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CHANGES OF STEREOSELECTIVITY AND RATE IN DIELS-ALDER REACTIONS BY HYDROPHOBIC SOLVENT EFFECTS AND BY BOVINE SERUM ALBUMIN.

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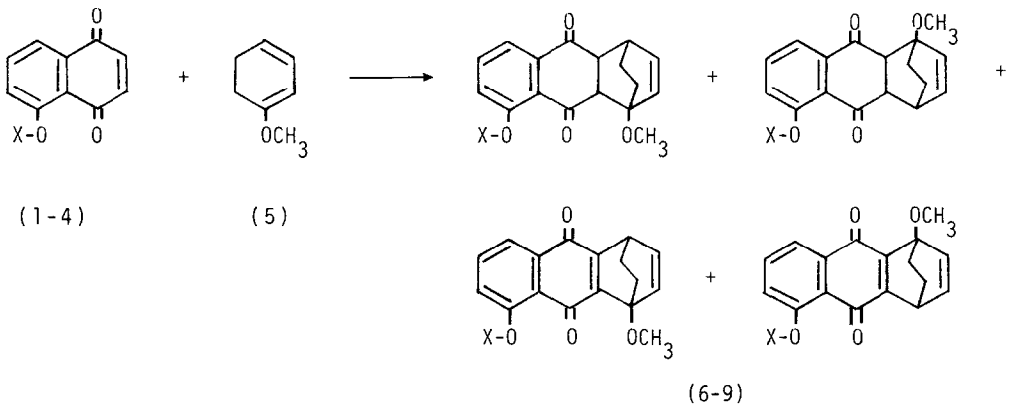
Abstract. The use of water instead of benzene as the solvent can strongly influence the stereoselectivity and the rate of Diels-Alder reactions of 1,4-naphthoquinone derivatives with different dienes. Enantiomeric excess (e.e.) up to 38% is reached in the presence of a catalytic amount of bovine serum albumin.

The profound effect of H_2O on both the rate and selectivity of Diels-Alder reactions[1] has been much debated, and is generally attributed to hydrophobic effects.[1a,c,d,h] Such effects, mainly responsible for the binding of substrates to the enzymes and for autoassociations in micelles, increase the reaction's rate and influence the stereoselectivity. In the presence of chiral auxiliaries asymmetric synthesis may occur, leading to optically active cycloadducts. Surprisingly there are only two recent examples of asymmetric aqueous Diels-Alder reactions: one dealing with glyco-organic substrates[1g], the other with maleic acid derivatives in the presence of cyclodextrins.[1h]

We report here that substituted 1,4-naphthoquinones react with different dienes in water at room temperature giving good to excellent yields. The starting dienophiles chosen (1-4,12) are precursors of anthracyclinones, very interesting compounds due to their potent antitumor properties.[2] The use of appropriate dienes permits the derivatisation of compounds with a wide range of functionalities, thus extending the scope of the Diels-Alder route to anthracyclinone analogues.[2]

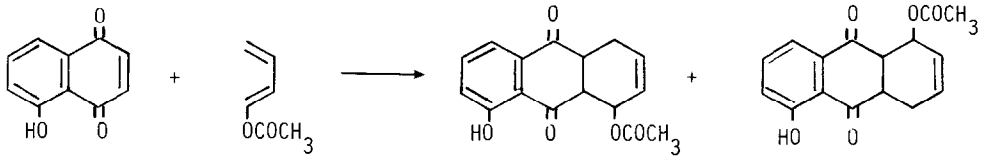
To check the potentiality of this process in the asymmetric induction the reaction was repeated in the presence of 0.05-0.1 molar equivalents of bovine serum albumin. The dienophile (0.5 mmol) and diene (0.45 mmol) were stirred together in 6.25 ml of water or benzene at room temperature and the resultant products purified by preparative layer chromatography. The enantiomeric excess was determined by ^1H NMR spectroscopy with $Eu(hfc)_3$ as the chiral shift reagent or by ^{19}F NMR spectroscopy of the (R)-(+)-methoxy-α-(trifluoromethyl)phenyl acetate derivatives.[4] Reaction time, chemical and optical yields are reported in the table.



