Intramolecular Catalysis. Part 8.[1] The Intramolecular Cannizzaro Reaction of Naphthalene-1,8-dicarbaldehyde and [α,α'-$^2H_2$]Naphthalene-1,8-dicarbaldehyde

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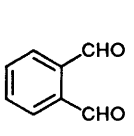
Naphthalene-1,8-dicarbaldehyde monohydrate has been shown to have a bridged (cyclic) structure in solution, as a *cis–trans* mixture. The hydrated dialdehyde, as well as the α,α'-dideuterio isomer, has been shown to undergo a Cannizzaro reaction in 70% (v/v) dioxane–water. The reaction has been found to be intramolecular and of the second order, *i.e.* first order in the monoanion of the hydrate and in base. The kinetic isotope effect, k_H/k_D, was found to be *ca.* 1.7 and the kinetic solvent isotope effect, k_{H_2O}/k_{D_2O}, *ca.* 0.60. The alkaline hydrolysis of the corresponding lactone of 8-(hydroxymethyl)-1-naphthoic acid (naphthalide) was studied under the same conditions. The lactone can be excluded as an intermediate in the intramolecular Cannizzaro reaction as it cannot be detected directly under conditions where it would be sufficiently long-lived. The evidence for the Cannizzaro reaction indicates a mechanistic pathway involving rate-determining hydride transfer in the chain tautomer of the dianion of the hydrate.

The aromatic dialdehydes, *o*-phthalaldehyde (**1**), biphenyl-2,2'-dicarbaldehyde (**2**) and phenanthrene-4,5-dicarbaldehyde (**3**),



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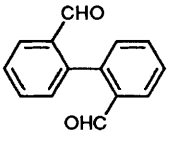

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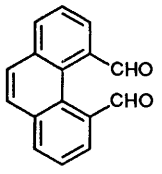

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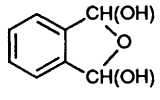
have been shown to undergo intramolecular Cannizzaro reactions in base solution and their mechanisms of reaction have been investigated.[2–5] Both **1** and **3** are hydrated to form cyclic hydrates (**4** and **5**) and form monoanions in base.



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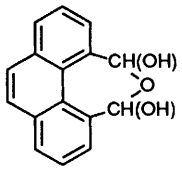

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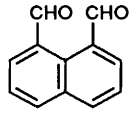
o-Phthalaldehyde rearranges from the monoanion both directly and by a reaction catalysed by base.[5] Phenanthrene-4,5-dicarbaldehyde rearranges from the monoanion by a reaction catalysed by base alone.[2] The unhydrated biphenyl-2,2'-dicarbaldehyde rearranges by a reaction which is second-order in base.[3]

The dialdehyde, naphthalene-1,8-dicarbaldehyde (**6**), forms a



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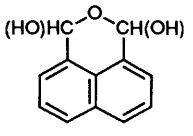

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hydrate which appears to be cyclic,[6] as shown in **7**. The latter compound has been shown to undergo a Cannizzaro reaction,[6] which was presumed to be intramolecular.

The present study is part of a series of investigations[2,3,5] of Cannizzaro reactions of aromatic dialdehydes made in order to elucidate the mechanistic pathways and the structural factors controlling such reactivity. The hydration and Cannizzaro reaction of naphthalene-1,8-dicarbaldehyde, as well as that of the α,α'-dideuterio compound, has been investigated in this study. The structure of the hydrate has been determined, as well as the extent of the hydration. The rates of the Cannizzaro reaction, activation parameters, kinetic solvent isotope and isotope effects, isotope labelling and studies of possible intermediates are reported.

