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Effect of Water on Chemo- and Endo-Selectivity in High Pressure Diels-Alder Furan Reactions. Hydrophobic or Polar Effects ?

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Key Words : Diels-Alder reactions, furans, high pressure, solvent effect, hydrophobicity, endoselectivity.

Abstract : Diels-Alder furan additions are less sensitive to pressure in aqueous solution than in organic solvents. In some cases, water affects chemo- and stereoselectivity. The interpretation takes into account hydrophobic as well as polar effects induced by water.

Since the discovery of dramatic rate accelerations in various Diels-Alder cycloadditions in aqueous solution[1], water has been considered as a promoting medium for diverse reactions[2]. The most economical interpretation rests on the hypothesis of hydrophobic packing of diene and dienophile, e.g. the entropy-driven association of water immiscible molecules. To this respect, it was asserted that Diels-Alder reactions in water must be accelerated as it is under pressure to occupy the smallest volume of cavity[3]. Water is a very special medium affecting not only kinetics, but also stereoselectivity[4-7]. A linear correlation was found for cyclopentadiene Diels-Alder reactions between endo:exo ratios and solvophobicity parameters[6], apparently arguing for hydrophobic interactions. A latter study showed that the correlation could be improved when polarity factors are also taken into account. Such physico-chemical refinements, however, increase the difficulty to rationalize the results as the effect of dipolar solute-solvent interactions is also reflected in the solvophobicity term.

We report here our results concerning high pressure mediated [4+2] cycloadditions involving furans[8]. Such reactions are strongly promoted by pressure whereas only insignificant yields are obtained under ambient pressure conditions[9]. The pressure effect was investigated in dichloromethane (organic solvent) and water respectively by comparing the yields at two pressures (Table 1).

Two relevant comments are in order :

- the pressure effect on the yields is generally weaker in water solution when compared to the yields obtained in dichloromethane. Entries 1 and 6 provide the most convincing examples ;
- water can deeply alter the chemoselectivity (entry 4) : 2-methylfuran and methyl vinyl ketone undergo in aqueous solution an exclusive addition-substitution reaction[10].

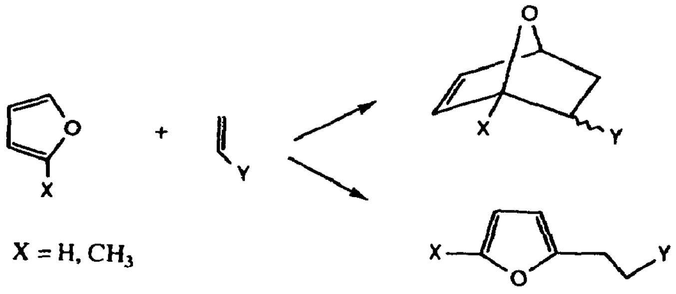

Table 1 : Addition reactions of furans in CH_2Cl_2 and H_2O. Pressure effect [a)]

Entry	X	Y	Medium	θ [b)]
1	H	$COCH_3$	water CH_2Cl_2	3.9 5.1
2	H	$COOCH_3$	water CH_2Cl_2	4.1 4.1
3	H	CN	water CH_2Cl_2	4.1 4.6
4	CH_3	$COCH_3$	water CH_2Cl_2	3.4 [c)] 4.6
5	CH_3	$COOCH_3$	water CH_2Cl_2	4.2 5.0
6	CH_3	CN	water CH_2Cl_2	3.1 5.3

a) 24 h, 32.8° C (except in entry 1 : 30.0° C).

b) θ is the yield ratio at 3000 vs 1100 bar respectively. Yields at atmospheric pressure were O or very low for most reactions carried out in CH_2Cl_2.

c) Exclusive addition-substitution reaction.

The endo percentage was examined for adducts isolated from experiments carried out at 3000 bar in water and in several organic solvents (Table 2).

