Dissociation Constants of the Cyanohydrins of Some Substituted Thian-4-ones †

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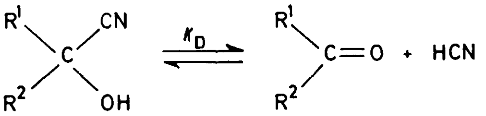
The dissociation constants of cyanohydrins of some substituted thian-4-ones and thian-4-one 1,1-dioxides have been determined at 25° in 80% dioxan. The polymethyl thian-4-one cyanohydrins and *r*-2,*t*-6-diphenyl-*c*-3-alkylthian-4-ones show increasing instability owing to the effect of axial crowding.

As a part of a conformational study[1,2] on some substituted thian-4-one derivatives, we wished to investigate the effect of substituents in various positions in the ring on the reactivity of thian-4-ones. Accordingly a series of substituted thian-4-ones was prepared and the dissociation constants of their cyanohydrins determined. The cyanohydrin reaction has been shown to be reversible and to involve base-catalysed nucleophilic attack of the cyanide ion on the carbonyl carbon.[3]

The equilibrium constant K_D of reaction (1) has been employed to study the steric crowding around the carbonyl function in cyclic ketones.[4-8] Steric crowding around the carbonyl group introduces torsional and steric interactions between the cyano- and hydroxy-groups of the cyanohydrin which are relieved when the cyanohydrin dissociates to the ketone and favour an equilibrium displaced towards ketone side. On the other hand the angle strain in the carbonyl compound is relieved when it is converted into the cyanohydrin. This shifts the position of the equilibrium towards the cyanohydrin. So the magnitude of the dissociation constant should give information about the preferred conformations of these thian-4-ones.

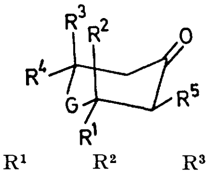


(1)

RESULTS AND DISCUSSION

The dissociation constants of the cyanohydrins of the thian-4-ones and their corresponding 1,1-dioxides are given in Tables 1 and 2. The cyanohydrins of *r*-2,*c*-6-diphenyl-*t*-3-alkylthian-4-ones have higher dissociation constant values than that of *r*-2,*c*-6-diphenylthian-4-one (2). The dissociation constants increase in the order H < Me < Et. *r*-2,*c*-6-Diphenylthian-4-one and its 3-alkyl derivatives have been shown to exist in chair conformation with the alkyl and the phenyl groups in the most stable equatorial position.[1,2] The higher dissociation constants of the cyanohydrins (Ia—c) of 3-alkyl-substituted thian-4-ones, may be due to a combination of the steric and inductive effects of the alkyl group, which will deactivate the carbonyl function and decrease the extent of cyanohydrin formation.

The dissociation constants of the cyanohydrins (II) are much higher than those of their corresponding *cis*-epimers (I) (wherein the two phenyl groups are *cis*-oriented) and the cyanohydrin of (2). The higher dissociation constants of the cyanohydrin (II) when compared with those of the cyanohydrin of (2) and (I) arise because of the increased steric crowding due to the bulky axial phenyl group. The higher dissociation constants of the cyanohydrins (III) and (IV), when compared to the cyanohydrin of (2) may be attributed to the increased CH_3–OH or –CN 1,3-interactions in these compounds.



	G	R^1	R^2	R^3	R^4	R^5
(1)	S	H	H	H	H	H
(2)	S	Ph	H	H	Ph	H
(3)	S	Ph	H	Ph	H	H
(4)	S	*p*-$MeOC_6H_4$	H	H	*p*-$MeOC_6H_4$	H
(5)	S	Ph	H	H	Ph	Me
(6)	S	H	Ph	H	Ph	Me
(7)	S	Ph	H	H	Ph	Et
(8)	S	H	Ph	H	Ph	Et
(9)	S	Ph	H	Me	Me	H
(10)	S	H	H	H	H	Pr^i
(11)	S	H	H	Me	Me	H
(12)	S	Me	Me	Me	Me	H
(13)	SO_2	Ph	H	H	Ph	H
(14)	SO_2	Ph	H	Ph	H	H
(15)	SO_2	Ph	H	H	Ph	Me
(16)	SO_2	H	Ph	H	Ph	Me
(17)	SO_2	Ph	H	H	Ph	Et
(18)	SO_2	H	Ph	H	Ph	Et
(19)	SO_2	Ph	H	Me	Me	H
(20)	SO_2	H	H	H	H	Pr^i

TABLE 1

Dissociation constants of cyanohydrins of some substituted thian-4-ones at 25° in 80% dioxan

