Kinetic Studies on the Rearrangement of Diels–Alder Adducts of Activated Benzoquinones with (*E*)-1-trimethylsiloxybuta-1,3-diene

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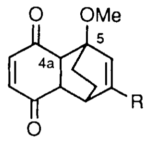
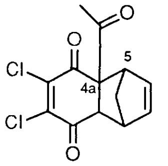
The acid-induced rearrangement of the 4a-derivatives of 4a,5-*trans*-4a,8a-*cis*-5-trimethylsiloxy-4a,5,8,8a-tetrahydro-1,4-naphthoquinones **4–6** in dioxane–water and THF–water solutions is the subject of a kinetic study. On the basis of spectrophotometric evidence, the incursion of 5-hydroxy-tetrahydronaphthalene-1,4-dione and arylcrotonaldehyde type intermediates in formation of the benzofuran from adducts **4–6**, is proposed. The effects on the reactions of the solvent composition, temperature, hydrochloric acid concentration, and substituent nature in the adducts are discussed. The results are rationalized and a schematic representation is provided.

There are reported examples of the rearrangement of Diels–Alder adducts which involve the selective cleavage of one of the two carbon–carbon bonds generated in the cycloaddition. Although this rearrangement has not been extensively utilized in organic synthesis, it has been successfully used in the synthesis of naturally occurring pyranoquinones,[1,2] in the construction of the skeleton of Amarylidaceae alkaloids[3] and in the synthesis of aromatic steroids.[4]

Birch *et al.*[5] reported the first example of this rearrangement in the adducts **1** and **2**, under acidic conditions, to afford dibenzofuran derivatives *via* the 4a,5-bond fission. Bruce *et al.*[6] reported the formation of similar dihydrobenzofurans by thermolysis of adduct **3** in benzene and acetic acid solutions, which also involves the selective 4a,5-bond cleavage. According to the mechanism proposed for this carbon–carbon cleavage,[5,6] the methoxy and acetyl groups in the adducts **1–3** favour the bond rupture by stabilization of the ionic intermediates.



1 R = H
2 R = OMe



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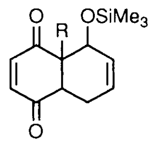
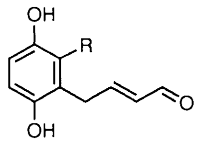
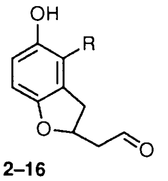
We have recently reported[7,8] that adducts **4–9** prepared by [4 + 2] cycloaddition of activated benzoquinones with (*E*)-1-trimethylsiloxybuta-1,3-diene,[9] undergo a facile rearrangement, under acidic conditions, to afford the arylcrotonaldehydes **10**, **11** and the dihydrobenzofurans **12–16**. A smooth cyclisation of arylcrotonaldehyde **10** to dihydrobenzofuran **13** under acid conditions was also observed. This synthetic evidence[7] and the formation of alcohols **17** and **18** from their corresponding adducts **7** and **8** indicate that a probable initial step of these rearrangements is hydrolysis of the silyl ethers **4–9** to afford the corresponding alcohols, which through a 4a,5 carbon–carbon cleavage rearrange to dihydrobenzofuran derivatives *via* arylcrotonaldehyde intermediates. Probably the absence of the alcohol intermediates such as **17** and **18** in the rearrangement of the adducts **4–6**, is due to the high reactivity of these intermediates, under the experimental conditions, to a 4a,5 carbon–carbon cleavage. In this paper we report a kinetic study of the acid-induced rearrangement of Diels–Alder adducts **4–6** in order to shed more light on the mechanism of this useful rearrangement.



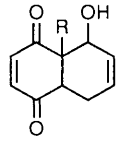
4–9



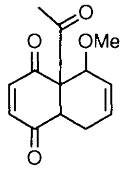
10, 11, 19



12–16



17,18



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	R
4, 12, 19	COMe
5, 10, 13	CHO
6, 11	CN
7, 14, 17	CO_2Me
8, 15, 18	NO_2
9, 16	COCH=CHPh

Experimental

HPLC analyses were performed in a Knauer Model 64 pump with a C-8 column, methanol–water, 70:30 v/v as eluent in the isocratic mode; flow rate, 1 cm^3 min^{-1}; UV detector, Perkin-Elmer LC-15.

