Acid-catalysed aromatization of anthranyl derivatives. A kinetic and thermodynamic study

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The acid-catalysed solvolysis reaction of 9-methoxy-9-methyl-9,10-dihydroanthracene (**2-OMe**) in 50 vol% acetonitrile in water at 25 °C provides the substitution product 9-hydroxy-9-methyl-9,10-dihydroanthracene (**2-OH**) and the elimination product 9-methylanthracene (**3**). The rate-ratio of substitution-to-elimination was measured as $k_S/k_E = 0.93$. The alcohol also undergoes acid-catalysed aromatization to give the thermodynamically favoured product **3**. The reaction enthalpy of this dehydration reaction was measured as $\Delta H = -10.2 \pm 1.0$ kcal mol^{-1}. The corresponding reaction of the secondary alcohol 9-hydroxy-9,10-dihydroanthracene (**1-OH**) has a reaction enthalpy of $\Delta H = -12.3 \pm 0.8$ kcal mol^{-1}. Addition of azide ion (0.25 M) gives rise to a large fraction of azide adduct **2-N$_3$**, which rapidly undergoes solvolysis. The "azide-clock" method yields rate constants for reaction of the carbocation to give alcohol and elimination product of $k_w = 2.2 \times 10^8$ s^{-1} and $k_e = 2.4 \times 10^8$ s^{-1}, respectively. The thermodynamic stability of the carbocation was estimated as $pK_R = -9.1$. The alkene 9-methylene-9,10-dihydroanthracene (**4**) undergoes a slow acid-catalysed aromatization to give **3**; no competing formation of **2-OH** was observed.
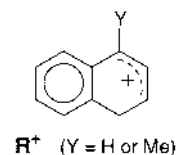
Introduction

We are interested in the mechanistic details of solvolysis reactions, *e.g.* the factors that govern the competition between substitution and elimination. Relatively stable, solvent-equilibrated, carbocations generally yield predominantly substitution in nucleophilic solvents such as water.[1–3] The reason is usually that the alcohol is thermodynamically more stable than the alkene and this is reflected in the relative energies of the transition states of the two competing reactions of the carbocationic intermediate.

Recently, results were reported on systems which provide nearly exclusively the elimination product despite the intermediacy of the resonance-stabilized benzallylic carbocations (**R$^+$**).[4,5] It was clearly shown that the very large predominance for dehydronation is due to the large thermodynamic stabilities of the aromatic products and not to an unusually slow reaction of the carbocation with water or added nucleophiles. Very large reaction enthalpies of $\Delta H = -23.7$ kcal mol^{-1} and $\Delta H = -21.7$ kcal mol^{-1}, respectively, were reported for the acid-catalysed dehydration reactions of the alcohols **A-OH** and **B-OH** (Scheme 1).[4,5]

R$^+$ (Y = H or Me)

reported results for the reactions of **A-OMe** and **B-OMe** (Scheme 1)[4,5] do not support this hypothesis since the former gives traces of alcohol (the rearranged isomer), and **B-OMe**, which provides a thermodynamically less stable alkene, does not give any traces of alcohol. In contrast, Leute and Winstein reported more than 30 years ago that the solvolysis of 9-acetoxy-9,10-dihydroanthracene in 60% acetone in water yields 24% of 9-hydroxy-9,10-dihydroanthracene and 76% of anthracene under kinetic control.[6] However, it is not clear whether the alcohol originates from direct reaction of the initially formed ion pair with solvent water within the solvent cage, or if the product ratio reflects the relative kinetic barriers for addition of water and dehydronation of the solvent-equilibrated carbocation (Scheme 2). We now report on a study of the acid-
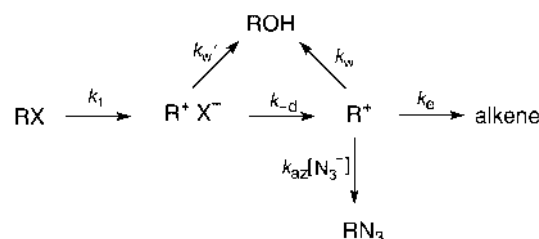
Scheme 1

