J Incl Phenom Macrocycl Chem (2012) 74:77–86
DOI 10.1007/s10847-011-0085-5

ORIGINAL ARTICLE

A kinetic and thermodynamic study of the α-cyclodextrin mediated reaction of a range of *p*-substituted phenyl methyl sulfides with binding and non-binding peroxyacids

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Received: 8 September 2011 / Accepted: 3 November 2011 / Published online: 24 November 2011

Abstract This paper presents a thermodynamic study of the rate and equilibria processes involved in the α-cyclodextrin mediated reaction of a range of 4-substituted phenyl methyl sulfides with two peroxyacids of different binding affinities. The results for the inclusion processes show that the formation of 1:1 and 2:1 (host:guest) complexes between α-cyclodextrin and phenyl methyl sulfides are generally enthalpically controlled, particularly so for the 2:1 complexes, as might be expected for a ternary complex. The data from this series of sulfides is presented as enthalpy-entropy compensation plots, yielding slopes of unity for each inclusion process. The formation of a 1:1 complex between cyclodextrin and the strongly associating 3-chloroperbenzoic acid (MCPBA) is also enthapically controlled. The other peroxyacid used, peroxomonosulfate, does not bind to α-cyclodextrin to any measurable degree. As described in our original study of this reaction system (Davies and Deary in J Chem Soc Perkin Trans 2:2423–2430, 1996), catalysis by α-cyclodextrin is effected by activation of the peroxide as a result its inclusion within the cyclodextrin cavity; hence for reactions of phenyl methyl sulfides with MCPBA, catalysis is observed, but is absent for PMS. In this study the reaction rates are analysed using the transition state pseudo-equilibrium approach of Tee (Carbohydr Res 192:181–195, 1989), whereby the transition state pseudoequilibrium constant K_{TS} reflects the stabilisation imparted to the transition state by the association with one molecule of cyclodextrin. Enthalpy- entropy compensation plots for K_{TS} give slopes close to unity; this is the first reported example of such plots being applied to transition state pseudoequilibrium constants.

Keywords α-cyclodextrin · Peroxyacids · Phenyl methyl sulfides · Enthalpy-entropy compensation

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Introduction

We have previously investigated the α-cyclodextrin mediated reaction of a range of 4-substituted phenyl methyl sulfides with alkyl peracids and peroxybenzoic acids [1]. The mechanism for the uncatalysed reaction of the sulfides with peroxides involves nucleophilic attack on the outer peroxidic oxygen by the sulfide sulphur, producing sulfoxide and the parent acid. The rate of reaction is first order in each of the reactants and is increased by substitution of electron donating groups at the para position of the aryl moiety of the sulfide.

Both the phenyl methyl sulfides and peroxyacids complex with α-cyclodextrin to various degrees, with the phenyl methyl sulfides forming both 2:1 (host:guest) and 1:1 complexes, and the peroxobenzoic acids forming 1:1 complexes (with the exception of 4-methylperoxobenzoic acid which forms a 2:1 host:guest complex [2]). Peracetic acid and the peroxomonosulfate anion show no appreciable binding, though longer chain aliphatic peroxyacids can form both 1:1 and 2:1 host:guest complexes [1–4].

Clearly the orientations of the reactant molecules within the cyclodextrin cavity will have a major influence on the reactivity. For 4-substituted phenyl methyl sulfides, it is likely that an orientation is taken up within the cyclodextrin cavity whereby the sulfur containing group always protrudes from the wider, secondary, rim of the cavity, irrespective of the nature of the substituent. This is because of predicted steric hindrance between the SCH_3 group of the sulfide and the 5-H-protons of the cyclodextrin cavity, resulting in an energetically unfavourable displacement of the benzene ring. This suggestion is supported by the behaviour of the phenyl methyl sulfides in a model developed by us for predicting cyclodextrin binding constants [4, 5]. Peroxyacids have been shown from linear free energy studies to orient with the peroxo group located at the narrow end of the cyclodextrin cavity [3], and whilst this might suggest that the reactions of the peroxo group would be sterically hindered, it does in fact seem to activate the peroxide [1]. We have shown that for those peracids which bind strongly to α-cyclodextrin, such as MCPBA, the observed second order rate constant for the sulfide oxidation increases to a maximum with increasing cyclodextrin concentration and thereafter non-productive binding of the sulfide (either 1:1 or 2:1 complexes) causes a decline in rate [1]. Weakly binding peracids, such as peracetic acid and peroxomonosulfate, show only a decline in rate constant with increasing cyclodextrin concentration, i.e., the dominant factor is the non-productive binding of the sulfides; this behaviour indicates that it is the bound peroxide that is the catalytic species. Further support for this conclusion is provided from linear free energy relationships for a range of peroxyacids and phenyl methyl sulfides where it has been shown that transition state stabilisation by one molecule of cyclodextrin demonstrates a far greater dependence on the stability of the ground state peracid-cyclodextrin complex than on the stability of the sulfide-cyclodextrin complex, i.e., the transition state resembles that of the peroxyacid-cyclodextrin complex [1]. One possible mechanism for the observed catalysis is that the cyclodextrin cavity facilitates the formation of an intramolecular hydrogen bonded structure for the peracid in the transition state that circumvents charge formation, in a similar way to that proposed by Curci and Edwards [6].