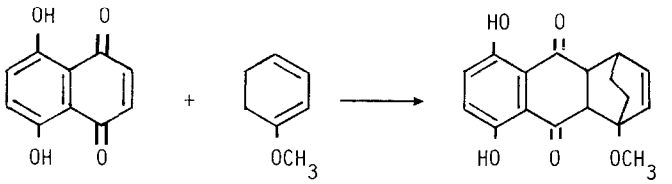
(1-4) (5) (6-9)

(1); (6a,6b,6c,6d) X = H (3); (8a,8b) X = $COCH_3$

(2); (7a,7b) X = CH_3 (4); (9a,9b) X = n-C_8H_{17}



(1) (10) (11a) (11b)



(12) (5) (13)

The greatest increase in the reaction rate, on changing the solvent from benzene to water, was obtained in the reaction of 5-methoxy-1,4-naphthoquinone (2) with 1-methoxycyclohexa-1,3-diene (5); intermediate behaviour was shown by juglone (1), 5-acetoxy (3) and 5-octyloxy-1,4-naphthoquinone (4). The more hydrophilic naphthazarin has, as expected, a similar reactivity towards 1-methoxycyclohexadiene (5) both in water and in benzene.

Furthermore the stereoselectivity of the reaction is strongly changed by varying the solvent. Regiochemical reversal has been observed in the reaction of 5-hydroxy (1) and 5-acetoxy-1,4-naphthoquinone (3) with different dienes[5] in organic solvents. Moreover juglone (1) and its methyl ether (2) reacted with (5) in benzene affording adducts (6a, 6b)

and (7a, 7b) in ratios 19:1 and 1:2.5, respectively.[6] These results were explained on the basis of frontier molecular orbital theory.[5f] The data obtained in the aqueous cycloaddition fit this trend. Starting from juglone (1) the regioselectivity of the cycloaddition with (5) is lower in water than in benzene, but the situation is reversed in the reaction of the 5-methoxy derivative (1) with the same diene (5) (see table).

The influence of bovine serum albumin on regio or enantioselectivity in Diels-Alder reactions has never been studied. The results indicate that the globular protein does not affect the regioisomer ratio of adduct. The highest enantiomeric excess (38%) was obtained in the cycloaddition of juglone (1) to diene (5), whereas racemic products (9a)-(9b) were formed starting from (4). The absence of asymmetric synthesis in the latter case can be easily explained since 5-octiloxy 1,4-naphthoquinone, in contrast with the other quinones (1-3), possibly for steric reasons, does not form complexes with BSA. This can be demonstrated by circular dichroism spectroscopy since the optical activity originating in the electronic transitions of the quinone chromophore reflects its interaction with protein chromophores in the neighbourhood of the binding site.[7] Further studies are required to explain why, it is only from juglone (1), that BSA leads to the dehydrogenated adducts (6c), (6d) a reaction which, to our knowledge, has no precedents in the literature.

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Table. Diels-Alder Reaction of 1,4 Substituted Naphthoquinones and Dienes at 25°C.

Entry	Dienophile	Diene	Condition	Time (h)	Adduct	Yield (%)	Regioisomer ratio	e.e. (%)
	1	5	H_2O	18	6a+6b	99	2.5:1	
	1	5	C_6H_6	18	6a+6b	65	9.5:1	
	1	5	H_2O/BSA[a]	18	6a+6b[b]	41	2.5:1	38[c,d]
	1	10	H_2O	44	11a+11b	44	2.8:1	
	1	10	C_6H_6	44	11a+11b	25	4:1	
	2	5	H_2O	18	7a+7b	99	1:7.5	
	2	5	C_6H_6	18	7a+7b	0	0	
	2	5	H_2O/BSA[a]	18	7a+7b	76	1:6	3
	3	5	H_2O	18	8a+8b	70	1:5.7	
	3	5	C_6H_6	18	8a+8b	20	1:6 ca	
	4	5	H_2O	18	9a+9b	58	1:4	
	4	5	C_6H_6	18	9a+9b	26	1:4	
	4	5	H_2O/BSA	18	9a+9b	67	1:3.5	0
	12	5	H_2O	18	13	23	-	
	12	5	C_6H_6	18	13	26	-	
	12	5	H_2O/BSA	18	13	56	-	12

[a] 0.05 Molar equivalents of BSA with respect to the dienophile. [b] Also the formation of 6c+6d was observed in 40% yield and with 1.75:1 regioisomer ratio of unknown, e.e. [c] For the major regioisomer only. [d] See ref. 8).

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