Proc. Indian Acad. Sci. (Chem. Sci.), Vol. 106, No. 1, February 1994, pp. 49–57.

Influence of cyclodextrin complexation on photo-Fries rearrangement of sulphonyl derivatives

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MS received 10 August 1993; revised 4 December 1993

Abstract. Cyclodextrin (CD) complexation shows remarkable selectivity in the photo-Fries rearrangement of sulphonate esters and sulphonanilide. An impressive regioselectivity is observed with meta-substituted sulphonate esters. The results are explained on the basis of selective modes of complexation of the substrates within the CD cavity. The observed results are compared with those of the photo-Fries rearrangement of esters and anilides.

Keywords. β-Cyclodextrin; sulphonate esters; sulphonanilides; photo-Fries rearrangement.

1. Introduction

Cyclodextrins (CDs) are well-known host molecules that find extensive use in complexation and catalysis studies (Bender and Komiyama 1978; Bergeron 1984; Ramamurthy and Eaton 1988). With well-defined cavities, small size and ease of functionalisation, they are found to be the ideal enzyme models (D'Souza and Bender 1987). Cyclodextrin complexation of guest molecules exhibit remarkable selectivity and catalysis in many thermal reactions. Inclusion complexation of CDs modifies the intramolecular photoreaction of guest molecules (Ramamurthy and Eaton 1988) by imposing constraints on the conformation and on the mobility of the reactive intermediates. Physical aspects of complexation have also been extensively studied (Bergeron 1984; Rebek 1984; Eftink *et al* 1989).

A striking feature of CD complexation is its ability to exert geometric control over the traffic of the entrapped molecular species resulting in selectivity in a variety of thermal and photochemical reactions. This has been explored judiciously in a large number of intramolecular photochemical reactions such as photo-Claisen (Syamala and Ramamurthy 1988), photo-Fries (Syamala *et al* 1988) and photochemistry of benzoin derivatives (Ramamurthy and Eaton 1988).

Photo-Fries rearrangement of aryl esters and anilides and the effect of CD complexation on the rearrangement (Chenevert and Plante 1983; Chenevert and Voyer 1984; Nasetta *et al* 1988; Syamala and Ramamurthy 1988; Veglia *et al* 1990) has been extensively reported. An earlier report on photolysis of benzenesulphonanilide

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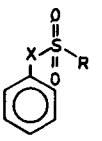
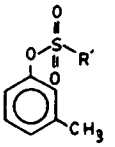




X	R		R′	
NH	Ph	1	Ph	4
O	Ph	2	p-tolyl	5
O	p-tolyl	3		

Figure 1. Structures of compounds 1–5.

(Nozaki *et al* 1966) in ethanol gave large amounts of aniline and small quantities of para-rearranged product in 34% conversion of benzenesulphonanilide. It was also reported that a careful examination of the residue by TLC excluded the presence of the ortho-isomer. Other work on the photo-Fries rearrangement of phenyl para-toluenesulphonate (Stratenus and Havinga 1966) in absolute ethanol and in solvents of different polarity viz. cyclohexane, benzene, alcohol and water indicated the formation of ortho- and para-hydroxyphenyl para-tolyl sulphone and phenol. But the relative yields of different photoproducts were not reported.

The present paper describes the detailed results of our studies on the influence of β-CD on photo-Fries rearrangement of benzenesulphonanilide 1 and sulphonate esters 2 and 3 and of meta-substituted sulphonate esters 4 and 5 (figure 1). Our preliminary results on the photo-Fries rearrangement of benzenesulphonanilide and sulphonate esters have already been reported (Pitchumani *et al* 1991, 1993).

2. Experimental

2.1 *Materials*

β-CD (Sigma) was used as received. Substrates 1 to 5 (figure 1) were prepared by reported procedures and were purified by repeated recrystallisation and their purity was ascertained by GC analysis, spectral data and melting points. Double-distilled water and distilled solvents were used. GC analyses were carried out on a Netel Chromatograph using a 10% SE-30 column.