As noted above, in addition to 1:1 complexes, 4-substituted phenyl methyl sulfides can also form 2:1 host:guest complexes with α-cyclodextrin. Probably the most remarkable aspect of this is the observation of cooperative binding, i.e., the binding constant for a second cyclodextrin molecule adding to the complex is significantly higher than that for the first [4]. In the case of methyl-p-tolyl sulfide for example, the binding constants for the 1:1 and 2:1 complexes were 41 and 1,000 $dm^3\ mol^{-1}$, respectively [4], i.e., the second step is 25 times greater than the first. At first sight it is difficult to reconcile this observation with how we might expect the second cyclodextrin to associate with the 1:1 complex: with the guest fully included in the cavity of the first cyclodextrin, only the $–SCH_3$ group will protrude, and so the question is how this might result in such an energetically favourable association for the second binding step. There is evidence that the driving force for such interactions is through substrate promoted dipole–dipole interactions between cyclodextrins, i.e., that the process of binding results in the development of a significant dipole within the cyclodextrin cavity, and that the dipole–dipole interaction between the two cyclodextrins is the driving force for the second binding step [7]. The protrusion of the $–SCH_3$ group into the primary rim of the cyclodextrin cavity of the second cyclodextrin cavity, dislodging the cavity water molecules, may be sufficient to reduce the overall distortion of the cyclodextrin ring, maximising the dipole moment along the longitudinal axis. The dipole moment of the second cyclodextrin molecule is then likely to approach the magnitude and direction of the first [7]. Depending on the orientation of the second molecule of cyclodextrin, hydrogen bonding interactions may also occur. There are, however, other possibilities and it may be that the entropic gain from the dislodgement of high energy water molecules at the narrow end of the cavity is sufficient to produce cooperative binding of the magnitudes observed.

The current work extends the study of this system to look at the thermodynamics of the complexation and kinetic processes. There have been no similar studies reported in the literature. The thermodynamic data from this study are presented in the form of enthalpy-entropy plots for the binding of the individual reactants and the transition state with one and two molecules of cyclodextrin. These plots are useful approaches to displaying thermodynamic data obtained for rate and equilibria processes where structural or solvent effects are being investigated. More often than not, such plots result in a linear relationship, termed enthalpy-entropy compensation. For a given rate or equilibrium process involving a series of structurally related molecules, enthalpy-entropy compensation occurs when the enthalpic gain for a given structural change to a molecule is offset, either partly or wholly, by an entropic penalty, and vice versa, resulting in a smaller than expected, or negligible, change to the overall free energy [8–10]. Whilst there is some uncertainty as to the physical meaning of the compensation effect, with some authors suggesting that it is merely a statistical artefact based on experimentally related quantities [11], the range of rate and equilibria processes where very good linear compensation relationships are observed is noteworthy. For complexation processes, the standard explanation for compensation effects is that structural changes that result in strengthened bonding interactions will always have an entropic cost in terms of reduced degrees of freedom of the molecules involved [12]. Several authors have also

interpreted these linear relationships in terms of the reorganisation of solvent molecules during the complexation process [8, 13] and have in some cases have inferred information about conformational and desolvation requirements of the molecules involved [14, 15].

Rekharsky and Inoue, who have been pre-eminent in the development of the field of enthalpy-entropy compensation as applied to host–guest binding in supramolecular structures, particularly cyclodextrins [14], have inferred the idea of a 'universal' compensation effect for these systems, one important implication of which is that it might be possible to obtain binding affinities approaching those of enzymes by designing host guest systems that *overcome* the compensation effect [16]. These authors have demonstrated such an example for the synthetic curcurbit [7] uril molecular host whereby the binding of ferrocene derivatives is characterised by a very favourable enthalpy, yet a disproportionately low entropic penalty, resulting in association constants of up to 3×10^{15} M^{-1}[16].

Experimental section

Materials

3-Chloroperbenzoic acid (MCPBA), was purchased from Sigma Chemical Company. It has purity of 80%, with the main impurity being the parent acid, 3-chlorobenzoic acid. As the MCPBA solid is sparingly soluble in water, solutions of 3-chloroprerbenzoic acid were normally prepared by adding the required amount to distilled water and stirring for about an hour using a magnetic stirrer. This was filtered with a Duran Buchner funnel (75 ml) with a sintered disc (45 mm) of 16-40 micrometer pore diameter. The concentration of MCPBA was determined iodometrically. The required concentration for the working solution was obtained by further dilution in distilled water. The stock solutions of the MCPBA required regular standardisation due to their decomposition. The other oxidant used was peroxomonosulfate (PMS) (Caro's Acid), which was purchased from Sigma Aldrich as the triple salt, $KHSO_5.KHSO_4.K_2SO_4$ and also standardised by iodometric titration.

The organic sulfides used as nucleophiles in this study were all obtained from Aldrich and were used without further purification. The solution of sulfide was prepared as previously stated [4].

Kinetics

Kinetic runs were made on an Applied Photophysics SX 17 stopped-flow spectrophotometer at temperatures of 15, 20, 25, 30, and 35 °C. The temperature of the spectrophotometer cell was maintained by circulating water from a thermostated bath around the injection syringes. The runs were conducted by monitoring the decrease in absorbance due to disappearance of sulfides, and absorbance versus time plots were fitted to an equation for a single exponential to obtain the observed pseudo-first order rate constants. The wavelengths at which the measurements were carried out are as previously stated [4]. The concentration of the sulfides, MCPBA and PMS were 1×10^{-5}, 2×10^{-4} and 4.8×10^{-4} M, respectively. The measurements were performed in 0.003 M nitric acid at pH 2.5, which is below the pK_a of the MCPBA. This was to ensure the peracid was completely protonated.