Experimental

Materials.—Naphthalene-1,8-dicarbaldehyde, as its hydrate, was prepared from acenaphthylene by ozonolysis using the method of Stille and Foster.[6] The product was recrystallised carefully from water to give colourless needles, m.p. 139–141 °C (lit.,[6] 140–141.5 °C). [α,α'-$^2H_2$]Naphthalene-1,8-dicarbaldehyde, as its hydrate, was prepared from [1,2-$^2H_2$]acenaphthylene by ozonolysis as described above. The preparation of [1,2-$^2H_2$]acenaphthylene was completed by the dehydration of [1,2,2-$^3H_2$]acenaphthen-1-ol[7] using thionyl chloride and pyridine by a method similar to that of Schwartz and Madan.[8] The purification and physical characteristics were as for the ordinary dialdehyde hydrate described above (purity > 95% by ^1H NMR spectroscopy). The lactone of 8-(hydroxymethyl)-1-naphthoic acid (naphthalide) was prepared by a crossed-Cannizzaro reaction between 8-formyl-1-naphthoic acid and formalin as described by Fuson and Munn[9] to give a colourless crystalline solid, m.p. 157–158 °C (lit.,[9] 156–157 °C).

Solvents were purified as described previously.[10]

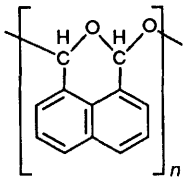
Measurements.—The ^1H and ^{13}C NMR spectra were measured using JEOL EX270 FT NMR and PMX60 NMR spectrometers. Tetramethylsilane was used as an internal standard, except in aqueous solutions where it was used externally. The ^1H NMR spectra of the hydrate of naphthalene-1,8-dicarbaldehyde in aqueous dioxane shows no formyl protons; but, in anhydrous dimethyl sulfoxide (DMSO), a very weak signal at δ 10.2 and two strong signals at δ 6.25 and 6.3 in a ratio of *ca.* 0.2 (low δ/high δ) were observed. This behaviour is very similar to that observed for the hydrates of *o*-phthalaldehyde and phenanthrene-4,5-dicarbaldehyde.[2,5] The

Table 1 Rate coefficients (k_2) for the intramolecular Cannizzaro reaction of naphthalene-1,8-dicarbaldehyde and alkaline hydrolysis of the lactone of 8-(hydroxymethyl)-1-naphthoic acid (naphthalide) at constant ionic strength (μ = 0.1 mol dm^{-3}) in 70% (v/v) dioxane–water at different temperatures[a]

	k_2/dm^3 mol^{-1} s^{-1}			
	30.0 °C	40.0 °C	50.0 °C	60.0 °C
Cannizzaro reaction	3.75 (6.23)[b] (2.24)[c]	8.20	17.4	36.6
Alkaline hydrolysis	32.0 °C 7.64	45.0 °C 14.9	60.0 °C 32.1	

[a] The rate coefficients were reproducible to ±3%. [b] k_2 for the Cannizzaro reaction in 70% (v/v) dioxane–deuterium oxide. [c] k_2 for the Cannizzaro reaction of [α,α′-$^2H_2$]naphthalene-1,8-dicarbaldehyde.

hydrate is the bridged (cyclic) monohydrate **7** which occurs as a *cis–trans* mixture. The hemiacetal protons of the *cis*-isomer are predicted to appear at 0.2–0.3 ppm towards low field relative to those of the *trans*-isomer, as shown by a general relation for such stereochemically related systems by Faye *et al.*[11] Thus, in the 1,8-naphthalene system, the *trans*-isomer appears to predominate. However, the *cis*-isomer of the hydrate of phenanthrene-4,5-dicarbaldehyde is clearly the prevalent species;[2] while the *cis*- and *trans*-isomers occur in approximately equal amounts for the hydrate of *o*-phthalaldehyde.[12] The ^{13}C NMR spectra of the hydrated dialdehyde in dimethyl sulfoxide showed the aromatic (multiplet) and semi-acetal carbons (singlet; δ 89), without any formyl carbon. These results confirm the nature of the bridged (cyclic) monohydrate **7**. Previous attempts[6] at dehydration of the hydrate of naphthalene-1,8-dicarbaldehyde gave a polymer, assigned the structure **8**, which



