluenesulfonic acid by the method of Rondstedt.⁴ The physical constants of the isolated sample were b.p. 132°C/760 mm Hg, n_D^{20} 1.4175, d_4^{20} 0.9283, $(R_D)_{obs}$. 35.39 (calc. 35.53). Purity \geq 99.95 %.

Table 1. 2,2,4-Trimethyl-1,3-dioxane.

m (mass *in vacuo*) = 1.00124 m (mass in air)
 W (energy equivalent of the calorimeter) = 1359.6 \pm 0.3 cal/°F
 $\Delta H_{vap}^{25^\circ C}$ = 10.02 \pm 0.3 kcal/mole
 $-\Delta nRT$ = 1.48 kcal/mole
 $\Delta H_c^\circ(\text{liq.}) = \Delta U_c^\circ(\text{liq.}) + \Delta nRT$.

m g	Δt °F	q_i cal	q_t cal	$-\Delta U_c^\circ(\text{liq.})$ kcal/mole	$-\Delta H_c^\circ(\text{liq.})$ kcal/mole
0.65962	3.802	10.36	17.42	1014.77	1016.25
0.65271	3.767	16.38	18.87	1014.53	1016.01
0.62668	3.612	15.40	10.23	1014.89	1016.37
0.75363	4.343	7.98	17.50	1015.65	1017.13
0.57742	3.327	6.13	12.04	1015.78	1017.26
0.68725	3.953	7.56	11.46	1014.52	1016.00
0.64520	3.717	8.54	13.78	1015.23	1016.71
0.72179	4.153	11.34	12.24	1014.20	1015.68

$-\Delta H_c^\circ(\text{liq.}) = 1016.4_3 \pm 0.20$ kcal/mole
 $-\Delta H_f^\circ(\text{liq.}) = 120.1_4 \pm 0.4$ kcal/mole
 $-\Delta H_f^\circ(\text{g}) = 110.1_2 \pm 0.7$ kcal/mole.

Table 2. 2,2,4,6-Tetramethyl-1,3-dioxane, isomer II. Sample D.

$m = 1.00128$ m
 $W_1 = 1359.6 \pm 0.3$ cal/°F (in experiments 1, 2, 3, and 7)
 $W_2 = 1360.6 \pm 0.4$ cal/°F (in experiments 4–6)
 $\Delta H_{vap}^{25^\circ C} = 10.32 \pm 0.3$ kcal/mole
 $-\Delta nRT = 1.78$ kcal/mole.

Exp.	m g	Δt °F	q_i cal	q_t cal	q_{gel} cal	$-\Delta U_c^\circ(\text{liq.})$ kcal/mole	$-\Delta H_c^\circ(\text{liq.})$ kcal/mole
1	0.66986	4.013	15.96	14.53		1168.20	1169.98
2	0.65303	3.910	17.78	14.71		1166.94	1168.72
3	0.53699	3.219	14.42	11.13		1168.63	1170.41
4	0.57984	3.870	17.50	12.58	544.18	1166.91	1168.69
5	0.60708	3.634	10.22	16.22		1168.41	1170.19
6	0.59476	3.973	20.02	12.80	558.21	1167.55	1169.33
7	0.47461	2.846	10.36	16.04		1167.86	1169.64

$-\Delta H_c^\circ(\text{liq.}) = 1169.57 \pm 0.27$ kcal/mole
 $-\Delta H_f^\circ(\text{liq.}) = 129.38 \pm 0.5$ kcal/mole
 $-\Delta H_f^\circ(\text{g}) = 119.06 \pm 0.8$ kcal/mole.

Table 3. 2,2,4,6-Tetramethyl-1,3-dioxane, isomer I.