Results

As outlined earlier, the equilibria and the reactions of 4-substituted phenyl methyl sulfides with peracids in α-cyclodextrin have previously been studied at 25 °C [1]. These results showed that sulfides form inclusion complexes with cyclodextrin at stoichiometric ratios of 1:1 and 2:1 (host:guest), and that 3-chloroperbenzoic acid (MCPBA) forms a 1:1 complex; peroxomonosulfate (PMS) does not bind at any detectable measure [3]. The variation of the observed second order rate constant k_{obs}, with [CD] is described in Eq. 1, the derivation for which can be found in our previous work [1].

$$k_{obs} = \frac{k_o + k_{1obs}[CD] + k_{2obs}[CD]^2}{\left(1 + K_{S11}[CD] + K_{S11}K_{S12}[CD]^2\right)} \times \frac{1}{(1 + K_P[CD])} \quad (1)$$

In Eq. 1 k_o denotes the second order rate constant for the uncatalysed reaction, K_{S11} and K_{S12} are the binding constants of 1:1 and 2:1 (host:guest) complexes between the 4-substituted phenyl methyl sulfides and α-cyclodextrin respectively, and K_P is the binding constant of the peracid. k_{1obs} and k_{2obs} are the first and second order rate constants in cyclodextrin (third and fourth order overall)

Illustrative plots of the observed second order rate constant, k_{obs}, against the cyclodextrin concentration for the reaction of a range of 4-substituted phenyl methyl sulfides at 25 °C with PMS and MCPBA are shown in Figs. 1 and 2, respectively; similar plots (not shown) were obtained at the other experimental temperatures used. The curves are the best fit to Eq. 1 in which the reactions for all of the sulfides with both peracids at one temperature are fitted simultaneously, keeping the binding constant for MCPBA as a common parameter and setting the association constant for PMS to zero [1]. k_{2obs} was also set to zero because poor fitting for all data was obtained when k_{2obs} was left as a parameter (not shown); this is reasonable from a chemical point of view since reactions involving two cyclodextrins (either 2:1

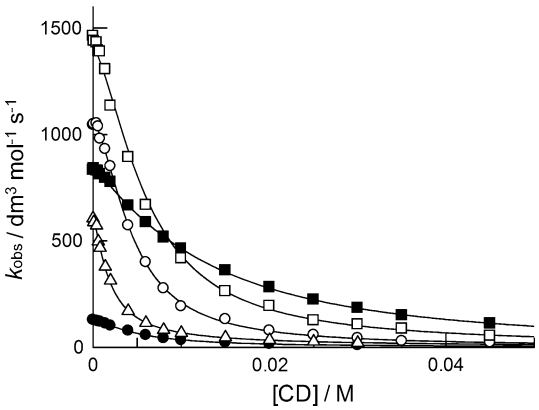

Fig. 1 Plots showing the different effects of α-cyclodextrin on the observed second order reaction rate, k_{obs}, for the reaction between a series of 4-substituted phenyl methyl sulfides and PMS at 25 °C in 0.003 M nitric acid. The symbols are: *open squares*, 4-OCH_3; *open circles*, 4-CH_3; *filled squares*, 4-CH_2OH; *filled circles*, 4-NO_2; and *open triangles*, 4-Br

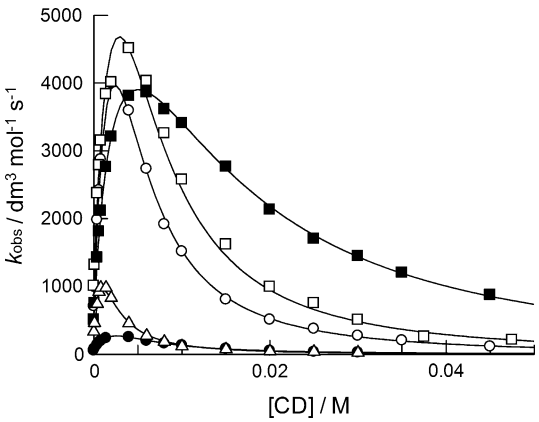

Fig. 2 Plots showing the different effects of α-cyclodextrin on the observed second order reaction rate, k_{obs}, for the reaction between a series of 4-substituted phenyl methyl sulfides and MCPBA at 25 °C in 0.003 M nitric acid. The symbols are: *open squares*, 4-OCH_3; *open circles*, 4-CH_3; *filled squares*, 4-CH_2OH; *filled circles*, 4-NO_2; and *open triangles*, 4-Br

CD:sulfide or 1:1 CD:sulfide and 1:1 CD:peroxyacid) are likely only to result in inhibition. Ks_{11}, Ks_{12}, K_P and k_{1obs} are output as parameters of the non-linear regression and are shown in Tables 1 and 2, k_0, the second order rate in the absence of cyclodextrin, was determined experimentally and is shown in Table 1.

Discussion

Inclusion thermodynamics

The binding constants shown in Table 1 for the 1:1 and 2:1 complexes between α-cyclodextrin and phenyl methyl sulfides, K_{S11} and K_{S12}, show reasonable agreement at 25 °C with those reported previously [1], even though experimental conditions and techniques differed between the studies (a kinetic approach was employed here, whereas our previous study used a spectrophotometric technique). With increasing temperature, the values of K_{S11}, K_{S12} and Kp all decreased, as expected from the results of other studies [14].