The adducts **4–6** and products **10–12** were prepared according to the reported method.[8] Dioxane (Dx), tetrahydrofuran (THF) and hydrochloric acid were reagent grade. Substrate and hydrochloric acid solutions were prepared daily using freshly distilled water and the corresponding solvent.

Kinetic Measurements.—Spectrophotometric cells containing 2.5 cm^3 of hydrochloric acid in the appropriate solvent mixture

Table 1 Pseudo-first-order rate constants (k_{obs}) for the reactions of **5** and **6** in THF–water[a] and dioxane–water[a] solution under different experimental conditions

	$10^3\ k_{obs}/s^{-1}$							
	5				**6**			
	THF–water			Dx–water	THF–water			Dx–water
10^2[HCl]/mol dm^{-3}	25 °C	35 °C	45 °C	25 °C	25 °C	35 °C	45 °C	25 °C
0.50	—	—	—	—	0.174	0.275	0.522	0.205
1.0	0.857	1.95	3.28	1.86	0.246	0.537	0.940	0.319
1.5	—	—	—	—	0.331	0.754	1.19	0.375
2.0	—	—	—	—	0.383	—	1.62	0.398
2.5	2.11	4.74	8.56	3.83	0.408	—	—	0.411
4.0	3.20	6.49	12.1	5.54	0.442	—	2.44	0.425
5.0	4.09	7.80	15.0	6.39	0.466	1.04	2.55	0.429
10	7.15	14.2	26.9	8.39	0.492	1.29	—	0.411
15	9.07	18.7	34.7	9.95	0.536	1.44	3.50	0.419
20	11.0	21.4	—	10.6	0.571	1.51	3.69	0.430
25	12.9	26.2	55.6	10.6	—	—	—	—
30	13.9	27.8	58.1	10.8	0.604	1.62	3.95	—
40	—	29.6	67.3	—	—	—	—	—
45	15.5	—	—	—	—	—	—	—
70	18.8	36.5	—	—	—	—	—	—
100	19.5	—	—	—	—	—	—	—

[a] 11.1 mol dm^{-3} in water.

Table 2 Effect of water on the pseudo-first-order rate constants (k_{obs}) of the reactions **5** and **6** at 25 °C and [HCl] = 0.07 mol dm^{-3}

	$10^4\ k_{obs}/s^{-1}$			
	5		**6**	
[H_2O]/mol dm^{-3}	THF	Dx	THF	Dx
11.1	56.5[a]	74.7[a]	5.15[a]	4.42[a]
7.22	40.7	54.4	3.26	2.90
6.11	35.8	42.4	2.95	2.46
5.00	31.6	34.5	2.72	2.20
3.88	28.2	28.0	2.38	2.01
1.94	18.8	15.2	—	—

[a] Calculated with eqn. (4) with the values of k_1 and K from Table 4.

Table 3 Pseudo-first-order rate constants for the first (k_{1obs}) and second (k_{2obs}) reaction of **4** in THF–water (11.1 mol dm^{-3} in water) solution under different experimental conditions

	$10^4\ k_{1obs}/s^{-1}$			$10^4\ k_{2obs}/s^{-1}$		
[HCl]/mol dm^{-3}	25 °C	35 °C	45 °C	25 °C	35 °C	45 °C
0.05	4.80	13.4	26.5	—	1.84	4.20
0.10	5.82	17.7	34.7	1.25	3.25	10.3
0.20	7.36	22.9	48.9	2.44	5.80	20.9
0.30	8.22	29.4	53.0	3.41	7.89	24.5
0.40	8.30	35.1	54.6	3.83	9.78	28.3
0.50	—	35.3	56.6	—	11.2	—
0.60	8.90	35.5	—	3.95	11.6	31.5

were placed in the thermostatted cell holder of a Perkin-Elmer Lambda 3 spectrophotometer. After thermal equilibration a substrate stock solution (10 mm^3) was injected into the cell to give an initial substrate concentration of (1–2) × 10^{-4} mol dm^{-3}. The reactions were studied by monitoring the absorbance increase at λ = 410 and 325 nm for the **5** and **6** rearrangement, respectively (corresponding to the arylcrotonaldehydes **10** and **11**, respectively). In the case of the rearrangement of **4**, 280–450 nm spectra were recorded at different times, and the kinetics measured at 325 and 370 nm.