$m = 1.00129 \text{ m}$									
$W_1 = 1361.6 \pm 0.2 \text{ cal/}^\circ\text{F}$ (in experiment 1)									
$W_2 = 1359.6 \pm 0.3 \text{ cal/}^\circ\text{F}$ (in experiment 2)									
$W_3 = 1360.6 \pm 0.4 \text{ cal/}^\circ\text{F}$ (in experiments 3–5)									
$\Delta H_{\text{vap}}^{25^\circ\text{C}} = 10.02 \pm 0.30 \text{ kcal/mole}$									
$-\Delta nRT = 1.78 \text{ kcal/mole}$									
$q_{\text{II}} = \text{correction due to isomer II present as impurity}$									
Expt.	m^{I} g	m^{II} g	Δt $^\circ\text{F}$	q_i cal	q_t cal	q_{II} cal	q_{gel} cal	$-\Delta U_c^\circ(\text{liq.})$ kcal/mole	$-\Delta H_c^\circ(\text{liq.})$ kcal/mole
1	0.54171	0.03153	3.441	14.70	16.28	255.68		1171.13	1172.91
2	0.46308	0.04027	3.021	16.38	6.05	326.55		1170.58	1172.36
3	0.53691	0.04353	3.891	15.96	12.72	352.99	549.16	1172.10	1173.88
4	0.53571	0.04344	3.890	17.92	13.02	352.26	559.12	1171.27	1173.05
5	0.55460	0.04497	4.028	18.06	13.45	364.66	583.11	1170.64	1172.42

Mixture A was used in experiment 2, mixture B in experiments 3–5 and mixture C in experiment 1.

$$-\Delta H_c^\circ(\text{liq.}) = 1172.92 \pm 0.27 \text{ kcal/mole}$$

$$-\Delta H_f^\circ(\text{liq.}) = 126.03 \pm 0.5 \text{ kcal/mole}$$

$$-\Delta H_f^\circ(\text{g}) = 116.01 \pm 0.8 \text{ kcal/mole}$$

Table 4. Combustion experiments with gelatin capsules.
 $W = 1360.6 \pm 0.4 \text{ cal/}^\circ\text{F}$.

m g	t $^\circ\text{F}$	q_i cal	q_t cal	$-\Delta U_c^\circ$ cal/g
0.6373	2.143	15.40	11.15	4533.53
0.6336	2.135	18.20	11.58	4537.72
0.6142	2.060	16.24	11.15	4518.80
0.6206	2.082	12.88	11.35	4525.52
0.6243	2.095	14.84	11.72	4523.30
0.6274	2.107	16.66	11.30	4524.74

Mean $4527.3 \pm 2.9 \text{ cal/g}$

Calorimetric measurements. Three mixtures were employed in the calorimetric measurements: A, containing 92 % of isomer I and 8 % of isomer II; B, containing 92.5 % of isomer I and 7.5 % of isomer II; C, containing 94.5 % of isomer I and 5.5 % of isomer II; and a sample D containing over 99.8 % of isomer II and less than 0.2 % of isomer I. In these experiments a Parr adiabatic bomb calorimeter was used as described by Pihlaja and Heikkilä⁵ except that some of the samples were sealed in gelatin capsules in which cases the heats of combustion of the samples were corrected for the heats of combustion of the capsules (q_{gel}). The results of the calorimetric experiments are shown in Tables 1–3. The equations from which the heats of combustion, heats of vaporization and heats of formation were calculated have been presented elsewhere.⁵ The results of calorimetric experiments to determine the heat liberated in the combustion of gelatin capsules are shown in Table 4.

RESULTS AND DISCUSSION

2,2,4-Trimethyl-1,3-dioxane exists mainly in the chair conformation where the methyl group at position 4 is equatorial (Fig. 1). The contribution of the methyl group at position 2a (*a* means axial) to the heat of formation of 2,2,4-trimethyl-1,3-dioxane can be calculated from the heat of formation of the latter compound evaluated in this work and the heat of formation of *cis*-2,4-dimethyl-1,3-dioxane reported by Pihlaja and Heikkilä.⁵

$$\begin{aligned}\Delta H_{2a} &= \Delta H_f^\circ(\text{g, 2,2,4-trimethyl-1,3-dioxane}) - \\ &\quad \Delta H_f^\circ(\text{g, cis-2,4-dimethyl-1,3-dioxane}) \\ &= (-110.1_2 + 102.2_6) \text{ kcal/mole} \\ &= -7.8_6 \pm 0.8 \text{ kcal/mole}\end{aligned}$$

The contribution to the heat of formation associated with the interaction between the axial methyl group at position 2 and the axial hydrogen atoms at positions 4 and 6 in 2,2-dimethyl-1,3-dioxane is

$$\Delta H_{2a}^i(\text{g}) = +11.7_5 - 7.8_6 = 3.8_9 \pm 0.7 \text{ kcal/mole}$$

since ΔH_{2e} , the group contribution of the equatorial methyl substituent at position 2, is -11.7_5 kcal/mole.⁵