Before discussing the data obtained for the thermodynamic study it is useful to review the processes that contribute to the overall entropy and enthalpy during complexation between substrates and cyclodextrins. Fluorescence correlation spectroscopy studies indicate that initially the cyclodextrin and substrate come together to form an encounter complexes at a diffusion controlled rate; these complexes have a lifetime of approximately 1 ns, during which time the two components collide in random orientations, a small fraction of which will be favourable to inclusion [17]. The available evidence then suggests that complexation is a two step process [18], with the first step involving the rapid inclusion of the guest molecule within the cyclodextrin cavity and the second step then involving conformational and solvation changes that relax the cyclodextrin around the guest molecule to form the stable complex; this is sometimes referred to as 'induced fit'. Cavity water molecules are dislodged during the complexation process and are returned to the bulk solvent. From a kinetic point of view there is evidence to show that either of the two steps can be rate determining, depending on the substrate [18].

Solvation plays a critical role in the binding thermodynamics for cyclodextrin. For non-polar guests it is likely that in bulk solution the solvating water molecules will be able to form the 'normal' compliment of hydrogen bonds (an average of 2.8 [19]), possibly slightly more [20], but clearly the freedom they have to do this is restricted because of the presence of an adjacent solute molecule. On transferring into the cyclodextrin cavity the bulk solvent will reorganise to fill the resultant void, giving rise to only a small enthalpy change since the total number of hydrogen bonds is likely to remain approximately the same, or possibly slightly reduced. There will, however, be a significant entropic gain because the water molecules now have more orientations in which they can form these bonds—this is the classical hydrophobic effect. For polar molecules, there is likely to be a larger enthalpic penalty from the loss of interaction with the solvent. On entering the cyclodextrin cavity there will be dislodgement of cavity water molecules; these 'high energy' molecules have limited orientation and are limited in the number of hydrogen bonds that they can form, so once released there will be both enthalpic and entropic gains as they acquire a normal compliment of hydrogen bonds.

As for the thermodynamics of the specific host guest complexation process, there will be a large enthalpic gain

Table 1 Temperature dependence of binding constants, rate constants and transition state pseudoequilbrium constants (±standard deviation) for the reaction of peroxyacids with 4-substituted phenyl methyl sulfides in the presence of α-cyclodextrin in 0.003 M nitric acid

Substituent	Temperature/ °C	Binding constants		Rate constants and transition state pseudoequilibrium constants					
				Reaction with MCPBA			Reaction with PMS		
		K_{s11}/ $dm^3\ mol^{-1}$	K_{s12}/ $dm^3\ mol^{-1}$	k_o/ $dm^3\ mol^{-1}\ s^{-1}$	k_{1obs}/ $10^3\ dm^6\ mol^{-2}\ s^{-1}$	K_{TS1}/ $dm^3\ mol^{-1}$	k_o/ $dm^3\ mol^{-1}\ s^{-1}$	k_{1obs}/ $10^3\ dm^6\ mol^{-2}\ s^{-1}$	K_{TS1}/ $dm^3\ mol^{-1}$
4-CH_3	15	133 ± 19	762 ± 136	446	4,049 ± 386	9,078 ± 865	771	10.8 ± 3.5	14 ± 5
	20	105 ± 35	582 ± 217	588	4,050 ± 320	6,888 ± 544	904	16.3 ± 4.3	18 ± 5
	25	84 ± 17	509.6 ± 120	710	4,060 ± 198	5,718 ± 279	1,045	22.1 ± 3.6	21 ± 3
	30	75 ± 10.8	380 ± 62	938	3,995 ± 151	4,260 ± 161	1,164	21.5 ± 3.0	18 ± 3
	35	69.6 ± 11	270 ± 49	1,200	3,790 ± 196	3,158 ± 163	1,360	18.5 ± 4.1	14 ± 3
4-OCH_3	15	51.7 ± 7	1,226 ± 209	640	4,360 ± 327	6,813 ± 511	1,171	25.0 ± 5.2	21 ± 4
	20	94 ± 25	333 ± 79	845	4,055 ± 317	4,799 ± 375	1,310	29.2 ± 6.6	22 ± 5
	25	79 ± 13	218 ± 52	1,006	4,200 ± 202	4,175 ± 201	1,463	31.3 ± 5.0	21 ± 3
	30	82.6 ± 8	128 ± 15	1,370	3,705 ± 149	2,704 ± 109	1,600	26.9 ± 4.0	17 ± 3
	35	60.5 ± 8	111 ± 17	1,780	3,240 ± 186	1,820 ± 104	1,760	20.8 ± 5.1	12 ± 3
4-NO_2	15	172.6 ± 29	398 ± 78	32.4	270 ± 22	8,333 ± 679	84	4.2 ± 1.0	50 ± 12
	20	157 ± 42	396 ± 124	42.3	319 ± 25	7,541 ± 591	106	1.8 ± 0.9	17 ± 9
	25	133 ± 19	197 ± 33	54.8	275 ± 13	5,018 ± 237	129	4.2 ± 0.8	33 ± 6
	30	106 ± 10	110 ± 14	82.5	254 ± 11	3,079 ± 133	164	3.3 ± 0.6	20 ± 24
	35	92 ± 13	120 ± 20	112	270 ± 15	2,411 ± 134	196	4.0 ± 1.0	20 ± 5
4-CH_2OH	15	75 ± 12	85 ± 17	319	2,585 ± 200	8,103 ± 627	566	2.5 ± 2.0	4 ± 3
	20	71 ± 14	61 ± 4.8	413	2,655 ± 186	6,429 ± 450	706	6.3 ± 3.1	9 ± 4
	25	68 ± 8	37 ± 6	510	2,845 ± 123	5,578 ± 241	834	3.8 ± 2.0	5 ± 3
	30	61.7 ± 5.6	22.6 ± 3.7	634	2,790 ± 98	4,401 ± 155	964	3.3 ± 1.7	3 ± 2
	35	54 ± 6	18.7 ± 4	775	2,710 ± 123	3,497 ± 159	1,128	3.8 ± 2.6	3 ± 2
4-Br	15	569 ± 84	1,245 ± 205	207	1,785 ± 218	8,623 ± 1053	452	210 ± 36	465 ± 80
	20	747 ± 133	452 ± 77	265	1,850 ± 199	6,981 ± 751	522	167 ± 31	320 ± 59
	25	530 ± 66	470.5 ± 57	332	1,875 ± 128	5,648 ± 386	606	165 ± 20	272 ± 33
	30	536 ± 40	238 ± 19	428	1,910 ± 90	4,463 ± 210	737	138 ± 13	187 ± 18
	35	741 ± 67	162 ± 15	536	2,505 ± 154	4,674 ± 287	858	204 ± 26	238 ± 30