Scheme 2

catalysed solvolysis of the tertiary anthranyl derivatives **2-OH** and **2-OMe** (Scheme 3) and the mechanistic details are discussed. These reactions are also of biochemical interest since hydrates of aromatic hydrocarbons have been proposed to be intermediates in the mammalian metabolism of the parent aromatic hydrocarbons.[7]

A major question about this type of aromatization reaction is whether the alcohol formation competes more successfully if the aromatization is thermodynamically less favoured. The

Table 1 Rate constants for the acid-catalysed solvolysis of 9-hydroxy-9-methyl-9,10-dihydroanthracene (**2-OH**) and 9-methoxy-9-methyl-9,10-dihydroanthracene (**2-OMe**) in 50 vol% acetonitrile in water at 25 °C

Substrate[a]	Nucleophile	$10^6 \, k_{obs}/s^{-1}$	$k_H/M^{-1}\,s^{-1}$	k_S/k_E	$k_{N_3}[N_3^-]/k_E$
2-OH[b]		48.7	0.185 (0.181)[c]		
2-OH[d]	0.25 M NaN₃	44.0	0.86		5.3
2-OMe[e]		85.3	0.29	0.93	
2-OMe[d]	0.25 M NaN₃	75.0	1.5		4.8
4[f]		7.8	225×10^{-6}		

[a] Substrate concentration 0.1 mM. [b] 0.1 M MeOCH₂CO₂H buffer, pH 3.58. [c] Rate constant measured with microcalorimetry. [d] 0.25 M NaN₃, 0.25 M HN₃ and 0.25 M NaClO₄, pH 4.29. [e] 0.1 M HOAc buffer, pH 3.53. [f] 0.1 M CF₃CO₂H buffer, pH 1.46.

Scheme 3
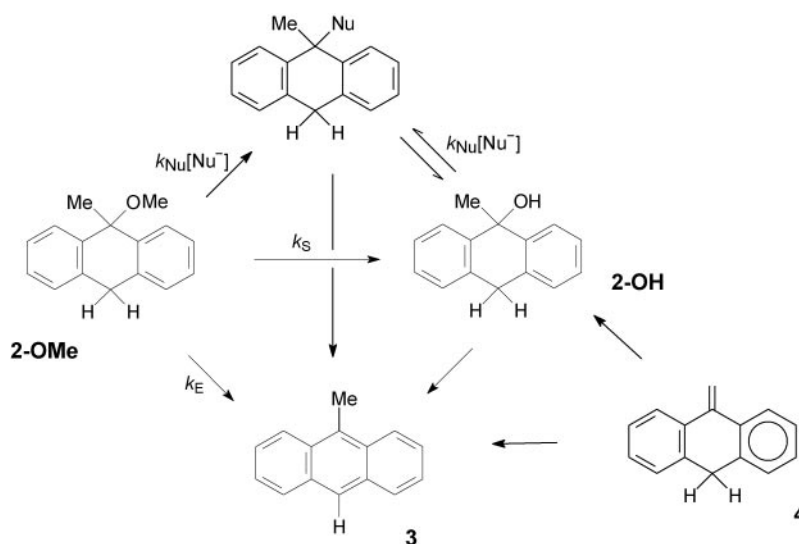
Results

The acid-catalysed solvolysis reaction of 9-methoxy-9-methyl-9,10-dihydroanthracene (**2-OMe**) in 50 vol% acetonitrile in water at 25 °C provides the substitution product 9-hydroxy-9-methyl-9,10-dihydroanthracene (**2-OH**) and the elimination product 9-methylanthracene (**3**) (Scheme 3). The reaction of **2-OH** exclusively provides the elimination product **3**. The much slower acid-catalysed reaction of 9-methylene-9,10-dihydroanthracene (**4**) also exclusively gives the anthracene product **3**. The kinetics of the reactions were studied by a sampling high-performance liquid chromatography procedure, or by following the appearance of 9-methylanthracene as a function of time by UV spectrophotometry. The measured rate constants are presented in Table 1. The separate rate constants (Scheme 3) were derived by a computer simulation of the measured relative concentrations (mol%) *versus* time (see Experimental).

