High-pressure effect on organic reactions in fluorophobic media

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ABSTRACT: The kinetic effect of fluorophobic interactions was examined in Diels–Alder reactions and the conjugate addition of amines to acrylonitrile at different pressures. Its magnitude is lower than for other solvophobic media (water, ethylene glycol). Activation volumes determined in perfluorohexane are less negative for Diels–Alder cycloadditions owing to reduced fluorophobic interactions under pressure, in line with a former study. At variance, the conjugate addition is more pressure sensitive in the fluorous medium owing to the combination of solvophobic acceleration and enhanced electrostriction. Some synthetic applications of the multiactivation method (pressure + fluorophobic activation) are presented with emphasis on the beneficial solvophobic properties of the fluorous medium. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: fluorophobic effects; pressure; activation volume; Diels–Alder reaction; conjugate addition; Passerini reaction

INTRODUCTION

The pressure dependence of rate constants ultimately yields the activation volume ΔV^*, the magnitude of which describes the volume profile. However, ΔV^* is seldom a one-component expression. In fact, it is known to be a composite quantity as it must accommodate two main effects, the structural volume variation ΔV_S^* when the reaction variable migrates from ground to transition state and the environmental volume term ΔV_m^* resulting from volume variations in solute–solvent interactions when the molecules enter the transition state:[1]

$$\Delta V^* = \Delta V_S^* + \Delta V_m^* \qquad (1)$$

This view seemed reasonably accepted until recently. However, during the last decade, additional activation volume components were reported, mostly connected with ΔV_m^*.[2] The idea is to consider not only electrostatic interactions ΔV_ε^*, but also to take into account solvophobic interactions ΔV_ϕ^* as

$$\Delta V_m^* = \Delta V_\varepsilon^* + \Delta V_\phi^* \qquad (2)$$

It is therefore necessary to examine carefully the possible medium effect in order to interpret ΔV^* correctly, particularly when mechanistic details are deduced.[3]

The occurrence of ΔV_m^* must be envisaged when rate constants are solvent dependent. For example, in ionogenic reactions or simply when the transition state is more polar than the initial and final states, the polarity of the medium influences reaction rate constants. This is also the case when the reaction system is subjected to solvophobic effects.[4] Such effects were shown to result from a concentration effect increasing the number of intermolecular collisions and also from stabilization of the activated complex by increased hydrogen bond interactions if the formation of these bonds is possible.[5] Solvophobic media for organic molecules are essentially water or water-like media (formamide, glycols) and fluorous hydrocarbons.

Perfluorohydrocarbons are unique as they show poor miscibility and solvating power toward most organic compounds. These properties have been exploited in organic synthesis: fluorous biphase chemistry[6] (a remarkable recent application includes hydroformylation reactions;[7] in addition, it should be pointed out that fluorophobic interactions may be observed only in non-amphiphilic fluorous media; for reactions carried out in the amphiphilic fluorous F-626 solvent, see Ref. 7d) and use as a surfactant-like system in supercritical carbon dioxide.[8] A case of fluorophobic acceleration in the Diels–Alder reaction of 9-hydroxymethylanthracene with *N*-ethylmaleimide has recently been reported.[9] It has also been shown that perfluorous organic solvents accelerate Michael reactions in solid-phase chemistry on resins.[10]

Solvophobic interactions result from the associative

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effect forcing the organic molecules together in order to minimize the solvent–hydrocarbon interfacial area (e.g. to remove the solvent-accessible non-polar surface area in the transition state). In hydrophobic media, the kinetic acceleration is due to (i) enforced hydrophobic interactions,[11] (ii) hydrogen bonding[12] and (iii) electrostatic interactions.[13] It is generally not easy to distinguish which effect is the main determining parameter of the kinetic alteration. As an example, in the cycloaddition of methyl vinyl ketone to isoprene, all three effects take part as shown by a pressure study.[14] At variance with water and water-like solvents, perfluorohydrocarbons are simpler structured liquids and, accordingly, fluorophobic interactions are expectedly easier to understand. Owing to their very low dielectric constant and solubility parameter, polarity effects are non-existent and hydrogen bonding properties extremely weak. If fluorophobic acceleration is observed, the kinetic effect must be ascribed to solvophobicity alone. A further advantage of using such media lies in the fact that they do not react with the quasi totality of reagents, at variance with alcohols and, *a fortiori*, with water which is usually not tolerated in many reactions.