Table 2 Temperature dependence of the 1:1 binding constant between α-cyclodextrin and 3-chloroperbenzoic in 0.003 M nitric acid

Temperature/°C	K_p/dm^3 mol^{-1}
15	492 ± 40
20	378 ± 47
25	331 ± 27
30	284 ± 19
35	234 ± 21

from the association, the magnitude of which will be dependent on the type of molecular interaction, but there will also be a large entropic penalty as the freedom of the molecule is curtailed inside the cyclodextrin. As discussed above, there are likely to be conformational changes in the cyclodextrin, and it has been argued that these can serve to increase the dipole–dipole interaction between host and guest because one of the cyclodextrin glucosidic residues is slightly tilted when uncomplexed and is brought into the same orientation as the other five residues as a consequence of complexation, resulting in a dipole moment that is both strengthened and more directionally favourable (it becomes parallel to the cyclodextrin axis). Finally, the bulk solvent water molecules will need to reorganise around the complex.

The net enthalpic and entropic contributions from both the solvent reorganisation and host–guest interactions gives rise to the $\Delta H°$ and $\Delta S°$ terms, and the overall free energy, $\Delta G°$, that is related to the association constant. Complexation involving α-cyclodextrin tends to be enthalpically controlled, because of the tight binding results in both strong van der Waals interactions and a restrained orientation of the guest within the cavity; complexes involving *β*-cyclodextrin, which has a larger cavity, tend to attract a smaller entropic penalty [14].

For the present work, the calculated thermodynamic parameters for 1:1 complex formation presented in Table 3 indicate that for the 4-CH_3, 4-CH_2OH and 4-NO_2 substituted phenyl methyl sulfides, the binding process is enthalpy driven. This is to be expected from the above discussion. However, for the 4-OCH_3 and 4-Br substituents there is a favourable entropy change, but unfavourable enthalpy change. It should, however, be noted that the errors on these latter two values are quite large. The significance of the enthalpy-entropy correlation will be discussed in a later section. For complexation between α-cyclodextrin and 3-chloroperbenzoic acid, the process is also enthalpy driven, with respective $\Delta H°$ and $\Delta S°$ values of -25.5 ± 0.98 kJ mol^{-1} and -37.2 ± 3.3 J mol^{-1} (Table 5).

For 2:1 (host:guest) complexation, Table 3 shows that large negative values are observed for both entropy and enthalpy for all sulfides, with the process overall being enthalpy driven. These results are consistent with our introductory comments concerning cooperativity in the binding of the second molecule of cyclodextrin to the complex. There will be a large enthalpic gain through dislodgement of the water molecules from the second cyclodextrin cavity (as they form the full complement of hydrogen bonds), as well as an entropic gain. Favourable enthalpic contributions would also arise from the dipole–dipole interaction of the cyclodextrins, as discussed earlier. The restricted orientations of the cyclodextrins and substrate in forming the ternary complex will account for the large negative entropy.

Reaction thermodynamics

The second order rate constants, k_0, for the uncatalysed reactions of both PMS and MCPBA with the sulfide series, which were determined directly, show good agreement with those obtained at 25 °C in the previous study [1]. The results, shown in Table 4, are characterised by large negative entropies that are in agreement with previous work carried out in protic solvents [6, 21] and also with theoretical predictions [22]. The large negative entropy is consistent with an orientation of reactants and solvent molecules in the transition state in which significant charge separation along the reaction coordinate is circumvented via a 1,4-intramolecular hydrogen transfer [23]. $\Delta S^{\ddagger}$ values for the reaction of the sulfides with PMS are more

Table 3 Calculated thermodynamic parameters for the reaction of ca. 2×10^{-4} M MCPBA and 4×10^{-4} M PMS with 1×10^{-5} M methyl *p*-tolyl sulfide, 4-(methylthio) benzyl alcohol, 4-nitrothioanisole and 4-methoxythioanisole in 3.0×10^{-3} M nitric acid at different temperatures