2.2 *Preparation and identification of complexes*

β-CD complexes of substrates were prepared by mixing equimolar quantities of guests and β-CD as per reported procedures (Syamala and Ramamurthy 1988; Syamala *et al* 1988). The precipitated inclusion complexes were filtered, washed with a small amount of diethyl ether to remove any uncomplexed substrate and dried (65°C). A typical solid sample for irradiation contained 60 mg of the substrate. Aqueous solutions of complexes were obtained by dissolving the solid complexes in excess of

Table 1. ^{1}H NMR chemical shifts (Hz) for β-CD complexes of 1 to 5[a] in D_2O.

Cyclodextrin proton	Uncomplexed cyclodextrin	1	2	4	5
H_1	1007·1	1007·0	1006·4	1003·7	998·9
H_2	722·7	721·9	724·9	703·7	703·7
H_3	784·9	765·2	766·2	723·7	717·7
H_4	709·9	705·3	707·5	698·7	693·7
H_5	763·0	746·9	750·5	723·7	717·7
H_6	769·7	768·2	773·9	761·7	763·7

[a]Spectrum of 3 is not recorded due to its poor solubility in D_2O.

water. Solutions of 5:1 complexes were prepared by placing an additional four equivalents of β-CD with the above aqueous solution and by stirring.

Complexation of substrate 1 to 5 with β-CD has been evidenced from the 200 MHz ^{1}H-NMR spectra in D_2O (table 1). Poor solubility prevented the ^{1}H-NMR analysis of 3. The measurement of dissociation constants (Benesi and Hildebrand 1949) of these complexes from absorption spectrophotometry furnished additional evidence for complex formation.

2.3 *Photolysis*

Solid β-CD complexes of substrates 1 to 5 were photolysed for 80 h in quartz tubes in an annular SAIC photoreactor fitted with eight (each 8 W) 254 nm mercury lamps. Aqueous solutions of CD complexes and homogeneous solutions in methanol and benzene of substrates 1 to 5 containing 50 mg/100 ml of solvent were irradiated in quartz tubes purged with nitrogen for 30 min in the same reactor. Irradiations were carried out for 8 to 10 h and the percentage conversion was below 50% in most cases and with 1, it was 20%. After irradiation the solid CD complexes were dissolved in excess water, and extracted with warm chloroform. The product mixture obtained after removal of the solvent was analysed by GC. In studies with solutions, after photolysis, the aqueous solutions were extracted with chloroform and after the removal of the chloroform, the products were analysed by GC.

The rearranged products isolated from the photolysis mixture were also characterised by comparison of their spectra with those of the products of thermal rearrangement of esters with anhydrous $AlCl_3$ (Aleykutty and Baliah 1954, 1956). In some cases, products were also obtained from the irradiation carried out with larger quantities followed by separation using TLC/column chromatography. The spectral data and GC retention times of all the products obtained by photolysis were compared with those obtained from thermal rearrangement (Aleykutty and Baliah 1954, 1956; Nozaki *et al* 1966). As the spectral data for most of the compounds are not reported, we report herein the NMR and IR data of the sulphones.

2.4 *Spectral data of the photoproducts*

The IR spectra were recorded in KBr/neat using a Perkin–Elmer 577 IR spectrophotometer and NMR measurements on a Bruker WH 200/270 MHz spectrometer

and on a Perkin–Elmer (R32) (90 MHz) spectrometer (in $CDCl_3$) with TMS as internal reference standard.