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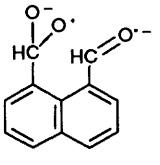
has a high m.p. and is only very slightly soluble in common solvents. We have confirmed these findings. However, only one isomer of the hydrate was isolated, as described above; whereas Stille and Foster[6] claimed two isomers. Azeotropic distillation of a solution of the hydrate in anhydrous benzene gave a solution whose ^1H and ^{13}C NMR spectra indicated a formyl group was present (signals at δ 9.9 and δ 189.5, respectively). However, attempted concentration of the benzene solution or isolation gave only the polymer. Thus, it was not possible to study the kinetics of the formation of the hydrated naphthalene-1,8-dicarbaldehyde, as previously completed for *o*-phthalaldehyde and phenanthrene-1,8-dicarbaldehyde.[2,5] However, both ^1H and ^{13}C NMR and UV spectral studies indicated that the dialdehyde under present study was completely hydrated in water and 70% (v/v) dioxane–water. The α,α′-dideuterio dialdehyde also appeared to be completely hydrated. The pK_a value for the hydrate could not be measured by UV spectroscopy as no changes were observed on apparent ionisation and a rapid rearrangement occurs in base. Other methods were precluded by the low solubility of the hydrated dialdehyde. The pK_a value can be estimated from that of the five-membered cyclic (bridged) monohydrate of *o*-phthalaldehyde[5] which is 11.83 at 30 °C in water. At the base concentrations studied here, the six-membered cyclic monohydrate of naphthalene-1,8-dicarbaldehyde can be assumed to be in the form of the monoanion (see below).

A UV spectrophotometeric method was used to study the Cannizzaro reaction of the dialdehyde and the alkaline hydrolysis of the lactone. The spectrophotometer used was Perkin-Elmer Lambda 5 and the cell temperature was controlled to ±0.05 °C by means of a Churchill thermocirculator. The technique used was essentially that previously described.[2,5] The Cannizzaro and alkaline hydrolysis reactions were followed at 295 and 312 nm, respectively. The UV spectra of the hydrated dialdehyde and lactone had λ_{max} at 285 and 314 nm, respectively.

The product of the Cannizzaro reaction was shown to be quantitatively the anion of 8-(hydroxymethyl)-1-naphthoic acid (**10**) by isolation of the corresponding lactone (**11**) and UV spectra comparison with the product. The substrate concentrations for the alkaline hydrolysis and Cannizzaro reaction were both *ca.* 1 × 10^{-4} mol dm^{-3} and the base concentrations were 5 × 10^{-3}–5 × 10^{-2} and 1.33 × 10^{-2}–5 × 10^{-2} mol dm^{-3}, respectively. The ionic strength was held constant (μ = 0.1 mol dm^{-3}) with sodium chloride. The reactions were found to be strictly first-order in substrates. The final absorbances were assumed to be those measured after ten half-lives and the results gave linear plots to *ca.* 80% reaction. There was no evidence of the formation of any relatively stable intermediate formation in the Cannizzaro reaction, *i.e.* good isosbestic points were found. The base was in at least a tenfold excess and the reactions were both found to be first-order in base over the range of base concentrations studied. Thus, the substrate must be completely present as either the unionised form or the monoanion. In view of the estimate of the pK_a of the hydrate in water as *ca.* 11.8 and the H_- value in 70% dioxane–water of *ca.* 13.3[13] at the lowest base concentration studied here, the latter appears to be the case. Thus, the monoanion of the hydrate is the 'real' substrate for the Cannizzaro reaction. The rate coefficient for the Cannizzaro reaction in 70% (v/v) dioxane–deuterium oxide was also measured and is shown in Table 1. The lactone products of the Cannizzaro reaction of the α,α′-dideuterio substrate in water and the ordinary substrate in D_2O showed no significant incorporation of the solvent isotope in the product.

SET Pathway.—Radical mechanisms for the Cannizzaro reaction have been suggested;[14] but have been considered to be



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excluded for the reactions in homogeneous aqueous solution. For the present system, a single electron transfer (SET) pathway would give an intermediate, the dianionic diradical **9**. It was possible to monitor the formation of **10** (methylene protons at 4.8 ppm) in [$^2H_6$]DMSO–D_2O containing OD^- by ^1H NMR spectroscopy using both spectrometers. It is possible that the conditions were not suitable for the observation of CIDNP in the formation of **10** from **9**, if the latter was an intermediate in the reaction.[15] However, there was no observation of such an effect. Thus, a simple hydride transfer remains the most likely process.