Parameters	4-CH_3	4-CH_2OH	4-NO_2	4-OCH_3	4-Br
$\Delta H°(K_{11})$ (kJ mol^{-1})	−24 ± 2.9	−11.7 ± 1.7	−24.3 ± 1.9	3.1 ± 13	2.8 ± 9
$\Delta S°(K_{11}, M^{-1})$ (J mol^{-1} K^{-1})	−43.6 ± 9.7	−4.5 ± 5.7	−41 ± 6.6	46 ± 43	64.7 ± 30.7
$\Delta G°(k_{11})$ (kJ mol^{-1})	−11	−10.3	−12	−10.6	−16.8
$\Delta H°(K_{12})$ (kJ mol^{-1})	−36.8 ± 3.3	−53 ± 8	−51.7 ± 9.2	−85.4 ± 16.5	−69.7 ± 11.4
$\Delta S°(K_{12,}\ M^{-1})$ (J mol^{-1} K^{-1})	−72.4 ± 11	−149.2 ± 26	−129.2 ± 30	−240 ± 54	−184 ± 38
$\Delta G°(k_{12})$ (kJ mol^{-1})	−15.3	−8.5	−13	−13.8	−12

Table 4 : Enthalpy and entropy of activation for the reaction of sulfides with peracids in the absence of α-cyclodextrin in 0.003 M^{-1} nitric acid

Parameters	4-CH_3	4-CH_2OH	4-NO_2	4-OCH_3	4-Br
$\Delta H^{\ddagger}(k_o)$ (kJ mol^{-1}) (MCPBA)	33.6 ± 1.7	30.1 ± 1.8	43.8 ± 0.99	34.8 ± 0.6	32.6 ± 0.42
$\Delta H^{\ddagger}(k_o)$ (kJ mol^{-1}) (PMS)	18.0 ± 0.6	22.5 ± 1.2	29.0 ± 2.4	12.5 ± 0.95	21.5 ± 0.72
$\Delta S^{\ddagger}(k_o)$ (J mol^{-1} K^{-1}) (MCPBA)	−77 ± 5.7	−92.2 ± 6	−63.58 ± 3.3	−70.1 ± 1.8	−86.9 ± 1.4
$\Delta S^{\ddagger}(k_o)$ (J mol^{-1} K^{-1}) (PMS)	−127 ± 2.2	−113 ± 0.4	−107 ± 0.7	−142 ± 3.2	−119 ± 2.4
$\Delta G^{\ddagger}(k_o)$ (kJ mol^{-1}) (MCPBA)	56.6	57.6	62.8	55.7	58.5
$\Delta G^{\ddagger}(k_o)$ (kJ mol^{-1}) (PMS)	55.9	56.2	60.9	54.8	57.0

unfavourable than those for MCPBA, though the $\Delta H^{\ddagger}$ is more favourable, consistent with the trends observed for the reaction of the bromide ion with PMS and peracetic acid [6]: the trends may reflect different transition state solvation requirements of charged and uncharged peroxyacids.

For α-cyclodextrin mediated reactions, the results for the strongly associating MCPBA show that over the range 15 to 35 °C the observed rate of reaction increases to a maximum with increasing cyclodextrin concentration and then declines, reflecting a balance between the catalytic effect of the cyclodextrin-bound peracid and the inhibitory effect of the cyclodextrin-bound sulfide (Fig. 2). The height and shape of these curves is dependent on the relative concentrations of these species at each cyclodextrin concentration that is in turn dependent on the association constants. The third order rate constant k_{1obs} (first order in cyclodextrin), determined from the fit to Eq. 1, shows reasonable agreement with those from previous study at 25 °C [1]. The temperature dependence for this parameter is somewhat odd from a conventional kinetic perspective, in that, depending on the sulfide, the trend with increasing temperature is either a decrease in rate constant (4-CH_3, 4-OCH_3), an increase (4-Br) or approximately no change (4-NO_2 and 4-CH_2OH). This behaviour is a consequence of k_{1obs} being a composite rate constant as shown in Eq. (2) where k_p and k_s represent the rate constants for the reaction of the complexed peroxyacid and sulfide, respectively and K_p and K_{s11} are the respective association constants. Clearly temperature will have a complex effect on the overall rate: decreasing the association constants, as we have seen, but increasing the rates of reaction of the complexed species; the balance of these factors and the magnitude of the association constants will determine the trend observed with increasing temperature. The calculation of $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ values for k_{1obs} is not chemically valid because of the varying concentrations of reactive species with temperature.

$$k_{1obs} = k_p K_p + k_s K_{s11} \quad (2)$$

For the charged, non-binding, PMS Fig. 1 shows that increasing cyclodextrin concentrations result only in a decline in the observed rate. As previously discussed, the –SCH_3 group is likely to protrude from the cyclodextrin cavity, so whilst available to participate in the reaction with PMS, there will be steric hindrance at the sulfur atom as a result of inclusion. It is important to stress that the bound sulfide is not completely unreactive: poor fits are obtained if k_{1obs} is set at zero for this reaction (not shown), and in the case of the 4-Br substituent the k_{1obs} value is comparatively high; this could be due to the bulky bromo group, located at the narrow end of the cavity, causing the included sulfide molecule to be displaced relative to the other members of the series, resulting in the –SCH_3 being located further away from the secondary hydroxyl rim, and thus less steric hindrance.

The effect of cyclodextrin on the reaction is discussed in terms of transition state stabilisation in the next section.