Thian-4-one	$10^3 K_D^{25°}$/mol l^{-1}
(1)	4.69 ± 0.01
(2)	11.26 ± 0.02
(3)	40.18 ± 0.09
(4)	11.97 ± 0.04
(5)	15.58 ± 0.05
(6)	96.36 ± 0.27
(7)	30.14 ± 0.02
(8)	126.17 ± 0.36
(9)	32.65 ± 0.05
(10)	21.97 ± 0.05
(11)	32.03 ± 0.07
(12)	213.46 ± 0.35

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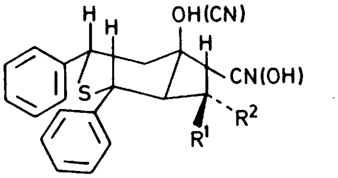
† From the Ph.D. thesis of P. Nanjappan, University of Madras, India.

TABLE 2

Dissociation constants of cyanohydrins of some substituted thian-4-one 1,1-dioxides at 25° in 80% dioxan

Thian-4-one 1,1-dioxide	$10^3 K_D^{25°}$/mol l^{-1}
(13)	7.44 ± 0.01
(14)	33.19 ± 0.07
(15)	11.01 ± 0.04
(16)	89.72 ± 0.09
(17)	24.43 ± 0.07
(18)	119.33 ± 0.37
(19)	27.14 ± 0.05
(20)	16.60 ± 0.02

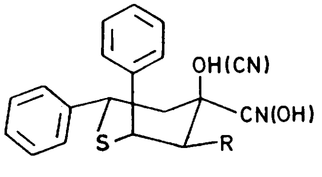
Thianone (**9**) may be considered as a biased system whereas 2,2-dimethylthian-4-one (**11**) is a mobile system. However, they have identical dissociation constants.



(I)

a; $R^1 = R^2 = H$

b; $R^1 = H$, $R^2 = CH_3$

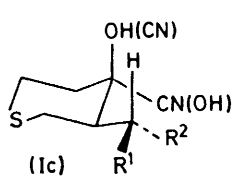


(II)

a; $R = H$

b; $R = CH_3$

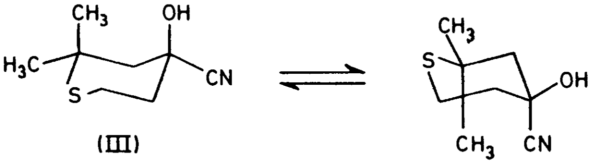
c; $R = C_2H_5$



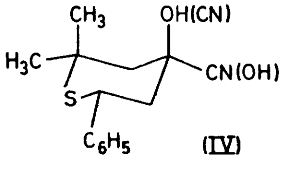
(Ic)

$R^1 = R^2 = CH_3$

The almost identical dissociation constants for these two compounds suggest that the CH_3–OH and CH_3–CN have comparable 1,3-interaction energies and also reveal that 2-Ph has little effect.



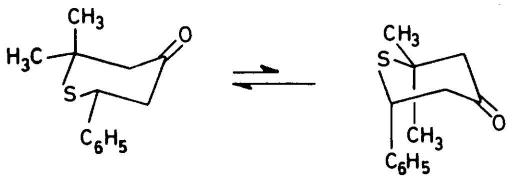
(III) (IIIa)



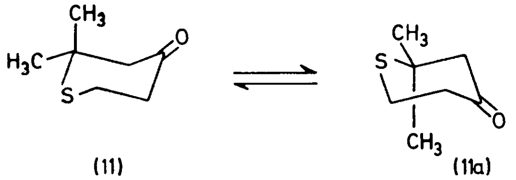
(IV)

The cyanohydrin of 2,2,6,6-tetramethylthian-4-one (**12**) has a dissociation constant 50 times greater than the cyanohydrin of unsubstituted thian-4-one (**1**). The principal factor contributing to this higher value is the non-bonded steric interaction between the axial methyl groups and the cyano- (or hydroxy)-group.

In general the dissociation constants of the cyanohydrins of thian-4-one 1,1-dioxides are somewhat lower than those of the corresponding thian-4-ones. It appears that the conversion of sulphide to sulphone flattens the thian ring system. The flattening of the ring presumably reduces the 1,3-interaction in the carbonyl carbon and shifts the position of equilibrium towards cyanohydrin.



(9) (9a)



(11) (11a)

EXPERIMENTAL

Compounds (1),[9] (2),[2] (3),[2] (5)—(9),[1] (15)—(19),[1] (11),[12] (12),[13] (13),[14] and (14) [14] were prepared as reported.