Results and Discussion

Hydration of Naphthalene-1,8-dicarbaldehyde.—The hydrate is the bridged structure **7**, as a *cis–trans* mixture. The reasons for

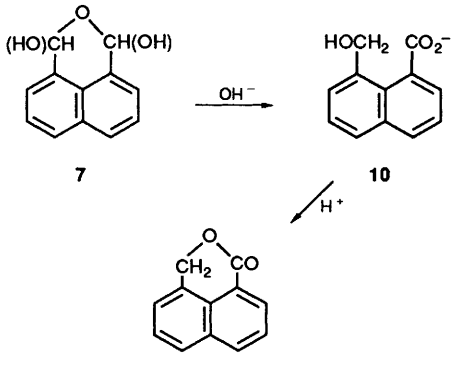
Table 2 Activation parameters, at constant ionic strength (μ = 0.1 mol dm^{-3}), for the intramolecular Cannizzaro reaction of naphthalene-1,8-dicarbaldehyde and the alkaline hydrolysis of the lactone of 8-(hydroxymethyl)-1-naphthoic acid (naphthalide) in 70% (v/v) dioxane–water at 30.0 °C[a]

	$\Delta H^{\ddagger}$/kcal mol^{-1} [b]	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1} [b]
Cannizzaro reaction	14.5	−8
Hydrolysis of lactone	9.8	−23

[a] Values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are considered accurate to within ±300 cal mol^{-1} and ±1 cal mol^{-1} K^{-1}, respectively. [b] 1 cal = 4.184 J.

the formation of the cyclic monohydrate of the dialdehyde appears to be the relief of unfavourable stereoelectronic effects, as discussed previously for related systems.[2] Steric effects will cause extensive or complete deconjugation between the two formyl and naphthalene groups in the dialdehyde, as in related systems.[16] Both repulsive dipole–dipole and steric 'bulk' interactions appear to be relieved on forming the hydrate.

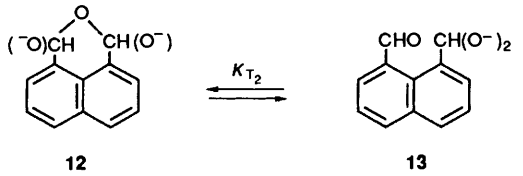
Cannizzaro Reaction.—The product of the Cannizzaro reaction of the hydrate of naphthalene-1,8-dicarbaldehyde (**7**) is the anion of 8-(hydroxymethyl)-1-naphthoic acid (**10**) as shown in Scheme 1 below. The reaction is completely intramolecular as shown by conducting the Cannizzaro reaction of the dialdehyde in D_2O or the dideuteriodialdehyde in water; both of which gave no significant incorporation of the solvent isotope in the product.



7 **10** **11**

Scheme 1

Kinetics of the Cannizzaro Reaction.—The intramolecular reaction is first order in the substrate (the anion of the hydrate) and first order in hydroxide anion. This clearly suggests the importance of the ring dianion **12** or its chain tautomer **13** (Scheme 2). As in previous studies of intramolecular Cannizzaro reactions,[2,5] the reaction is *ca.* 1.7 times faster in D_2O than H_2O. The greater basicity or nucleophilicity of OD^- in D_2O than of OH^- in H_2O[17] is thus involved and the rate-determining step does not involve the ionisation process itself, as the latter would be expected to give rise to a primary isotope effect in the opposite direction.



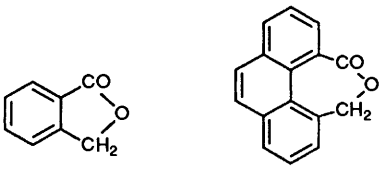
12 **13**

Scheme 2

Kinetic Isotope Effect.—The kinetic isotope effect, k_H/k_D, of *ca.* 1.7 is very similar to those observed in other intramolecular[2,3,5] and intermolecular[18] Cannizzaro reactions. The effect requires correction for the reverse secondary effect on addition to a formyl group[5] and this gives k_H/k_D equal to *ca.* 2.3. This value, like those of other hydride transfer reactions,[19] is small. The usual explanation for this is that hydride transfer occurs through a bent transition state, but recent theoretical treatments indicate it results from extensive participation in the reaction coordinate of degrees of freedom other than asymmetric carbon-hydrogen stretching.[20] A linear transition state for hydride transfer is stereochemically impossible for the system under present study, as in a previous case.[2]