The effect of water is apparently puzzling. In two cases (3 and 5), there are only minor changes in endo selectivity in spite of the wide polarity range of the solvents. In contrast, reaction listed as entry 1 shows endo

Table 2 : Solvent effect on endo selectivity [a])

Medium	% endo			
	Reaction 1	Reaction 3	Reaction 5	Reaction 6
$(C_2H_5)_2O$	80	66	60	-
CH_2Cl_2	74	67	60	31
CH_3OH	52	65	59	30
H_2O	62	67	63	26
H_2O + LiCl b)	72	66	60	25
H_2O + $LiClO_4$ b)	60	60	60	28
LPDE c)	34	-	54	-

a) Determined for adducts synthesized at 3000 bar and 32° C in reactions designed as entries 1,3,5,6 in Table 1.
b) 3 M solution.
c) Lithium perchlorate in diethyl ether (5 M). Values at 1 bar taken from ref. 11.

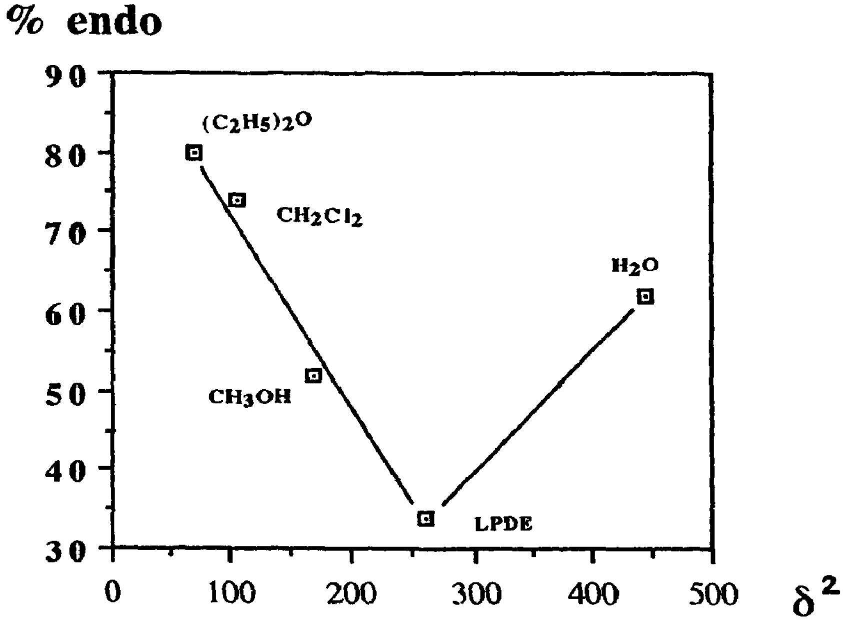

Figure 1 : Endoselectivity versus cohesive energy density δ^2 of solvent in the high pressure addition of methyl vinyl keton to furan.

preference strongly depending on the medium. To this respect, polarity is a determining parameter. The highest endo selectivity value is obtained in diethyl ether solution and the lowest in LPDE which is a highly polar medium[12]. There is a seemingly linear correlation between endo selectivity and the cohesive energy density δ^2 (Figure 1). The linear trend, however, is not followed in aqueous solution since the endo selectivity in water is raised to 62 % although water is even more polar than LPDE. The result may be rationalized by taking into account not only polarity effects, but also hydrophobic interactions. Water favors the more compact endo transition state, a result conforming to previous reports and tentatively ascribed to the operation of enhanced hydrophobic effects[5,6]. This hypothesis is conforted by the NMR results obtained when the reaction is carried out in aqueous solution of LiCl (a salt which stimulates the hydrophobic effect, e.g. salting-out effect) and of $LiClO_4$ which increases the solubility of hydrocarbons in water (salting-in effect). The endo selectivity reaches 72 % in the first case and 60 % in the latter. Reaction 1 is a clear example highlighting the simultaneous operation of polarity and hydrophobicity properties of water in a Diels-Alder reaction. A similar, though much smaller, effect is observed in reaction 6 (2-methylfuran + acrylonitrile). In this case, the endo selectivity seems not to depend on δ^2, however, shows a weak sensitivity to hydrophobic effects (in the opposite direction if compared to reaction 1). It should be pointed out that, from the viewpoint of high pressure kinetics, reactions 1 and 6 are also the most affected when the solvent changes from CH_2Cl_2 to water.

In conclusion, water can alter kinetics, chemo- and endoselectivity of high pressure Diels-Alder reactions through polarity and hydrophobic effects, the weight of each depending on the reaction partners. We are currently investigating the water effect on the volume of activation of high pressure [4 + 2] cycloadditions.

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