In all cases under hydrochloric acid excess, pseudo-first-order rate constants (k_{1obs} and k_{2obs} for the reactions of **4** and k_{obs} for the rearrangement reactions of **5** and **6**) were obtained, determined as slopes of $\log(A_\infty - A_t)$ *vs.* time plots, where A_∞ and A_t are the absorbances at 'infinity' and 't' times, respectively. The experimental conditions of the kinetics and the observed rate constants are shown in Tables 1–3. The activation parameters were obtained from Eyring plots.

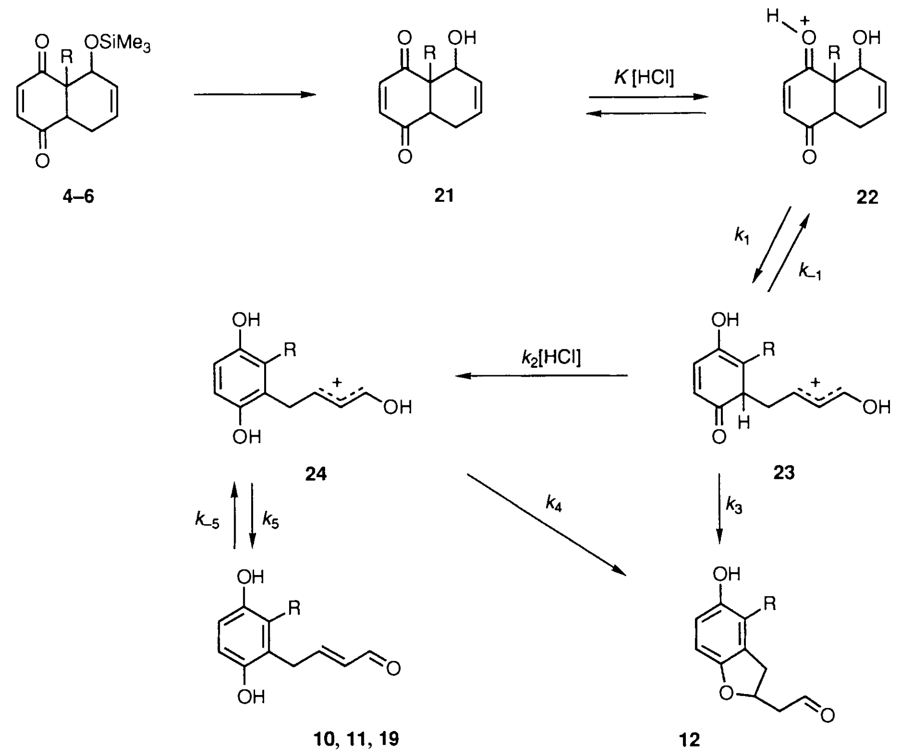
Results and Discussion

The spectrophotometric and HPLC analyses of the reaction mixtures, which were obtained by treatment of compounds **4–6** with hydrochloric acid in aqueous tetrahydrofuran and dioxane solutions, show the presence of the corresponding rearrangement products. These substances were identified in the mixtures by comparison with authentic samples of the dihydrobenzofuran **12** and arylcrotonaldehydes **10** and **11**.

The spectrophotometric analysis of the rearrangement of adduct **4** indicates that its conversion to the furan **12** occurs through, at least, one intermediate. In fact, the spectra recorded at short reaction times showed the appearance of a band at 325 nm followed by the appearance of a second band at 370 nm with the formation of an isosbestic point at 342 nm. The wavelength at 370 nm corresponds to the absorption of dihydrobenzofuran chromophore of **12**.

Taking into account our previous results on the isolation of the stable arylcrotonaldehyde **10** generated from adduct **5** and its smooth cyclisation to benzofuran **13** under acid conditions, we can assume that the detected absorption band at 325 nm belongs to arylcrotonaldehyde **19**. The high reactivity to cyclisation of the arylcrotonaldehyde **19** is probably related to the steric effect of the methyl of the chelated acetyl group. This effect would be expected to be less important in the stable arylcrotonaldehyde **10** due to the smaller size of the chelated formyl group. Interestingly, we have not detected benzofuran compounds in the rearrangement of adduct **6**. In this case the high stability of the arylcrotonaldehyde **11** is probably due to the low steric interaction between the cyano and oxobutenyl substituents.