The rate of solvolysis of **2-OMe** does not increase with an increase in formate buffer concentration (up to 0.6 M with 0.50 M NaCl added) in 33% acetonitrile in water, which indicates that the acid catalysis is of specific rather than of general type. A similar behaviour was observed with **2-OH** (Fig. 1), so there is no significant general base catalysis on the dehydronation reaction of the carbocation intermediate.

Addition of azide ion gives rise to the azide substitution product **2-N₃**, but there is no rate increase for **2-OMe** with increasing azide buffer concentration. We therefore conclude that there is no bimolecular substitution reaction with this strong nucleophile. The azide product **2-N₃** is not stable but reacts to give **2-OH** and **3** with a rate constant of ~240 × 10⁻⁶ s⁻¹.

The nucleophilic selectivity toward azide and water is large. It can be expressed as a ratio of second-order rate constants in accord with eqn. (1). The selectivity cannot be obtained directly from the product ratio because of the fast decomposition of the azide product. Instead, k_w is derived from k_e employing eqn. (3). The rate constant for dehydronation of the carbocation
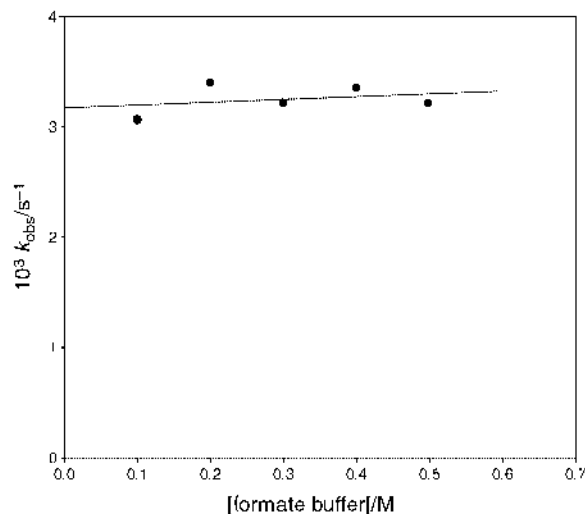

Fig. 1 The rate constant (k_{obs}) for disappearance of **2-OH** as a function of formate buffer concentration in 33.3 vol% acetonitrile in water at pH 3.12 containing 0.50 M NaCl.

intermediate (k_e, Scheme 2) is obtained from the measured rate constants assuming a diffusion rate constant of $k_{N_3} = 5 \times 10^9 \, M^{-1}\,s^{-1}$ [eqn. (2)].

$$k_{N_3}/k_{HOH} = \{(k_{N_3}[N_3^-])/k_S\}/([N_3^-]/[HOH]) \quad (1)$$

$$k_e = \{k_E/(k_{N_3}[N_3^-])\}(k_{N_3}[N_3^-]) \quad (2)$$

$$k_w = (k_S/k_E)k_e \quad (3)$$

Calorimetric measurements

The acid-catalyzed reactions of **1-OH** and **2-OH** have also been

Table 2 Heat of reactions for the dehydration of **1-OH** and **2-OH**, and of 1-hydroxy-1-methyl-1,4-dihydronaphthalene (**B-OH**), 1-hydroxy-1,4-dihydronaphthalene (**A-OH**), and 2-hydroxy-1,2-dihydronaphthalene (**C-OH**) at 25 °C

Substrate	Solvent	$P_0{}^a$/μW	ΔH/kcal mol^{-1}
1-OH[b]	MeCN–H$_2$O 1 : 1	11	-12.3 ± 0.8[c]
2-OH[d]	MeCN–H$_2$O 1 : 1	1.4	-10.2 ± 1.0[e]
B-OH[f]	Glycerol–H$_2$O 1 : 3	27.5	-21.7 ± 0.9
A-OH[g]	Glycerol–H$_2$O 1 : 3	20.0	-23.7 ± 0.4
C-OH[g]	Glycerol–H$_2$O 1 : 3	12.0	-18.4 ± 0.2

[a] Heat flow at time zero. [b] Substrate concentration 1.0 mM; 0.1 M 2-methoxyacetate buffer, pH 3.58. [c] Standard deviation, average of 9 runs. [d] Substrate concentration 0.27 mM; 0.1 M 2-methoxyacetate buffer, pH 3.58. [e] Standard deviation, average of 4 runs. [f] Ref. 5. [g] Ref. 4.

studied by heat-flow microcalorimetry. The reactions were run in 50 vol% acetonitrile in water. The observed decrease in heat flow after the equilibration period (see Experimental) reflects the pseudo-first-order behaviour of the reaction. The measured rate constants agree with those obtained by the spectrophotometric technique (Table 1). The measured reaction enthalpies are given in Table 2 which also includes the data measured previously for the closely related naphthalene hydrates.