4-Aminodiphenyl sulphone:
IR (KBr) (cm^{-1}) : 3430–3350 (broad), 2950, 1430, 1135–1100.
2-Hydroxydiphenyl sulphone:
IR (KBr) (cm^{-1}) : 3500–3400 (broad), 3010, 1290–1280, 1140–1090.
^{1}H-NMR ($CDCl_3$) δ : 4·5(*s*, 1 H), 6·9(*m*, 2 H), 7·5(*m*, 3 H), 7·7–7·8(*m*, 2 H), 7·9(*d*, 2 H).
4-Hydroxydiphenyl sulphone:
IR (KBr) (cm^{-1}) : 3590–3520 (broad), 3020, 1290, 1150–1100.
^{1}H-NMR ($CDCl_3$) δ : 3·96(*s*, 1 H), 6·9(*d*, 2 H), 7·5(*d*, 3 H), 7·73–7·78(*d*, 2 H), 7·92 (*dd*, 2 H).
2-Hydroxyphenyl p-tolyl sulphone:
IR (KBr) (cm^{-1}) : 3540–3500 (broad), 3010, 1290, 1140–1090.
^{1}H-NMR ($CDCl_3$) δ : 2·4(*s*, 3 H), 3·67(*s*, 1 H), 6·91–6·95(*d*, 2 H), 7·27–7·46(*m*, 3 H), 7·74–7·79(*m*, 3 H).
4-Hydroxyphenyl p-tolyl sulphone:
IR (KBr) (cm^{-1}) : 3490–3480 (broad), 3010, 1290, 1148–1090.
^{1}H-NMR ($CDCl_3$) δ : 2·35(*s*, 3 H), 3·5(*s*, 1 H), 6·85–6·95(*m*, 2 H), 7·4(*m*, 2 H), 7·55–7·7 (*m*, 2 H), 7·95(*d*, 2 H).
2-Hydroxy-4-methyldiphenyl sulphone:
IR (KBr) (cm^{-1}) : 3340–3220 (broad), 3020, 1350, 1140–1115.
^{1}H-NMR ($CDCl_3$) δ : 2·3(*s*, 3 H), 6·8(*m*, 2 H), 7·44–7·60(*m*, 4 H), 7·84–7·96(*m*, 2 H), 9·5(*s*, 1 H).
4-Hydroxy-2-methyldiphenyl sulphone:
IR (neat) (cm^{-1}) : 3360, 2900, 1350, 1175–1075.
^{1}H-NMR ($CDCl_3$) δ : 2·3(*s*, 3 H), 6·35(*s*, 1 H), 6·75–6·95(*m*, 2 H), 7·15(*m*, 1 H), 7·55–7·7 (*m*, 3 H), 7·85–8·00(*m*, 2 H).
2-Hydroxy-4,4'-dimethyldiphenyl sulphone:
IR (KBr) (cm^{-1}) : 3280, 2990, 1575, 1395, 1285–1270, 1130–1075.
^{1}H-NMR ($CDCl_3$) δ : 2·22(*s*, 3 H), 2·32(*s*, 3 H), 6·7–6·8(*m*, 2 H), 7·25–7·6(*m*, 3 H), 7·8–7·9(*m*, 2 H)
(The signal for the hydroxyl proton was not observed between 0 and 10δ)
4-Hydroxy-2,4'-dimethyldiphenyl sulphone
IR (neat) (cm^{-1}) : 3360–3300 (broad), 3000, 1390, 1175–1125.
^{1}H-NMR ($CDCl_3$) δ : 2·22(*s*, 3 H), 2·3(*s*, 3 H), 6·5(*s*, 1 H), 6·65–6·85(*m*, 2 H), 7·2–7·7 (*m*, 3 H), 7·8–7·9(*m*, 2 H).

2.5 *Measurement of dissociation constants*

A spectrophotometric method (Benesi and Hildebrand 1949) was used to measure the dissociation constants of the β-CD complex. Stock solutions containing (10×10^{-3} M) of the substrate in methanol was prepared. 100 μl aliquots from this were added to 10 ml standard flasks. Varying volumes (0 to 2 ml) of β-CD were added to this from a stock solution of 1×10^{-2} M of CD. The solutions were magnetically stirred and their absorption spectra were recorded (JASCO 7800 UV/Vis Spectrophotometer) in the range of 225–350 nm.

Substrate		λmax (nm)	*Dissociation constant* (M^{-1})
Benzenesulphonanilide	1	271	$2{\cdot}70 \times 10^{-4}$
Phenyl benzenesulphonate	2	264	$3{\cdot}00 \times 10^{-4}$
Phenyl *p*-toluenesulphonate	3	261	$1{\cdot}08 \times 10^{-4}$
m-Tolyl benzenesulphonate	4	263	$1{\cdot}53 \times 10^{-4}$
m-Tolyl *p*-toluenesulphonate	5	226	$3{\cdot}17 \times 10^{-3}$

3. Results and discussion

3.1 *Photo-Fries rearrangement of sulphonate derivatives*

Inclusion complexes of substrates 1 to 5 with β-CD were prepared by mixing equimolar quantities of guests and the host CD. Aqueous solutions of 1:1 and 5:1 complexes were also employed in our studies. The presence of an inclusion complex in the solid state was inferred from the fact that a known weight of the complex extracted in chloroform yields one equivalent of guest molecule showing that a stoichiometric 1:1 complex was formed between the host and guest molecules in each case.