It is noteworthy that the spectrophotometric analyses



Scheme 1

showed induction times in the rearrangement of the adducts studied, which are probably related to the participation of intermediates in a step prior to the 4a,5 carbon–carbon cleavage. Taking into account the reluctance of adduct **20** to rearrange, it is reasonable to assume that the induction times are related to the participation of alcohol intermediates, which in the case of the acid treatment of the adducts **7** and **8** are stable compounds (**17** and **18**) and only undergo rearrangement by further treatment under more acidic conditions.[7] Since the kinetics of the examined reactions were measured after the induction times, we have assumed that the parameters obtained are related to the 4a,5 carbon–carbon bond fission in the alcohol intermediate generated from the respective adducts.

Table 1 summarizes the experimental results for the reactions of **5** and **6**. At low acid concentration the values of k_{obs} increase with increasing acid concentration, but at higher concentrations reach a limiting value and plots of $1/k_{obs}$ *vs.* 1/[HCl] are linear.

The reactions outlined in Scheme 1 show the probable pathway for the rearrangement mechanism of adducts **4–6**. In this, the adducts undergo hydrolysis to the corresponding alcohols **21**; the protonated alcohols **22**, lead by way of ring opening to the cation intermediate **23** that may undergo deprotonation–enolization reactions to give the corresponding arylcrotonaldehyde *via* the intermediate **24**. This route also considers that the dihydrobenzofurans can be generated from cation **23** and from arylcrotonaldehyde intermediates *via* **24**, by means of a 5-*exo-trig* cyclisation.[10]

As was mentioned above, the reaction of substrates **5** and **6** leads to the formation of the corresponding arylcrotonaldehydes **10** and **11** as the only products; therefore in order to explain the kinetic results, all the reactions leading to dihydrobenzofurans must be disregarded.

With this and the assumption that the hydrolysis reaction was completed (the measurements were performed after the induction times), eqn. (1) represents the model of the rearrangement reactions derived from Scheme 1 when R = CHO or CN. Assuming the steady-state condition for **23** and **24**, eqn. (2) can be derived. There are two possibilities to transform eqn. (2) into an equation that is in accord with experimental behaviour.

$$\mathbf{21} \underset{}{\overset{K[\mathrm{HCl}]}{\rightleftharpoons}} \mathbf{22} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{23} \xrightarrow{k_2[\mathrm{HCl}]} \mathbf{24} \xrightarrow{\text{fast}} \mathbf{10, 11} \quad (1)$$

$$k_{obs} = k_1k_2K[\mathrm{HCl}]^2/\{(K[\mathrm{HCl}] + 1)(k_{-1} + k_2[\mathrm{HCl}])\} \quad (2)$$

(1) If the protonation equilibria of the alcohols are fully displaced towards **22** ($K[\mathrm{HCl}] \gg 1$) over the range of hydrochloric acid concentration used in this study, eqn. (3) is obtained. From the slope and intercept of the plots of k_{obs}^{-1} *vs.* $[\mathrm{HCl}]^{-1}$ the initial values of k_1 and k_2/k_{-1} can be determined.

$$k_{obs} = k_1k_2[\mathrm{HCl}](k_{-1} + k_2[\mathrm{HCl}])^{-1} \quad (3)$$

Nevertheless we have disregarded the possibility that equilibria **21** $\rightleftharpoons$ **22** is fully displaced toward **22** due to the expected low basicities of **21** (the protonation p*K* of the cyclohex-2-enone is -3.60[11] and for some α,β-unsaturated ketosteroids the value ranges from -2.8 to -4.7).[12]

(2) On the assumption that the enolization step is very much quicker than the intramolecular trapping of the protonated aldehyde ($k_2[\mathrm{HCl}] \gg k_{-1}$), the ring opening is the rate determining step, and eqn. (4) is obtained. From the slope and intercept of the plots of k_{obs}^{-1} *vs.* $[\mathrm{HCl}]^{-1}$ the initial values of k_1 and K can be determined, which were adjusted by iterative fitting of eqn. (4) and the experimental plots of k_{obs} *vs.* [HCl]. Figs. 1 and 2 show the agreement between experimental and calculated k_{obs}. Table 4 summarizes the adjusted k_1 and K values obtained for these reactions.