Discussion

The acid-catalysed solvolysis of **2-OMe** is concluded to involve rate-limiting ionization since there is no increase in the rate of reaction in the presence of added azide ion. This is in contrast to the structurally related substrate Ph$_2$(Me)COMe which undergoes a much slower acid-catalysed solvolysis reaction owing to rate-limiting addition of water.[8] Another contributing factor to the higher reactivity of **2-OMe** is the cyclic nature of the carbocation,[9] and probably the development of partial aromaticity in the transition state of the ionization step. The solvolysis of **2-OMe** provides nearly as much elimination as substitution (Table 1). This is not what is usually seen in solvolysis reactions proceeding *via* relatively stable carbocations.[1–3] For example, the structurally related carbocation Ph$_2$(Me)C$^+$ yields predominantly substitution under the same conditions.[8] The reason is concluded to be the large thermodynamic stability of the aromatic elimination product 9-methylanthracene (**3**, Scheme 3) in accord with our previous studies of aromatization reactions. Thus, the extremely large k_E/k_S ratio of approximately 1600 measured for the solvolysis of **A-OMe** in 25 vol% acetonitrile in water has been concluded to be the result of a reduced activation barrier for dehydronation caused by partial aromaticity in the carbocation and not to an unusually slow addition of water.[4]

The rate constant (k_e) for dehydronation of the carbocation to give **3** (Scheme 2) has been measured by the "azide-clock" method assuming that the reaction with azide ion is diffusion-controlled with a rate constant of 5×10^9 M^{-1} s^{-1}.[3,10] Flash-photolysis experiments have shown that carbocations with $k_w > 1 \times 10^5$ s^{-1} react with azide ion in a diffusion-controlled process in aqueous acetonitrile.[10] The rate constant measured in this manner with the ether **2-OMe** is $k_e = 2.4 \times 10^8$ s^{-1}. A similar value, $k_e = 2.2 \times 10^8$ s^{-1}, was measured with the alcohol **2-OH**. The rate constant (k_w) for addition of water to the carbocation could not be obtained in the usual way. It was derived from the measured k_e value (see Results). The value, $k_w = 2.2 \times 10^8$ s^{-1}, is slightly larger than that measured for Ph$_2$(Me)C$^+$, $k_w = 1.7 \times 10^8$ s^{-1}.[8b] An azide molecule is 625 times more reactive than a water molecule toward the carbocation.

The pK_R for the pseudo acid–base equilibrium for cation hydration [eqns. (4) and (5)] is a measure of the thermodynamic

$$\text{R}^+ + \text{H}_2\text{O} \underset{k_H}{\overset{k_w}{\rightleftharpoons}} \text{ROH} + \text{H}^+ \qquad (4)$$
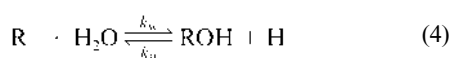
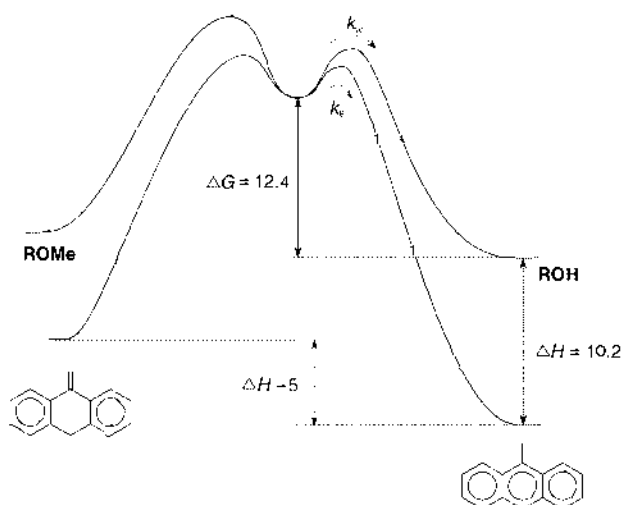$$K_R = k_w/k_H = [\text{ROH}][\text{H}^+]/[\text{R}^+] \qquad (5)$$