Additional evidence for complexation was obtained from ^{1}H-NMR analysis of D_2O solutions of the complexes (table 1). While the chemical shifts of the outer

Table 2. Product distribution upon irradiation of sulphonyl derivatives under various conditions.[a,b]

Medium	Yield of photoproducts (%)[c] A	B	C
Benzenesulphonanilide	1 (X = NH; R = Ph)		
Benzene	—	18·1	81·9
Methanol	—	15·4	84·6
β-CD-water (1:1)[d]	21·4	60·7	17·9
β-CD-water (5:1)	29·4	62·4	8·5
β-CD-solid (1:1)	99·0	—	—
Phenyl benzenesulphonate	2 (X = O; R = Ph)		
Benzene	13·5	2·0	84·5
Methanol	18·0	7·0	75·0
β-CD-water (1:1)[d]	44·0	56·0	—
β-CD-water (5:1)	54·0	46·0	—
β-CD-solid (1:1)	99·0	—	—
Phenyl para-toluenesulphonate	3 (X = O; R = *p*-tolyl)		
Benzene	10·0	21·0	68·9
Methanol	23·0	18·0	59·0
β-CD-water (1:1)[d]	42·0	58·0	—
β-CD-water (5:1)	63·6	36·4	—
β-CD-solid (1:1)	99·0	—	—

[a]Analysed by GC, error limit ± 5%; [b]solution irradiations were carried out after purging with nitrogen for 30 min; [c]letters A–C refer to structures of products indicated in schemes 1 and 2; [d]ratio of CD to guest

Table 3. Product distribution on photolysis of *m*-substituted sulphonate esters 4 and 5.[a,b]

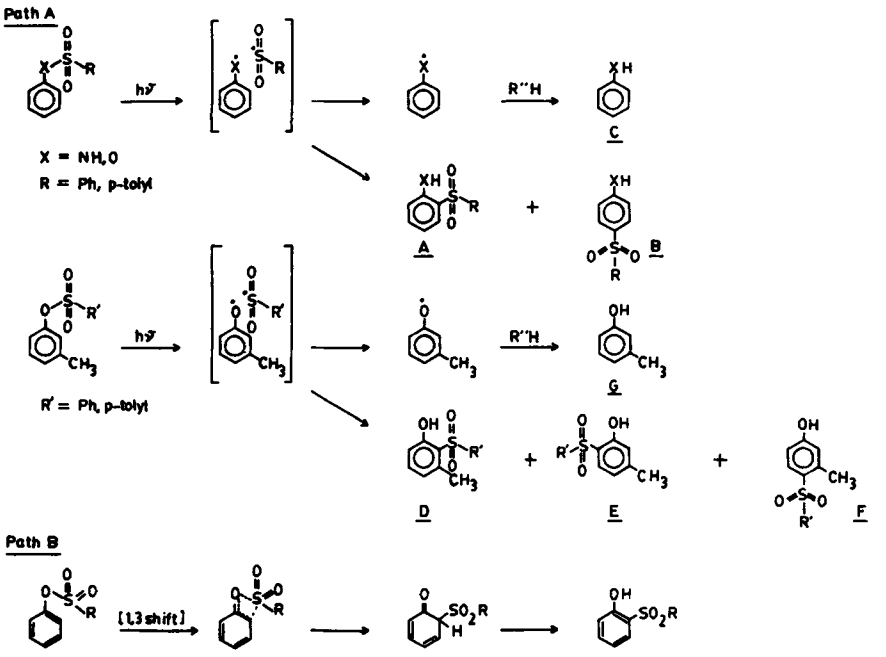
Medium	Yield of photoproducts (%)[c]			
	D	E	F	G
m-Tolyl benzenesulphonate		4 (R = phenyl)		
Benzene	1	12	60	27
Methanol	3	20	54	23
β-CD-water (1:1)[d]	9	23	45	23
β-CD-water (5:1)	16	28	31	25
β-CD-solid (1:1)	—	77	23	—
m-Tolyl p-toluenesulphonate		5 (R = *p*-tolyl)		
Benzene	—	9	49	42
Methanol	14	23	34	29
β-CD-water (1:1)[d]	13	12	43	32
β-CD-water (5:1)	17	20	31	33
β-CD-solid (1:1)	—	61	39	—