Transition state stabilisation

The transition state pseudoequilibrium approach described in our previous studies [1, 24, 25] was applied to the rate constants obtained at each of the temperatures in the present study. This approach was originally developed for enzymology by Kurz [26] and later adapted for systems involving cyclodextrins by Tee [27, 28].

The transition state pseudoequlibrium constant, K_{TS1}, reflects the stabilisation imparted to the transition state by the association with one molecule of α-cyclodextrin; it is determined from the quotient of the k_{1obs} and k_0 values obtained for the reaction of the phenyl methyl sulfides with the peroxyacid [1, 2, 24]. The values are shown in Table 1 for MCPBA and PMS. The logarithm of this quantity is proportional to the Gibbs free energy for the binding of the transition state to cyclodextrin and can be correlated with other free energy parameters in order to obtain information about the structure of the transition state. For this reaction, the previous observation of a good correlation between the natural logarithms of K_{TS1} and the binding constants for substituted peroxobenzoic acids indicated that the transition state for the reaction of peroxobenzoic acids with nucleophiles resembled the 1:1 cyclodextrin-peroxide complex, rather than sulfide-cyclodextrin complex [1, 25].

Table 5 The calculated thermodynamic parameters for the reaction of ca. 2×10^{-4} M MCPBA and 4×10^{-4} M PMS with 1×10^{-5} M *p*-tolyl methyl sulfide, 4-(methylthio)benzyl alcohol, 4-nintrothionasole and 4-methoxythionasole, and 4-bromothioanisole in 3.0×10^{-3} M nitric acid at different temperatures

Parameters	4-CH_3	4-CH_2OH	4-NO_2	4-OCH_3	4-Br
$\Delta H°(K_{TS1})$ (kJ mol^{-1}) (MCPBA)	−38.2 ± 2.3	−30.4 ± 3.4	−49.7 ± 5	−47.3 ± 3.7	−24.8 ± 5.8
$\Delta S°(K_{TS1})$ (J mol^{-1} K^{-1}) (MCPBA)	−56.8 ± 7.7	−30.6 ± 11.3	−96.6 ± 16.8	−90.6 ± 12.4	−11.1 ± 19
$\Delta G°(K_{TS1})$ (kJ mol^{-1}) (MCPBA)	−21.3	−21.3	−20.9	−20.3	−21.5
$\Delta H°(K_{TS1})$ (kJ mol^{-1}) (PMS)	−0.3 ± 10	−24.3 ± 17	−24.9 ± 20	−20.1 ± 6.6	−27.9 ± 9.8
$\Delta S°(K_{TS1})$ (J mol^{-1} K^{-1}) (PMS)	24.5 ± 34	−69.3 ± 58	−56.6 ± 68	−43.3 ± 22	−46.9 ± 33
$\Delta G°(K_{TS1})$ (kJ mol^{-1}) (PMS)	−7.0	−3.7	−8.0	−7.2	−14.0
$\Delta H°(K_P)$ (kJ mol^{-1})	−25.5 ± 0.98				
$\Delta S°(K_P)$ (kJ mol^{-1})	−37.2 ± 3.3				

The inclusion of the peroxo group at the primary end of the cyclodextrin cavity activates it to attack by the sulfide.

For the reaction with MCPBA, K_{TS1} decreases with temperature mirroring that of the cyclodextrin-peroxyacid complex and is consistent with that complex being the catalytic species, as previously proposed. For the reaction with PMS, the numbers are relatively small, and the trends are difficult to determine in the context of the large relative errors for k_{1obs}. Nevertheless, there are clear differences in the K_{TS1} values, with 4-bromophenyl methyl sulfide demonstrating a significantly higher value than the other sulfides.

The enthalpies and entropies of the association of the transition state with one molecule of cyclodextrin, shown in Table 5, are discussed in the context of enthalpy-entropy compensation in the next section.

Enthalpy-entropy compensation for ground state and transition state binding constants

Plots of enthalpy against entropy are a useful tool for visualising thermodynamic data obtained from complexation processes, though the interpretation of any observed compensation effects is subject to much debate.

Ground and transition state complexation data are plotted in Fig. 3. We have used $T\Delta S°$ as the entropy measure, where T is 298.15 K, because this gives a more intuitive plot since a slope of unity infers complete compensation (the use of $\Delta S°$ yields a quantity known as the compensation temperature). To our knowledge, this is the first example of an enthalpy-entropy compensation plot for transition state pseudo-equilibrium constants reported in the literature. Similarly, there have been no reported enthalpy-entropy plots for the complexation of phenyl methyl sulfides with α-cyclodextrin, either for 1:1 or 2:1 complexes.

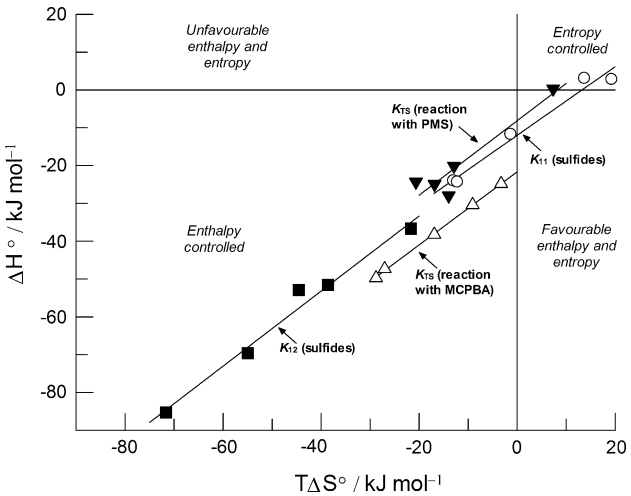

Fig. 3 Enthalpy-entropy compensation plot for the complexation of α-cyclodextrin with substituted phenyl methyl sulfides, K_{11} and K_{12}, and with the transition state, K_{TS}, for the reaction of the same series of sulfides with 3-chloroperbenzoic (MCPBA) and peroxomonosulfate (PMS). The different thermodynamic domains are also indicated