Activation Parameters for the Cannizzaro Reaction.—The entropy and enthalpy of activation for the intramolecular Cannizzaro reaction are shown in Table 2. The latter is typical for a bimolecular reaction; while the former is close to the value found for the same process for *o*-phthalaldehyde.[5] Thus, the formation of the transition state for the 1,8-naphthalene system requires less orientation and ordering than the 4,5-phenanthrene system;[2] but it is energetically more favourable than that of both the 1,2-benzene and 4,5-phenanthrene systems. The system under study has a six-membered ring transition state, whereas the 1,2-benzene and 4,5-phenanthrene systems involve five- and six-membered rings, respectively.

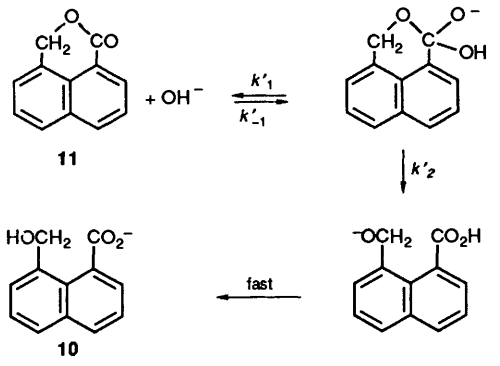
Lactone Hydrolysis.—The rate coefficients for the alkaline hydrolysis of the lactone of 8-(hydroxymethyl)-1-naphthoic acid (naphthalide) (**11**) at various temperatures are shown in Table 1, with the activation parameters shown in Table 2. The alkaline hydrolysis of simple aliphatic lactones has been reviewed.[21] The rate of hydrolysis of the lactone in this study is significantly faster than that of phthalide (**14**) and the lactone of 5-(hydroxymethyl)phenanthrene-4-carboxylic acid (**15**). In



14 **15**

70% aqueous dioxane at 60 °C the relative rates are *ca.* 140(1,8-naphthalene system):8.1(1,2-benzene system):1(4,5-phenanthrene system). This is in accord with the order of reactivity of the simple, related methyl pseudo-esters undergoing alkaline hydrolysis, *i.e.* ring size 6 > 5 > 7.[22] However, the reactivity of the more comprehensive series of related α-substituted pseudo-esters undergoing alkaline hydrolysis is more complex.[22] Thus, a series of naphthalide pseudo-esters are more susceptible to steric 'bulk' effects than the corresponding series of phthalide pseudo-esters.[22] On this basis, it is possible to predict that the reactivity ratio would be greatest for the simple naphthalide/phthalide comparison, as is observed. The activation parameters for the lactone hydrolysis are shown in Table 2. The entropy of activation for the hydrolysis of naphthalide is almost identical with that for the corresponding lactone of the 4,5-phenanthrene system; but the enthalpy of activation for the naphthalide is significantly smaller. The latter result could possibly arise from the relative ring strain effects. However, the situation is more complex, as indicated above and shown by our previous study of the alkaline hydrolysis of pseudo-esters.[22]

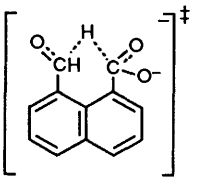
Scheme 3 shows the suggested mechanistic pathway for the alkaline hydrolysis of the lactone, with k'_1 as the rate-determining step. A mechanism for the Cannizzaro reaction, which would involve a lactone intermediate for an intramolecular reaction, has not been supported by the results of



Scheme 3

previous studies.[2,3] It can be concluded from this study that the lactone cannot be an intermediate in the Cannizzaro reaction. At 60 °C, the rate of hydrolysis of the lactone is only slightly slower than the Cannizzaro reaction. If the lactone was formed in the latter reaction, there would be no simple isosbestic point formed in the Cannizzaro reaction; the rate plots would be complex and the UV spectral changes would indicate the presence of the intermediate. Such evidence was not observed.