$$k_{obs} = k_1K[\mathrm{HCl}](K[\mathrm{HCl}] + 1)^{-1} \quad (4)$$

Table 4 shows that the rate constant k_1 for the carbon–carbon cleavage is greater in THF–water than in dioxane–water mixture. This fact indicates that the transition state for the ring opening is more polar than the carbocation **22**. It is noteworthy

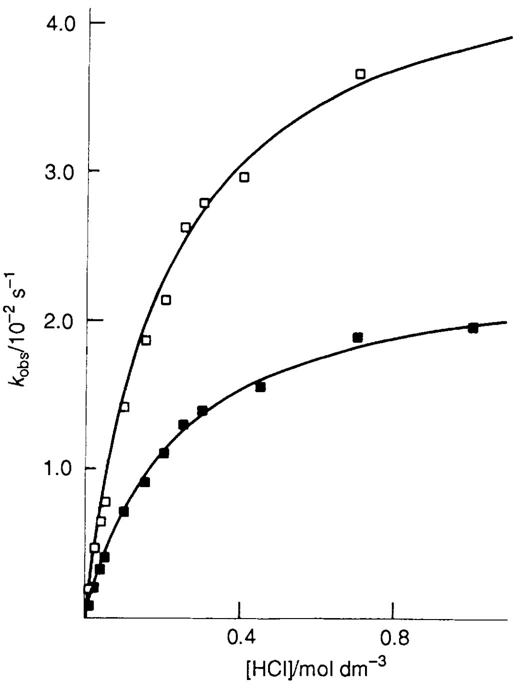


Fig. 1 Dependence of the observed rate constants (k_{obs}) on hydrochloric acid concentration for the reaction of **5** in THF–water (11.1 mol dm^{-3} in water) solution at 25 °C (■) and 30 °C (□). The lines are calculated with eqn. (4) with the values of k_1 and K from Table 4; the points are experimental.

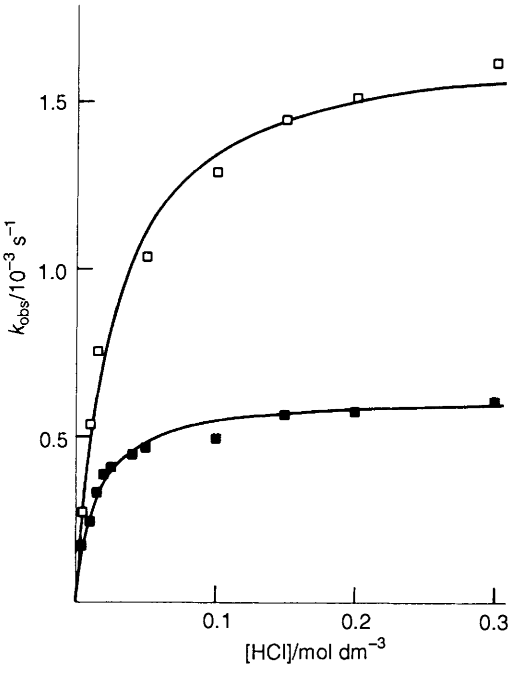


Fig. 2 Dependence of the observed rate constants (k_{obs}) on hydrochloric acid concentration for the reaction of **6** in THF–water (11.1 mol dm^{-3} in water) solution at 25 °C (■) and 30 °C (□). The lines are calculated with eqn. (4) with the values of k_1 and K from Table 4; the points are experimental.

that in both solvent mixtures k_1 is about 30 times greater for **5** than for **6**. The proton of the hydroxylic group at the 2-position in compounds **10** and **11** resonates at δ 11.20 and 9.40–8.50 respectively,[8] which indicates a better chelating ability for the formyl group in these compounds. Taking into account the structural analogy of **10** and **11** with **23**, probably the greater reactivity of **5** than **6** is due to the differences on chelating ability which renders a more stable transition state for the reaction of **22** (R = CHO).

Table 4 k_1 and K values for reaction of **4**, **5** and **6** in THF–water[a] and dioxane–water[a] at different temperatures

Substrate	Co-solvent	T/°C	10^3k_1/s^{-1}	K/dm^3 mol^{-1}
4	THF	25	0.92	21
4	THF	35	4.10	9
4	THF	45	6.40	14
5	THF	25	24.0	4.4
5	THF	35	46.5	4.8
5	THF	45	147	2.3
5	Dx	25	12.8	20
6	THF	25	0.62	70
6	THF	35	1.70	38
6	THF	45	4.40	30
6	Dx	25	0.47	230

[a] 11.1 mol dm^{-3} in water.