Fig. 2 Schematic energy diagram showing activation barriers and thermodynamic parameters (in kcal mol^{-1}).

stability of a carbocation. The measured parameters $k_w = 2.4 \times 10^8$ s^{-1} and $k_H = 0.185$ M^{-1} s^{-1} yields p$K_R = -9.1$ ($\Delta G = 12.4$ kcal mol^{-1}). This value is of the same order of magnitude as that of the 1-(4-methoxyphenyl)ethyl carbocation (p$K_R = -8.6$ in 50% aqueous trifluoroethanol), but which shows a 7000-fold larger substitution-to-elimination ratio.[3]

The reactivity of **2-OH** is much less (173 times) than that of 1-hydroxy-1-methyl-1,4-dihydronaphthalene (**B-OH**), but the rate-ratio of the corresponding ethers is only 77 times. The reason for this difference is that the reaction of the substrate **2-OH**, in contrast to **B-OH**,[5] exhibits significant return. Measured kinetic and thermodynamic parameters for these reactions and for some other aromatization reactions are collected in Table 3. The schematic energy diagram shown in Fig. 2 could be used for predicting some relations between kinetic and thermodynamic parameters. A more stable carbocation, corresponding to a larger (less negative) pK_R, should increase the reaction rates for the ether and the alcohol in accord with the expected close resemblance between the rate-limiting ionization transition state and the carbocation. It should also increase the barrier for addition of water (k_w) to the cation. However, there is not a good correlation between the reactivity, as expressed by the second-order rate constant of the acid-catalysed reaction of the methyl ether, and the pK_R value (Table 3). The table shows only a very limited number of reactions, both secondary and tertiary substrates, and a reasonable correlation may exist for the two separate classes of substrates.

The magnitude of the enthalpy of the aromatization reaction should mainly reflect the stability of the aromatic alkene product. A higher stability should be connected with a more stable carbocation owing to more partial aromatization in the cation and, accordingly, gives rise to larger ionization rates of the substrates (*i.e.*, increase k_H). This effect is not easily seen in the

Table 3 Kinetic and thermodynamic parameters of some aromatization reactions at 25 °C

Substrate	ΔH/kcal mol^{-1}	pK_R	$k_H{}^a$/M^{-1} s^{-1}	$k_S/k_E{}^b$	k_w/s^{-1}	k_e/s^{-1}
2-OH	-10.2	-9.1	0.185	0.9	2.2×10^8	2.4×10^8
1-OH	-12.3	-5.9^g	0.28	0.9	$1.3 \times 10^{7\,g}$	$2.3 \times 10^{7\,g}$
B-OH^c	-20.8	>-4.8	32	<0.003	$<2 \times 10^6$	6×10^8
A-OH^d	-23.7	~-6.6	~2.5	0.0006	$\sim1 \times 10^7$	$\sim1.6 \times 10^{10}$
1,2-benzene hydrate^e	-39.9	-2.4^g	1.7			
4	$\sim-5^f$		225×10^{-6}		(2.2×10^8)	(2.4×10^8)

^{a} In 50 vol% acetonitrile in water. ^{b} Measured with the methyl ethers. ^{c} Ref. 5. ^{d} Ref. 4; data extrapolated from 25 vol% acetonitrile in water. ^{e} Ref. 15. ^{f} Ref. 11. ^{g} In water, ref. 16.

limited amount of recorded data, but the predicted increase in k_e with increase in reaction enthalpy is in accord with the experimental data (Table 3). The effect is not large for the two structurally related compounds 1-methoxy-1-methyl-1,4-dihydronaphthalene (**B-OMe**) and **2-OMe**. Thus, a difference in reaction enthalpy of more than 10 kcal mol^{-1} corresponds to an approximately three-fold increase in k_e.