Two configurations can be proposed for 2,2,4,6-tetramethyl-1,3-dioxane, one in which the methyl substituents at positions 4 and 6 are both equatorial or axial and one in which one of these two substituents is axial and the other equatorial. The former configuration is a *meso* form and the latter a DL form (Fig. 2). The diequatorial conformation of the *cis* configuration is so much more stable than the diaxial conformation that the proportion of the latter is negligible. Since the enthalpy of interaction of an axial methyl group at position 2 in 2,2-dimethyl-1,3-dioxane is about twice as great as the enthalpy of interaction of an axial methyl group in cyclohexane derivatives,⁶ it may be concluded that the energy of interaction between the axial methyl groups at positions 2 and 4 (or 6) in the *trans* configuration of 2,2,4,6-tetramethyl-1,3-dioxane (as chair form) is also at least twice as great as the energy of interaction between axial methyl groups at the same positions in cyclohexane derivatives and hence equal to about 7.4 kcal/mole.³

The enthalpy of interaction between an axial methyl group and an axial hydrogen atom in methyl-substituted cyclohexane derivatives is about 0.95 kcal/mole,⁶ and hence although the energy of interaction between an axial methyl group at position 2 and an axial methyl group at position 4 in methyl-

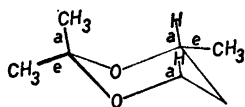


Fig. 1. Stable chair conformation of 2,2,4-trimethyl-1,3-dioxane.

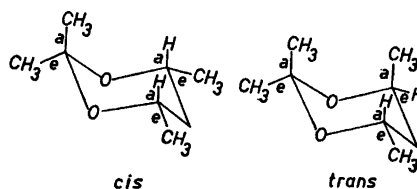


Fig. 2. Chair conformations of *cis*- and *trans*-2,2,4,6-tetramethyl-1,3-dioxanes.

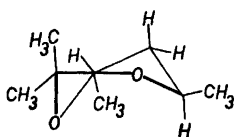


Fig. 3. Stable skew-boat conformation of *trans*-2,2,4,6-tetramethyl-1,3-dioxane.

1,3-dioxanes is about 1.94 kcal/mole ($= 3.89/2$), the energy of interaction between an axial methyl group at position 4 and an axial methyl group at position 6 in methyl-1,3-dioxanes may be expected to be of the same magnitude as the energy of diaxial methyl-hydrogen interaction in cyclohexane derivatives since the carbon-oxygen bond length is only 1.43 Å, whereas the length of the carbon-carbon bond is 1.54 Å.

Consequently the interaction enthalpy of *cis*-2,2,4,6-tetramethyl-1,3-dioxane is about 3.9 kcal/mole. The interaction enthalpy of the chair form of *trans*-2,2,4,6-tetramethyl-1,3-dioxane is of the order of $0.95 + 1.94 + 7.4 = 10.3$ kcal/mole and hence its enthalpy is about 6.4 kcal/mole greater than the enthalpy of the chair form of the *cis* configuration. The heat of formation, $\Delta H_f^\circ(g)$, of the more volatile isomer I of 2,2,4,6-tetramethyl-1,3-dioxane was found experimentally to be $-116.0_1 \pm 0.8$ kcal/mole, and that of the less volatile isomer II $-119.0_8 \pm 0.8$ kcal/mole, and hence the enthalpy of the former isomer is about $3.0_5 \pm 0.8$ kcal/mole greater than that of the latter isomer. It hence follows that the isomer I is *trans*-2,2,4,6-tetramethyl-1,3-dioxane and the isomer II *cis*-2,2,4,6-tetramethyl-1,3-dioxane, in accordance with conclusions based on other data.¹

The large difference between the calculated and observed enthalpy differences may be attributed to the occurrence of *trans*-2,2,4,6-tetramethyl-1,3-dioxane in the flexible form (skew-boat)¹ (Fig. 3) in which the large diaxial methyl-methyl interaction is largely eliminated. The enthalpy of the flexible form of the 1,3-dioxane ring has been estimated to be about 2.2 kcal/mole greater than the enthalpy of the chair form,⁷ and hence the energy relief when the *trans*-2,2,4,6-tetramethyl-1,3-dioxane changes from the chair form to the flexible form is about $6.4 + 2.2 - 3.0 = 5.6$ kcal/mole. This energy relief is almost three times as great as the increase in enthalpy associated with the conversion of the chair form into the flexible form.

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