Table 6 Comparison of extra-thermodynamic parameters derived from Fig. 3

Complexation process	Slope (±standard error)	$T\Delta S°_{(\Delta H° = 0)}$/kJ mol^{-1} (±standard error)
K_{11}(sulfides)	0.907 (±0.084)	11.99 (±1.10)
K_{12} (sulfides)	0.993 (±0.084),	13.57 (±4.13)
K_{TS} (MCPBA)	0.966 (±0.014)	21.65 (±0.28)
K_{TS} (PMS)	0.985 (±0.199)	8.14 (±2.98)

The slopes of the enthalpy-entropy compensation plots are summarised in Table 6 and are all very close to 1, though in the case of K_{TS} (PMS) this seems somewhat fortuitous given the clustered nature of the points. Slopes of unity in enthalpy-entropy plots are consistent with the

literature for a wide variety of host–guest systems including α, β, γ and modified cyclodextrins [14] 18-crown-6 ether and cryptant-222 [13]. Nevertheless, there are also examples, including for α-cyclodextrin, where binding of related series yields slopes that are significantly lower [29] or higher [30] than 1. Rekharsky and Inoue, looking at complexation of a range of substrates with cyclodextrins have interpreted the magnitude of the slope as the degree of conformational change undergone by the cyclodextrins as a result of complexation, though such interpretations were based on a meta-analysis of the binding thermodynamics of a wide range of structurally unrelated molecules, separately with each of the native cyclodextrins and also with modified cyclodextrins [14].

In addition to the slope, the other important parameter that arises from enthalpy-entropy compensation plots is the intercept on the x-axis, denoted here as $T\Delta S^{\circ}_{(\Delta H^{\circ} = 0)}$. This parameter, which is the entropic component in the absence of any enthalpic contribution, has been interpreted as the degree of desolvation of the cyclodextrin and guest molecule as a result of complexation [14]. Intercepts in the region of 8–17 kJ mol^{-1} were interpreted as indicating significant desolvation [14]. The respective values for the current data, which fall within or close to this range, are listed in Table 6. It is also true, however, in cases where the slope is unity, as is often the case, including for the present study, that $T\Delta S^{\circ}_{(\Delta H = 0)}$ is numerically equal to the average ΔG° value for the respective series. This is, in essence, the conclusion of Exner, who states that "[plots of ΔH° against ΔS°] can express only the trivial fact that ΔG° is approximately constant" [11]. This is an important point and is pertinent to the question of what can be reasonably interpreted from enthalpy-entropy compensation plots: accepting that these relationships are not statistical artefacts, can this extra-thermodynamic measure be used to probe the nature of conformational changes, solvent reorganisation and substrate orientation during complexation or is it simply a representation of average binding affinity for series of structurally related molecules?

Considering the data series in Fig. 3, firstly for K_{11}, the binding constant for 1:1 host:guest inclusion complexes between α-cyclodextrin and *para*-substituted phenyl methyl sulfides, there is a degree of scatter in the data, though a clear compensation relationship is apparent. We should not necessarily expect good enthalpy-entropy compensation for this series, i.e., a good linear correlation, because as discussed in the introduction, steric hindrance between the $-SCH_3$ group and the 5-H-protons of the cyclodextrin cavity may result in either an orientation that is opposite to that favoured from a consideration of factors such as dipole or polarisability, or cause the displacement of the aryl moiety from its most energetically favourable position. i.e., this series does not represent a truly *homologous* host–guest series. For such a series the same substituent should be directed into the cavity, with a variable para-substituent protruding from it at the secondary end; here the enthalpy gain and entropic penalty associated with the binding of guest should be similar in each case, and provided the *p*-substituent does not appreciably interact with the secondary hydroxyl rim, the main contribution to $\delta\Delta H^{\circ}$ and $\delta\Delta S^{\circ}$ is likely to be from solvent reorganisation, with a prediction of good enthalpy-entropy compensation. Turning now to the K_{12} data, here we might expect, and indeed do, see good enthalpy-entropy compensation because essentially the binding process is similar in each case, i.e., the addition of a second cyclodextrin molecule to a host:guest complex in which the $-SCH_3$ group protrudes from the secondary rim of the first cyclodextrin.

For the transition state binding processes, in the case of the K_{TS1} for PMS, the transition state will resemble cyclodextrin-sulfide complex in the ground state reacting with the unbound peroxyacid: good enthalpy-entropy compensation might not be expected for this series for the reasons already discussed. In the case of K_{TS1} for the reaction with MCPBA, good compensation should be expected, and indeed is observed, because the cyclodextrin complexed transition state is very similar in each case: the complexed MCPBA reacting with the uncomplexed sulfide; the only significant difference affecting the enthalpy and entropy is how the solvent molecules reorganise around the different *p*-substituents on the phenyl methyl sulfide. This series is displaced to a more negative intercept on the y-axis, reflecting the much greater average ΔG°.

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