The aim of this paper is to report our recent results on the effect of pressure on possible fluorophobic interactions and to correlate the results with previous ΔV^* data determined in dissociating and/or solvophobic media. The synthetic aspect will also be considered.

RESULTS

Solvophobic interactions are directly related to the solubility of reactants. Partial solubility is required to observe reaction. However, there is no solvophobic effect in reactions where the substrates are fully dissolved. For the fluorous hydrocarbon, we selected a prototypical fluorous medium, perfluorohexane, and for reactions, we investigated Diels–Alder reactions and the conjugate addition of amines to acrylic compounds previously
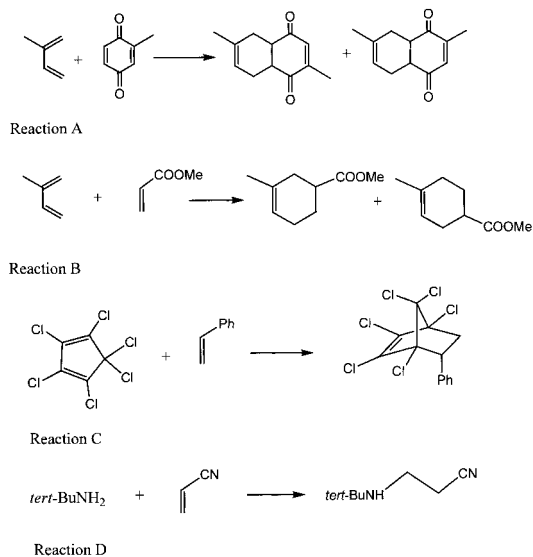
Scheme 1

examined under pressure in our laboratory.[14,15] All these reactions are characterized by fairly negative activation volumes. We first studied the solvent effect at atmospheric pressure. In a second step, we report the pressure effect in these reactions according to the medium.

Effect of solvent at ambient pressure

We followed the kinetics of the $[4 + 2]$ cycloaddition of toluquinone to isoprene (reaction A) and the conjugate addition of *tert*-butylamine to acrylonitrile (reaction D) in different solvents of various polarities defined by their δ^2 values (cohesion energy density) (Scheme 1, Table 1). The lowest rate constants are found in chloroform for both reactions. Interestingly, the relative k ratios (ρ values) are around 3 and 11 for the respective reactions in perfluorohexane, despite the lower polarity. Although the rate increase in the fluorous medium is relatively modest compared with the corresponding ρ values in water and

Table 1. Solvent effect in the Diels–Alder reaction and conjugate addition[a]

| Solvent | δ^2 | Diel–Alder reaction (reaction A) | | Conjugate addition (reaction D) | |
		$10^5 k$	ρ[b]	$10^6 k$	ρ[b]
C_6F_{14}	35	2.62	3.0	17.8	11.1
$CHCl_3$	86	0.87	1.0	1.6	1.0
CH_2Cl_2	104	—	—	1.9	1.2
CF_3CH_2OH (TFE)	154	28.7	33	—	—
C_2H_5OH	161	2.23	2.6	—	—
CH_3OH	208	—	—	6.1	3.8
$HOCH_2CH_2OH$	213	45	52	87	54
$HCONH_2$	369	71	82	165	103
H_2O	547	1270	1460	820	683

[a] Conditions: $P = 0.1$ MPa, reaction A 303.5 K, reaction D 300.7 or 317.2 K (see Ref. 14); k is given in $dm^3\,mol^{-1}\,s^{-1}$.