On the other hand, in both solvent mixtures, the K values for **6** are greater than those for **5** and for each substrate the K values are greater in dioxane–water than in THF–water mixtures in accord with what is expected.

The change from dioxane–water to THF–water favours the rearrangement reaction (the k_1 value increases); but this change decreases the K. In order to shed more light on the solvent effect, the reactions were studied in dioxane and THF with different water contents. Table 2 shows that, for the same [HCl], in both solvents, k_{obs} increases as water concentration increases, indicating that the rearrangement reaction is favoured in the more polar media. This suggests a greater effect on k_1 than on K. It is noteworthy that for the same water content, k_{obs} for **6** is larger in THF; but at the greater water content k_{obs} for **5** is larger in dioxane. This apparent discrepancy can be explained because in some cases k_{obs} is near the limiting k_1 (*e.g.* the reaction of **6** in dioxane–water 11.1 mol dm^{-3} in water).

In Table 3 are summarized the experimental results for the reaction of **4**. Taking into account that the empirical equation of the first reaction of **4** is equal to those of **5** and **6** we also use eqns. (1) and (4) for the former reaction. Table 4 shows the k_1 and K values obtained at the different temperatures.

On the other hand, considering the reaction from arylcrotonaldehyde **19** to dihydrobenzofuran **12**, the reaction Scheme 1 reduces to eqn. (5) and eqn. (6) can be derived. Table 5

$$\mathbf{19} \overset{K_{-5}}{\rightleftharpoons} \mathbf{24} \xrightarrow{k_4} \mathbf{12} \qquad (5)$$

$$k_{2obs} = k_4K_{-5}[\mathrm{HCl}](1 + K_{-5}[\mathrm{HCl}])^{-1} \qquad (6)$$

shows the k_4 and K_{-5} ($K_{-5} = k_{-5}/k_5$) values obtained by iterative fitting of the experimental results of Table 3 to eqn. (6), using the initial values obtained from k_{2obs}^{-1} *vs.* [HCl]$^{-1}$ plots. From the values of k_1 at the different temperatures (Table 4), the following activation parameters were obtained: $\Delta H^{\ddagger}$ of 75 ± 25, 60 ± 4 and 74 ± 3 kJ mol^{-1} and $\Delta S^{\ddagger}$ of −50 ± 80, −70 ± 20 and −56 ± 3 J K^{-1} mol^{-1} for **4**, **5** and **6** respectively.

Since the step above is unimolecular (ring opening), the activation entropy found seems larger than expected.[13] In solution it is difficult to interpret the entropy changes of a reaction since these are dominated by solvent effects, especially in water and other polar solvents.[14–17] The negative values indicate that solvation is important in the formation of the transition state of the opening step, suggesting a transition state more polar than reactants.

Both $\Delta S^{\ddagger}$ and the role of solvent points out that the reaction

Table 5 k_4 and K_{-5} values for the reaction of **4** in THF–water (11.1 mol dm^{-3} in water) at different temperatures

T/°C	K_{-5}/mol^{-1} dm^3	10^4k_4/s^{-1}
25	2	8
35	1.5	25
45	4.8	42

may proceed through rather polar transition states. In this work the ionic strength was not maintained constant and probably the salt additions may affect the kinetic data to some extent;* nevertheless in the reactions of **5** and **6** in dioxane–water (Table 1) the effect appears not to be very important because a 'plateau' is obtained with a range of [HCl] of about 0.2–0.3 mol dm^{-3} for **5** and 0.04–0.2 mol dm^{-3} for **6**.

Since in the reaction of **4** the initial formation of the kinetically favoured product, probably arylcrotonaldehyde **19**, is followed by a slower second reaction to the thermodynamically more favoured dihydrobenzofuran **12**, it is also possible that in the reaction of **5** the arylcrotonaldehyde **10** (which appears in this study as final product) cyclises very slowly to dihydrobenzofuran **13** as described.[8]

In conclusion, according to the results obtained in this study on the dependence of some rearrangement reactions on catalyst concentration, solvent polarity, and the nature of the substituents in the adducts, the most probable rearrangement mechanism for the reactions of **4**–**6** is that described by Scheme 1.

Acknowledgements

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