The absence of an effect of general bases on the reaction rate of **2-OH** is consistent with a very exothermic dehydronation step (k_e) with a very small amount of hydron transfer in the transition state in accord with what has been found previously for the naphthalene-producing solvolysis reactions.[4]

Hydronation of the alkene **4** (Scheme 3) should yield the same carbocation intermediate as the reactions of **2-OMe** and **2-OH**. However, the second-order rate constant for this reaction is approximately 800 times smaller than that of the reaction of **2-OH** (Table 1) and this explains why no trace of **2-OH** is observed during the reaction. Any **2-OH** formed is expected to be converted quickly to **3** under these acidic conditions. The enthalpy of the aromatization of **4** has been measured as 5.1 and 3.4 kcal mol^{-1} with ICR and calorimetry (CCl$_4$), respectively, and calculated as 7.7 kcal mol^{-1}.[11]

Experimental

General procedures

NMR spectra were recorded at 25 °C with a Varian Unity 300 MHz spectrometer. Chemical shifts are indirectly referenced to TMS *via* the solvent signal (chloroform-d_1 7.26 and 77.0 ppm). The high-performance liquid chromatography analyses were carried out with a Hewlett-Packard 1090 liquid chromatograph equipped with a diode-array detector on an Inertsil 5 ODS-2 (3 × 100 mm) reversed-phase column. The mobile phase was a solution of acetonitrile in water. The reactions were studied at constant temperature maintained with a HETO 01 PT 623 thermostat bath kept at 25.00 ± 0.03 °C. A Kontron Uvicon 930 spectrophotometer equipped with an automatic cell changer kept at constant temperature with water from the thermostat bath was used for some of the kinetic studies. The pH was measured using a Radiometer PHM82 pH meter with an Ingold micro glass electrode. The pH values given are those measured before mixing with the organic solvent.

The microcalorimetric experiments were carried out with a dual channel calorimeter (Thermometric Thermal Activity Monitor 2277). The signals were recorded both on a two-channel potentiometric recorder and with a computer.

Materials

Merck silica gel 60 (240–400 mesh) was used for flash chromatography. Diethyl ether and tetrahydrofuran were distilled under nitrogen from sodium and benzophenone. Methanol and acetonitrile were of HPLC quality and HPLC UV gradient quality, respectively. The commercially available 9-methylanthracene (**3**) (99%, Lancaster) was purified by recrystallization from pentane. All other chemicals used for the kinetic

experiments were of reagent grade and used without further purification.

Syntheses

9-Hydroxy-9-methyl-9,10-dihydroanthracene (**2-OH**) was prepared from anthranone and methylmagnesium iodide. Methylation with methyl iodide in dichloromethane in the presence of freshly prepared silver oxide afforded 9-methoxy-9-methyl-9,10-dihydroanthracene (**2-OMe**). The substrates were purified by recrystallization from pentane. Analysis by NMR and HPLC confirmed high purity. 9-Methylene-9,10-dihydroanthracene (**4**) was prepared by lithium aluminium hydride reduction of (9-anthranylmethyl)trimethylammonium chloride.[12]

Kinetics and product studies

HPLC procedure. The reaction solutions were prepared by mixing acetonitrile or methanol with water at room temperature, *ca.* 22 °C. The reactions were initiated by addition of a few microlitres of the substrate dissolved in acetonitrile to a 2 ml HPLC vial containing 1.2 ml of the thermostatted reaction solution to give a final substrate concentration of 0.1–0.2 mM. The reaction flask was sealed with a gas-tight PTFE septum and placed in a thermostatted aluminium block in the HPLC apparatus. At appropriate intervals, samples were automatically injected onto the column and analysed. The rate constants for the disappearance of the substrates were calculated from plots of substrate peak area *versus* time by means of a non-linear regression computer program. Very good pseudo-first-order behaviour was observed for all the reactions studied.

The azide product **2-N₃** was not isolated but identified by its UV spectrum, which is similar to that of **2-OH**. The relative response factors of alcohol (**2-OH**) and 9-methylanthracene (**3**) were determined in a separate experiment. The relative response factor of **2-N₃** at 219 nm was assumed to be the same as that of **2-OH**. The separate rate constants for the reactions (Scheme 3) were evaluated by computer simulation based upon the product composition data, obtained from the HPLC peak areas and the relative response factors and the phenomenological reaction scheme (Scheme 3).