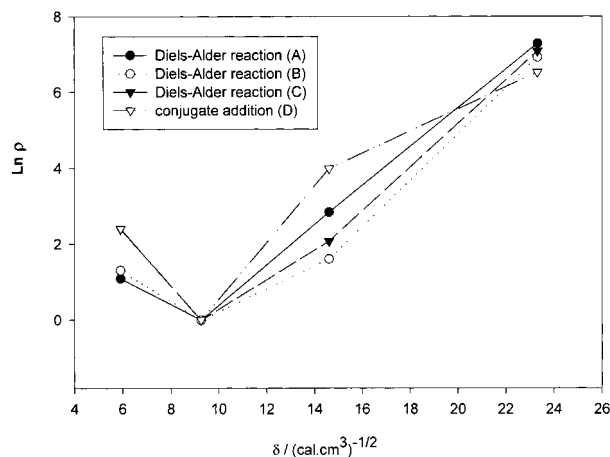**Figure 1.** Semi-logarithmic plot of ρ against solubility parameter δ for four solvents [C_6F_{14}, $CHCl_3$, $(CH_2OH)_2$, H_2O]. The ρ value for the styrene reaction in C_6F_{14} is 2.41

water-like media, it is perceptible. In fact, according to Hildebrand's theory, in the absence of solvophobic interactions the ratios should be less than unity. The k ratios determined in C_6F_{14} are indicative of the existence of fluorophobic interactions. The rate increase with increasing polarity of the medium must be interpreted differently according to the reaction. The conjugate addition is an ionogenic reaction with formation of zwitterions, obviously promoted in a more polar medium. Fluorophobic effects also intervene, as testified by the higher k values in C_6F_{14}. On the other hand, the rate increase in the Diels–Alder reaction is only partly due to increased electrostatic interactions. This is highlighted by comparison of the ρ values in ethanol and TFE, which have similar δ^2 values. The ρ value is 2.6 in ethanol, but about 33 in TFE. The latter alcohol is known to develop a strong hydrogen-bonding network with carbonyl groups.[16] This is also the case for ethylene glycol, formamide and water. Solvophobic interactions take also much importance in these media, particularly in water ($\rho = 1460$).

In order to extend these results, we investigated the kinetics of two other Diels–Alder cycloadditions, consisting of one normal electron demand reaction (iso-

prene + methyl acrylate) (reaction B) and one inverse electron demand reaction (hexachlorocyclopentadiene + styrene) (reaction C) (Scheme 1).

According to Fig. 1, there is a minimum for ρ (in $CHCl_3$). The kinetic behavior of the four reactions resembles the results reported for the Diels–Alder cycloaddition between *N*-ethylmaleimide and 9-hydroxymethylanthracene.[9] For the latter reaction, the minimum is even more pronounced owing to the extremely low solubility of both reactants in perfluorohexane, hence resulting in enforced fluorophobic interactions.

Dependence of ΔV^* on solvent

As outlined in the Introduction, solvophobic interactions affect ΔV^*. In a previous study, we showed how ΔV_m^* followed Eqn. (2).[14] The situation can be rather complex if the medium is water or a water-like solvent. Different activation volume terms are possibly involved which act in divergent ways during the progression of the reaction towards the transition state. In these media ΔV_ϕ^* itself must acknowledge the volume expansion due to the decrease of hydrophobic interactions and the volume shrinkage ascribed to the promotion of hydrogen bonding by pressure. It is expected that the activation volumes determined for reactions carried out in fluorophobic media would be simpler to interpret as ΔV_ϕ^* should be exclusively ascribed to solvophobic interactions. Accordingly, we followed the kinetics of the reactions described in the first part of the paper in the 0–100 MPa pressure range (Table 2) using perfluorohexane as the medium.