[a]Analysed by GC, error limit ± 5%; [b]solution irradiations were carried out after purging with nitrogen for 30 min; [c]letters refer to structure of products indicated in schemes 1 and 2; [d]ratio of CD to guest.

protons H_1, H_2 and H_4 of β-CD were not much influenced, the protons H_3 and H_5 undergo notable upfield shifts in their resonance positions upon complexation. These results, based on literature reports (Demarco and Thakkar 1970; Chung *et al* 1990), can be construed as evidence for complex formation between β-CD and substrate. The changes in chemical shifts of the inner H_3 and H_5 protons arise due to the diamagnetic anisotropic effect of the phenyl ring.

Measurement of dissociation constants for substrates 1 to 5 in aqueous solution (Benesi and Hildebrand 1949) lends further support for complex formation. Addition of CD to any substrate from 1 to 5 does not cause any shift in absorption maxima. However, the changes observed in absorption intensities (at the wavelengths mentioned earlier) are used to calculate the dissociation constants.

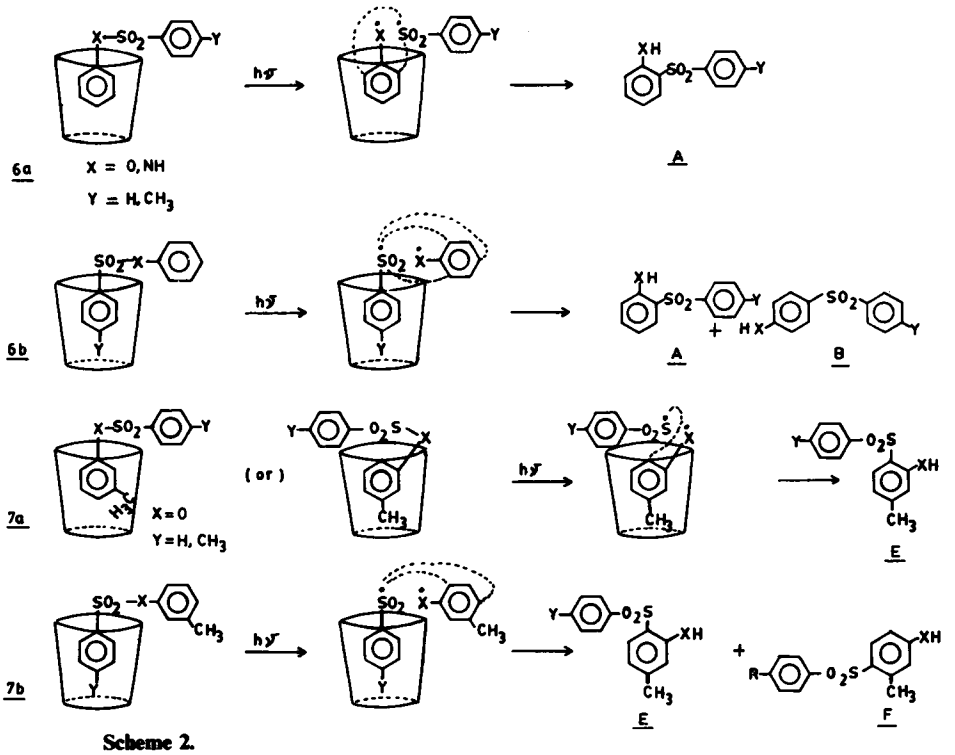
The product distribution on irradiation of substrates 1 to 5 in homogeneous solution and on their β-CD complexes are presented in tables 2 and 3. Photoproducts in each case were characterised on the basis of their ^{1}H-NMR and IR spectral data. Photolysis of substrates 1 to 3 in isotropic media, namely benzene and methanol, largely yield the cleavage product C along with small quantities of A and B. This may be explained on the basis of the mechanism given in scheme 1 (path A). Path A, presumably from the energetically higher level, leads to the dissociation of the [X–SO_2] bond, giving rise to a radical pair. Path B, probably from the energetically lower level, seems to operate by a concerted [1,3] or [1,5] shift of the sulphonyl group (Bellus 1971). Irradiation of an aqueous solution of β-CD results in the formation of A and B in very significant amounts at the expense of C. With 2 and 3, formation of the cleavage product C is totally suppressed. Increase in the amount of β-CD in aqueous solution (in 5:1 ratio of β-CD: substrate) causes an increase in the amount of *o*-isomer A. With β-CD solid complexes of substrates 1 to 3, photolysis produces a near quantitative yield of A.