3-Isopropylthian-4-one (10).—*2-(1-Methylethyl)penta-1,4-dien-3-one*. A mixture of diethylamine hydrochloride (55 g, 0.5 mol), formaldehyde (35%; 42 g, 0.5 mol), 4-methylpentan-2-one (25.4 g, 0.25 mol) and concentrated HCl (2 ml) was taken in a sealed ampoule and heated at 100° for 15 h, cooled, opened, and the mixture was concentrated under vacuum at 100°. Then the Mannich base was decomposed at 150—220° under diminished pressure (1—2 mmHg) to give 2-(1-methylethyl)penta-1,4-dien-3-one and the product (14 g) was redistilled, b.p. 31° at 1 mmHg (lit.,[15] 58.5—60° at 28 mmHg).

Into a solution of 2-(1-methylethyl)penta-1,4-dien-3-one (10.6 g, 0.085 mol) and potassium hydroxide (1 g, 0.018 mol) in ethanol (110 ml), hydrogen sulphide gas was bubbled for 8 h at 60—70°. The mixture was then poured into water (1 000 ml), extracted with ether, and dried ($MgSO_4$). Removal of ether and vacuum distillation of the residue gave *3-isopropylthian-4-one* (10), b.p. 40—60° at 3—5 mmHg). This was purified through its semicarbazone and crystallised from ethanol (3 g, 22.2%), m.p. 184—186°, b.p. 51—52° at 2 mmHg, $\nu_{max.}$ (film) 1 702 cm^{-1} (C=O), δ 0.93 [6 H, d, J 6 Hz, $HC(CH_3)_2$], 2.18 (2 H, m, 3-H and $CHMe_2$), 2.64 (2 H, t, J 7 Hz, 5-H), 3.48 (2 H, d, J 7 Hz, 2-H), and 3.68 (2 H, t, J 6 Hz, 6-H) (Found: C, 60.9; H, 8.95; S, 20.4. $C_8H_{14}OS$ requires C, 60.7; H, 8.9; S, 20.25%).

3-Isopropylthian-4-one 1,1-Dioxide (20).—30% Hydrogen peroxide (5 ml) was added dropwise to a solution of 3-isopropylthian-4-one (1 g, 0.0063 mol) in glacial acetic acid (5 ml). The mixture was left at room temperature for 72 h and was poured into water (500 ml), extracted with chloroform, and the organic layer was dried ($MgSO_4$). Removal of the solvent by rotary evaporation gave the *sulphone* (20) (0.9 g, 75%), m.p. 125—126° (from ethanol–water), $\nu_{max.}$ (KBr) 1 710 (C=O), 1 320 and 1 126 cm^{-1} (SO_2) (Found: C, 50.6; H, 7.45. $C_8H_{14}O_3S$ requires C, 50.5; H, 7.4%).

Solvents.—Dioxan (Merck) was purified as reported in the literature.[16] Dioxan (80 vol) was mixed with conductivity water (20 vol) and the resulting solvent had d_4^{25} 1.0350. Triethylamine (AnalaR; B.D.H.) was distilled in an inert atmosphere after drying over potassium hydroxide pellets, b.p. 89°.

Hydrogen Cyanide Solution.—Exactly equal volumes of 0.1M solution of KCN and $HClO_4$ in 80% dioxan were mixed and refrigerated for 4 h. The clear solution was decanted off from the precipitated $KClO_4$ and stored in the refrigerator.

Cyanohydrin Formation.—The formation of the cyanohydrin was studied in 80% dioxan. The procedure was essentially that of Lapworth and Manske.[17] A calculated quantity of the thian-4-one (0.01M) was dissolved in 80% dioxan in a 50-ml standard flask and hydrogen cyanide stock solution (20 ml) was added. A catalyst solution (1 ml) of 2% triethylamine in 80% dioxan was added, the flask made up to the mark, and allowed to equilibrate at 25.0 ± 0.1° for 36 h. A blank was used (without the thian-4-one) in order to determine the initial concentration of hydrogen cyanide and to eliminate errors due to evaporation. Portions (10 ml) of the solution were withdrawn, added to excess of silver nitrate (0.05M) containing 1% nitric acid and after removing the precipitated silver cyanide by filtration, the excess of silver nitrate was titrated with standard ammonium thiocyanate solution (0.05M) using iron(III) ammonium sulphate as indicator. The dissociation constant (K_D) was computed using equation (2) where a is

$$K_D = (a - x)(b - x)/x \qquad (2)$$

initial [thianone], b is initial [HCN], and x is the equilibrium [cyanohydrin]. Each experiment was repeated four times and the constancy of various determinations of K_D is illustrated by the values obtained with thian-4-one (1): $10^3 \times K_D$ = 4.68, 4.70, 4.70, 4.67, mean 4.69 ± 0.01 mol l^{-1}.

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