The ΔV^* values were compared with those previously reported for the same reactions in other media[14,15] (Table 3). The results are instructive. Overall, one can distinguish three trends (within uncertainty limits):

1. The conjugate addition of *tert*-butylamine (reaction D) conforming to the expected electrostriction shows a regular trend, e.g. a strong increase in ΔV^* with increasing polarity of the medium. $\Delta V^* = -65\ cm^3mol^{-1}$ in C_6F_{14}, which is the least polar medium (for a thorough description of electrostriction

Table 2. Kinetic pressure effect on reactions A–D in perfluorohexane[a]

Pressure (MPa)	A (303.5 K)	B (335.2 K)	C (323.3 K)	D (317.2 K)
0.1	2.62×10^{-5}	2.80×10^{-6}	2.32×10^{-5}	1.78×10^{-5}
25	2.95	3.85	3.11	3.38
35	3.74	4.35	3.41	3.85
50	4.10	5.15	4.27	5.23
60	—	—	—	6.28
75	4.22	6.62	4.85	8.33
100	—	8.65	6.47	—
$(\Delta V^*)_T$ (cm^3mol^{-1})	-27	-36	-32	-65

[a] k (in $dm^3\ mol^{-1}\ s^{-1}$).
[b] Precision of ΔV^* values is estimated to be $\pm 1.5\ cm^3mol^{-1}$ for Diels–Alder cycloadditions and 10% in reaction D.

Table 3. Dependence of the activation volume ΔV_T^* on solubility parameter δ of the medium (cm^3 mol^{-1})

Medium	δ (cal cm^3)$^{-1/2}$	A (303.5 K)	B (335.2 K)	C (323.3 K)	D (317.2 K)
C$_6$F$_{14}$	5.9	−27	−36	−32	−65
CHCl$_3$	9.27	−39	−39	−35	−55
C$_2$H$_5$OH	12.7	−36	nd	nd	nd
CH$_3$OH	14.4	nd	−38	−33	−35
HCONH$_2$	14.6	−33	nd	nd	−23
H$_2$O	23.39	nd	−37	−28	−25

phenomena, see Ref. 17). However, considering also the results detailed in Table 1, ΔV^* should contain a volume term due to fluorophobic interactions. This volume is probably low, masked by the very negative value for ΔV^*.

2. The Diels–Alder reaction between isoprene and methyl acrylate (reaction B) is characterized by a quasi insensitivity of ΔV^* towards medium polarity. This is in line with an earlier observation explained by equally matched volume effects along the reaction coordinate.[14]

3. Two Diels–Alder reactions (reactions A and C) exhibit a maximum in the ΔV^* diagram. For both reactions fluorophobic interactions should be relatively important leading to $\Delta V_\phi^* > 0$, thereby increasing ΔV^*. The maximum is observed in weakly polar solvents such as CHCl$_3$.

Application to high-pressure organic synthesis

Remembering the beneficial kinetic effect of hydrophobic interactions, fluorophobic activation of organic reactions could be a means to overcome difficult syntheses. Considering the results detailed above, the kinetics of the multiactivation process (pressure + solvophobic activation) should be regarded as a compromise between (i) enhanced rate constant in perfluorohexane vs organic solvents at ambient pressure, and (ii) reduced sensitivity to pressure for isopolar reactions making ΔV_T^* less negative in C$_6$F$_{14}$ than in other solvents of low polarity.

We examined several types of reactions which occur sluggishly or not at all under normal conditions (Diels–Alder, Michael-like and Passerini reactions) (Scheme 2). Table 4 reports the results. It should be pointed out that the yields reported may change on varying the reagent concentrations, owing to the heterogeneous, even biphasic system, obtained by mixing the reagents with the fluorous medium.