When starting from pure **2-OMe**, the concentrations of **2-OMe**, **2-OH**, and **3** are described by the eqns. (6)–(8) (Scheme 4).[13] An analogous procedure was employed for the reaction of

$$\text{mol\% } \textbf{2-OMe} = a\,e^{-m_1 t} + (100 - a)e^{-m_2 t} \qquad (6)$$

$$\text{mol\% } \textbf{2-OH} = b\,e^{-m_1 t} - b\,e^{-m_2 t} \qquad (7)$$

$$\text{mol\% } \textbf{3} = 100 - \text{mol\% } \textbf{2-OMe} - \text{mol\% } \textbf{2-OH} \qquad (8)$$

Scheme 4
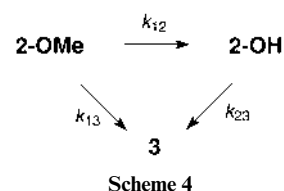
2-OH in the presence of azide ion. The reaction system with **2-OMe** as substrate and with azide ion added is more complex. This system was simulated by neglecting the formation of the small amounts of **2-OH** from **2-OMe** and **2-N₃**.

where
$a = 100 (k_{12} + k_{13} - m_2)/(m_1 - m_2)$
$b = 100 k_{12}/(m_2 - m_1)$
$m_1 = [(k_{12} + k_{13} + k_{21} + k_{23})^2/4 - k_{12}k_{23} - (k_{21} + k_{23})k_{13}]^{1/2} + 1/2(k_{12} + k_{13} + k_{21} + k_{23})$
$m_2 = -[(k_{12} + k_{13} + k_{21} + k_{23})^2/4 - k_{12}k_{23} - (k_{21} + k_{23})k_{13}]^{1/2} + 1/2(k_{12} + k_{13} + k_{21} + k_{23})$

UV Spectrophotometric procedure. The reactions were run in 3 ml standard quartz cells using the above-mentioned equipment. Addition of a few microlitres of a concentrated solution of the substrate in acetonitrile to 2.5 ml of prethermostatted reaction solution gave an initial concentration of the substrate in the reaction flask of about 0.1 mM. The increase in absorbance at 253 nm was followed as a function of time and the pseudo-first-order rate constant calculated by a non-linear regression computer program.

Microcalorimetric procedure. This technique has the advantage that both kinetic data and reaction heats are obtained from the same kinetic experiment. The reactions were run in parallel in the two channels, both composed of a sample compartment and a reference compartment. Glass vials (3 ml) were used as reaction and reference vessels. All four vessels were filled at the same time with 2.5 ml of premixed reaction solution (organic solvent and aqueous buffer). After this step, 20 μl of substrate in acetonitrile were added to the two reaction vessels while 20 μl of pure acetonitrile were added to the reference vessels. The vials were sealed with gas-tight PTFE septa and slowly introduced into the compartments of the instrument for about 15 min of pre-thermostatting. They were then lowered further down into the detection chambers. The recording of the first-order heat-flow decay was started after a total equilibration time of 30–45 min. The reactions were followed for at least ten half-lives.

The microcalorimeter was statically calibrated after a kinetic experiment using the reaction solutions. The cooling constant of the instrument was found to be 140 s, *i.e.*, no correction for this parameter was necessary for calculation of the rate constants of the reaction heat decay.[14] The rate constants were obtained from data of heat flow *versus* time by means of a non-linear regression computer program. Very good first-order rate constants (k_{obs}) were measured. These agree well with those measured in the kinetics using the UV-spectrophotometric technique (Table 1).

The extrapolated heat flow at time zero (P_0) was used for calculation of the reaction heat (ΔH) according to eqn. (9), where n is the amount of substrate (mol) in the reaction vial.

$$P_0 = \Delta H k_{obs} n \qquad (9)$$

The estimated errors are considered as maximum errors derived from maximum systematic errors and random errors. The maximum errors of the directly measured quantities were thus allowed to propagate as systematic errors into derived quantities, *e.g.*, reaction rate constants.

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