Scheme 1.

Irradiation of *m*-methyl substituted sulphonate esters 4 and 5 also provides interesting results. Photolysis in isotropic media results in a mixture of E, F and G in significant quantities (table 3). When aqueous solutions of the β-CD complexes, particularly with higher ratios of β-CD, are photolysed there is a small increase in the yield of the *o*-rearranged products D and E at the expense of F, while the cleavage product G almost remains unchanged. Irradiation of solid β-CD complexes of 4 and 5 yields one of the *o*-isomers E in larger yield along with *p*-isomer F. Since the mobility expected in solution is denied in the solid state, formation of cleavage product G is totally suppressed. Another interesting observation is that the amount of *o*-isomer E obtained is larger with 4 than with 5.

The observed results may be explained by proposing specific modes of complexation of the substrates within the CD cavity. The remarkable *o*-selectivity observed with solid β-CD complexes of 1 to 3 is attributed to the formation of an inclusion complex with either of the aryl rings going into the cavity (6a and 6b, scheme 2). Among the possible orientations 6a and 6b, the contribution of 6a is expected to be more than 6b with 1 to 3 since the bulkier sulphonyl group might experience steric hindrance for penetration into the CD cavity. In 6a, the β-CD cavity protects the *p*-position of the aryl ring from the attack of the phenylsulphonyl radical, thus exposing only the two *o*-positions. Similarly, in 6b also, the tight packing of the neighbouring molecules in a solid complex causes a cage-like environment forcing the phenylsulphonyl radical to attack the exposed *o*-position or to recombine. Formation of the ortho rearranged product may also take place exclusively via concerted path B (scheme 1) with subsequent aromatization. This is quite probable in a solid complex with its tight packing and restricted mobility.



Scheme 2.

With *m*-methyl substituted sulphonate esters 4 and 5 also, orientations 7a and 7b (similar to 6a and 6b as in substrates 1 to 3) may be visualised. The sterically more hindered ortho-isomer D is found to be absent in solid complexes resulting in regio-selectivity between the two ortho-isomers. However, the remarkable ortho-selectivity observed in solid complexes of 1 to 3 is not realised here and a mixture of ortho-(E) and para-(F) isomers are obtained.

This may be explained by the fact that the introduction of *m*-methyl group in the benzene ring requires more space for inclusion in β-CD and hence the contribution of orientation 7a is effectively reduced. Thus, with the increasing contribution from 7b, (in comparison with 6b for 1 to 3), it is likely that more of the *p*-isomer is formed in this case.

It is believed that the complexes in the aqueous phase may also have similar structures 6a, 6b, 7a and 7b as in the solid state and that there may be dynamic equilibrium between the complexed and the uncomplexed substrates. As a result there may be reactions involving both the free and the bound substrates and this explains the poorer selectivity in the aqueous phase as compared to the solid state.

3.2 *Comparison with photo-Fries rearrangement of anilides and esters*

When the results of the present investigation are compared with those of the photo-Fries rearrangement of anilides and esters (Syamala *et al* 1988), some interesting features are observed. As in the case of β-CD complexes of anilides and esters, in

solid state irradiation of β-CD complexes of 1 to 3 also ortho-rearranged products are obtained exclusively. While irradiation of solid complexes of *m*-methyl substituted derivatives 4 and 5 results in poorer selectivity, yielding one of the ortho-isomers in major yield and the para-isomer in small amounts, that of corresponding methyl derivatives of anilides and esters leads to remarkable regioselectivity between the two ortho-isomers with no para-isomer. Our results may be explained as due to the presence of two aryl rings on either side leading to random penetration resulting in poor selectivity in comparison to anilides and esters (where most of the substrates studied have only one aryl ring). This variation in selectivity may also be due to the relative significance and contributions of the various conformations of β-CD inclusion complexes as discussed earlier. The presence of a bulkier sulphonyl group may also have contributed to the present observation.

Acknowledgements

The financial assistance provided by the University Grants Commission, New Delhi is gratefully acknowledged. PV thanks the Madurai Kamaraj University for the award of a research fellowship.

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