According to Table 4, for each reaction, operation in perfluorohexane improves the yield, although modestly when compared with a solubilizing organic medium. The improvement can certainly be ascribed fully or partly to fluorophobic interactions. An interesting result is displayed in entry 1 (R = CH$_3$). The addition of methyl vinyl

Entry 1

Entry 2
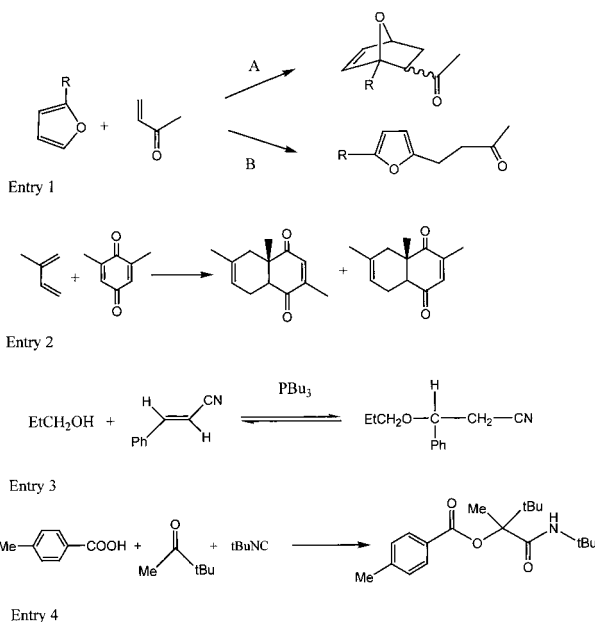
Entry 3

Entry 4

Scheme 2.

Table 4. High-pressure (300 MPa) synthesis in C$_6$F$_{14}$ [a]

Entry	Medium	Type	Yield (%)	Ref.
1 (R = H)[b]	CHCl$_3$	Diels–Alder	17	18
	C$_6$F$_{14}$	d° (idem)	40	
1 (R = CH$_3$)[c]	CHCl$_3$	Michael-like	16	17,19,20
	C$_6$F$_{14}$	Diels–Alder	32	
2	Acetone	Diels–Alder[d]	8[e]	21
	C$_6$F$_{14}$	d° (idem)	13[e]	
3	Propanol	Michael-like[f]	13	22
	C$_6$F$_{14}$	d° (idem)	30	
4	Pinacolone	Passerini[g]	13	23
	C$_6$F$_{14}$	d° (idem)	40	

[a] Total volume 2.5 ml. No reaction in the non-fluorous medium at 0.1 MPa under the conditions used.
[b] Furan 1.37 mmol, vinyl ketone 1.2 mmol, 30 °C, 16 h.
[c] Methylfuran 1.0 mmol, vinyl ketone 0.9 mmol, 30 °C, 16 h.
[d] Isoprene 0.75 mmol, 2,6-dimethylbenzoquinone 0.30 mmol, 20 °C, 24 h.
[e] The ratio of the two regioisomers (about 1:1) does not change with the medium.
[f] Cinnamonitrile 1.8 mmol, propanol 2.0 mmol, P(C$_4$H$_9$)$_3$ 0.3 mmol, 50 °C, 24 h.
[g] Benzoic acid 0.45 mmol, ketone 0.40 mmol, *tert*-butyl isocyanide 0.50 mmol, 25 °C, 16.5 h.

Table 5. High-pressure (300 MPa) synthesis in solvophobic media[a]

Reaction	Medium	Yield (%)	Endo (%)	Selectivity (%)[b]
Entry 1 (R = H)	Water	87	61	100
	Formamide	97	60	100
	Ethylene glycol	86	61	100
	Perfluorohexane	40	76	100
Entry 1 (R = CH$_3$)	Water	72	—	0
	Formamide	60	53	80
	Ethylene glycol	70	47	35
	Perfluorohexane	32	48	95
Entry 4 (Passerini reaction)	Water	2		
	Ethylene glycol	0		
	Perfluorohexane	30		

[a] Conditions as in Table 4.
[b] Chemoselectivity with respect to cycloaddition.

ketone to 2-methylfuran can proceed according to two different pathways: [4 + 2] cycloaddition (pathway A)[19] or/and Michael-like addition (pathway B)[17,20] (Scheme 2). The reaction in water or water-like solvents occurs mostly (65–100%) according to pathway B, whereas the situation is reversed in the fluorous medium (see Table 5).