Proposed Mechanism for the Cannizzaro Reaction.—The suggested mechanistic pathway for the intramolecular Cannizzaro reaction of naphthalene-1,8-dicarbaldehyde is shown in Scheme 4. The most likely path is that *via* the chain dianion tautomer **13**. The formation of the latter would precede the rate-determining step, k'_3. The transition state would then be **14**, in which the hydride transfer occurs from the dianionic group to the electrophilic centre of the formyl carbonyl group. This would involve a six-membered ring system, which would be relatively strain-free but not planar.



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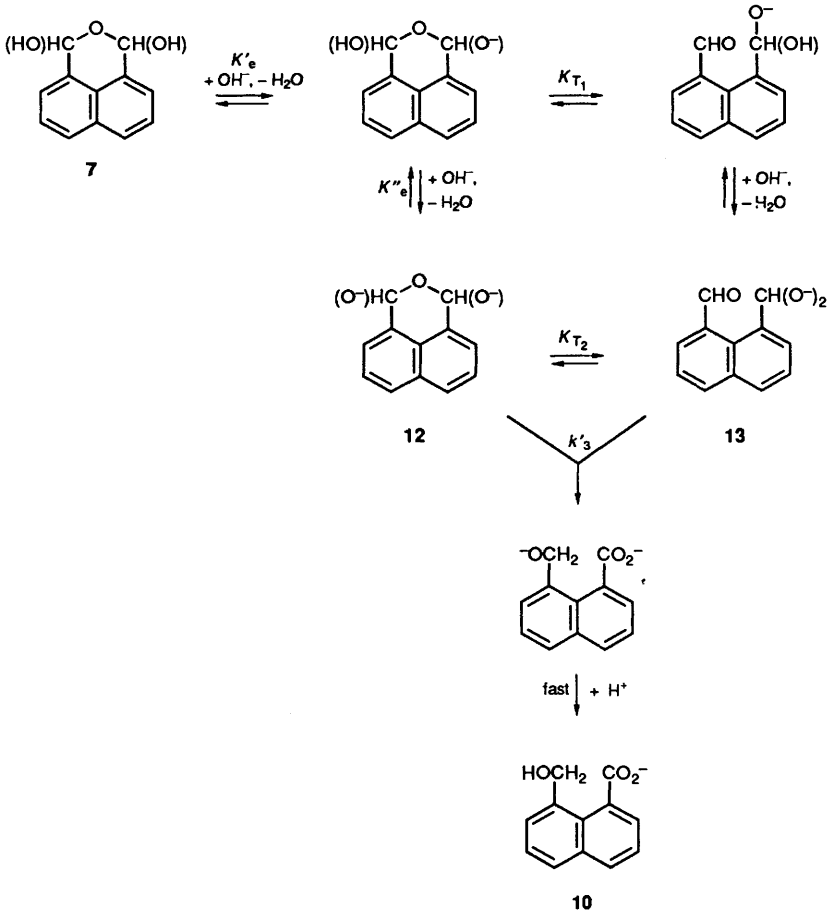
It is now possible to compare the intramolecular Cannizzaro reactions of *o*-phthalaldehyde,[5] phenanthrene-4,5-dicarbaldehyde [2] and naphthalene-1,8-dicarbaldehyde. Thus, at 60 °C, the 1,8-naphthalene and 4,5-phenanthrene systems are 4×10^3 and 7×10^2 more reactive than the 1,2-benzene system. The factors giving rise to such effects appear to be the differences in the stereochemical and steric 'bulk' effects in the systems under study. Our previous studies of both ring–chain tautomerism in formyl carboxylic acids [23] and intramolecular catalysis in the alkaline hydrolysis of formyl esters [16,24] in related systems indicate similar effects on both the equilibria and rate processes to those found here. The implications of these results to the understanding of the factors responsible for rate enhancements in enzymic and related model reactions will be discussed in a subsequent report.[25]



Scheme 4

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