We compared the yields obtained in different solvophobic media (Table 5). The furan Diels–Alder reaction (entry 1, R = H) proceeds chemoselectively in all solvophobic media affording endo and exo cycloadducts. This is a difficult reaction which occurs at ambient pressure only under adequate catalytic activation.[21] At 300 MPa the yields range from modest to excellent. In this reaction, water and water-like media are more appropriate than perfluorohexane. The endo preference is higher in the latter owing to two factors, low polarity and the solvophobic effect.[24] The methylfuran Diels–Alder reaction (entry 1, R = CH$_3$), however, is better performed in the fluorous medium since the chemoselectivity regarding the cycloaddition is highest whereas only pathway B is followed in water. This is ascribed to the negative electrostatic potential developed around the oxygen atom in methylfuran which is enhanced in water.[25] The selectivity results in ethylene glycol and formamide may be related to small quantities of water whereas the perfluorous compound is a highly demixing system.

At variance, the Passerini multicomponent reaction described in entry 4 is a highly sterically hindered reaction.[23] It does not proceed in water and ethylene glycol at 300 MPa. Perfluorohexane is the medium of choice, making the multiactivation method as a useful tool for the synthesis of sterically congested Passerini products which could be of real interest as bioactive substances.[26]

EXPERIMENTAL

Kinetic determinations

Isoprene, styrene, methyl acrylate, methyl vinyl ketone and acrylonitrile were distilled before use. Other reagents were used as received. Solvents were dried. Kinetic measurements were performed as follows. Weighed reagents and internal standard (1,2,3-trimethoxybenzene or bibenzyl, depending on the reaction) were introduced in PTFE tubes of large volume (15 ml) for the runs in perfluorohexane. In order to obtain homogeneous values of rate constants, the concentration of substrates was chosen low enough (about 2×10^{-3} mol dm^{-3}). For runs in the other solvents, 2.5 ml tubes were used. After completing the residual volume with the solvent, the tube was closed and vigorously shaken for about 30 s before introduction into a thermostated ($\pm 0.1\,°C$) high-pressure vessel. After reaction, the non-fluorous solvents were removed in vacuo, whereas the fluorous medium was easily separated from the biphasic system and re-used in subsequent runs. The residue was then analyzed by ^{1}H NMR spectroscopy (300 MHz). The kinetic data were reproducible to better than 5% (runs in the fluorous medium) and 2–3% (runs in the other solvents).

Activation volumes were determined in two ways: (i) from the initial slope of the plot of log k against pressure and (ii) from derivatization of the polynomial log $k = a + bP + cP^2$.

Synthetic runs

The synthetic runs reported in Tables 4 and 5 were carried out in the same way as those described in Refs 17–23.

CONCLUSION

Fluorophobic effects are demonstrated in Diels–Alder reactions and conjugate additions of amines to acrylic compounds. Their intensity is lower than for other solvophobic media such as water and water-like solvents. The pressure effect in these reactions carried out in

perfluorohexane is in line with the low polarity and the magnitude of the solvophobicity of the medium. The considerable promotion by pressure of the conjugate addition in the fluorous medium must be ascribed mainly to electrostriction effects and, only partly, to fluorophobic interactions. The activation volume is less negative for Diels–Alder reactions because fluorophobic interactions are decreased when the pressure is increased. However, despite the lower sensitivity to pressure, many reactions may be activated when they are carried out in perfluorohexane at 300 MPa, particularly hetero-Diels–Alder reactions involving furans for which the chemo- or/and stereoselectivity is improved. It might be of interest to explore the synthetic field in more detail by increasing the number of reactions possibly affected by fluorophobic interactions.

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