Aldol Reactions of Formaldehyde in Non-aqueous Media

IX.* Mechanism of the Base-catalyzed Reaction of Fluorene with Formaldehyde in Ethanol-Dimethyl Sulfoxide

BENGT WESSLÉN

Department of Organic Chemistry, Chalmers University of Technology and University of Göteborg, Göteborg, Sweden

The rate-controlling step in the ethoxide-catalyzed reaction of fluorene and formaldehyde in a mixture of dimethyl sulfoxide (DMSO) and ethanol was found to be the formation of 9-fluorenyl anion. The logarithm of the rate constant was shown to be linearly dependent on the concentration of DMSO in the reaction medium, the rate at 90 % DMSO (by volume) being about five powers of ten greater than that obtained at 30 % DMSO.

Polar aprotic solvents, such as dimethyl sulfoxide (DMSO), have been shown to greatly accelerate many anion-catalyzed reactions, mainly due to poor solvation of the anionic catalyst.[1-4] The base-catalyzed reaction between fluorene and paraformaldehyde, for example, was found to give 9,9-bis(hydroxymethyl)fluorene (5) very rapidly when carried out in DMSO, even though the paraformaldehyde was not dissolved at the beginning of the reaction.[5]

In the present investigation the kinetics of the ethoxide-catalyzed reaction of fluorene with formaldehyde were studied. Because of the low solubility of paraformaldehyde in pure DMSO the reaction was carried out in a mixture of DMSO and ethanol. Since the rate of reaction was found to decrease considerably on addition of ethanol to the solvent, the influence of the solvent composition on the reaction rate was also studied.

RESULTS AND DISCUSSION

The ethoxide-catalyzed reaction of fluorene (1) with formaldehyde in DMSO has previously been shown to yield 9,9-bis(hydroxymethyl)fluorene (5) at a great rate.[5] Further investigation of the reaction revealed that in

---

* Part VIII: *Acta Chem. Scand.* **23** (1969) 1033.

addition to compound *5* the dibenzofulvene *6* as well as polymeric by-products were formed. The latter products probably arose by anion-catalyzed poly-merization of the fulvene *6*.[6]

SCHEME 1
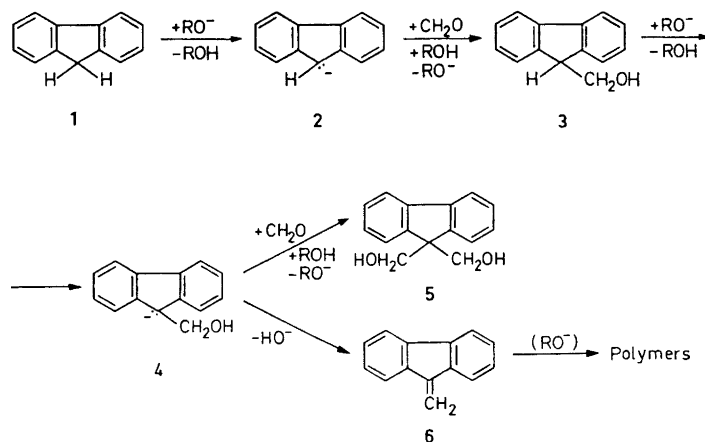
The reaction of fluorene with formaldehyde is assumed to involve formation of the carbanions *2* and *4* (Scheme 1), as well as the intermediate 9-(hydroxymethyl)fluorene (*3*) (*cf.* Ref. 7). If the reaction was carried out in the presence of an excess of formaldehyde, it was not possible to detect the latter compound in the reaction mixtures by means of thin layer chromatography or vapour phase chromatography. If equimolar amounts of the reactants were used the bis-hydroxymethyl compound *5* was obtained as the main product together with the fulvene *6* and polymers, as well as unchanged fluorene. In this case a minor amount of an additional reaction product, which is believed to be the mono-hydroxymethyl compound *3*, was detected by thin layer chromatography and vapour phase chromatography. Apparently compound *3* reacted further as rapidly as it was formed.

When potassium ethoxide is added to a solution of fluorene in DMSO, a strong red colour, which obviously is derived from the 9-fluorenyl anion (*2*),[7] immediately develops. Similar treatment of a mixture of fluorene, paraformaldehyde, and DMSO, however, only caused a transient faint red colouration. This observation indicated that addition of formaldehyde to the 9-fluorenyl anion (*2*) occurred very rapidly and that proton abstraction from fluorene by ethoxide ions to form carbanion *2* may be the rate- determining process. This hypothesis could not, however, be verified by kinetic experiments, since the reaction was carried out in a heterogeneous system. Furthermore, the reaction was so rapid that no accuracy in the kinetic measurements was to be expected. By addition of a protic solvent such as ethanol to the reaction medium two advantages were gained. The reaction was considerably slowed down and it became possible to perform the reaction in a homogeneous system,

since paraformaldehyde is soluble in ethanol with formation of an equilibrium mixture of ethyl hemiformal and formaldehyde. When the reaction was carried out under these conditions the products were the same as without any ethanol present, *viz.* 9,9-bis(hydroxymethyl)fluorene (5) and dibenzofulvene (6), together with some polymeric by-products.

Kinetic measurements were carried out in a medium containing 55 % DMSO, by volume, and at a temperature of $18° \pm 0.1°$. As shown in Fig. 1
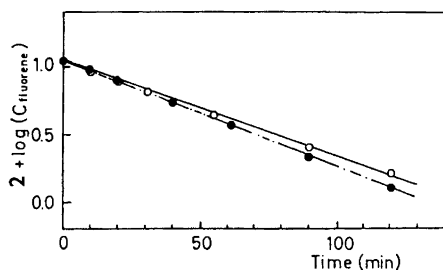

Fig. 1. First-order plot of the base-catalyzed reaction of fluorene with form-aldehyde in DMSO-ethanol (55:45, by volume). Concentration of formaldehyde, 0.25 M (O), and 1.50 M (●); concentration of potassium ethoxide, 12.8 mM; temperature, $18.0° \pm 0.1°$.
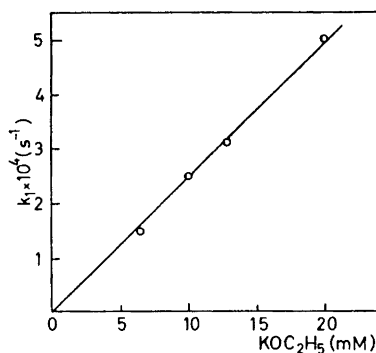
Fig. 2. Dependence of the pseudo-first-order rate constant (k_1) for the base-catalyzed reaction of fluorene with form-aldehyde in DMSO-ethanol (55:45, by volume) on the concentration of potassium ethoxide. Temperature, $18.0° \pm 0.1°$.

the rate of consumption of fluorene was found to obey first-order kinetics over a period of at least three half-lives when an excess of formaldehyde (13 moles of CH_2O per mole of fluorene) was used. First-order kinetics were also obtained when only the amount of formaldehyde calculated for formation of 5 (2 moles of CH_2O per mole of fluorene) was present (Fig. 1). The reaction rates were practically the same in both experiments. In Table 1 pseudo-first-order rate constants obtained at different initial concentrations of formaldehyde are given. It is clearly shown that there is no appreciable change in the reaction rate on increasing the formaldehyde concentration from 0.125 to 1.50 M CH_2O. Apparently the reaction is of first order with respect to fluorene and of zero order with respect to formaldehyde. The decrease in rate observed at high concentrations of formaldehyde might have been due to increased formation of ethyl hemiformal anion from ethoxide ions and the hemiformal:

$$C_2H_5O^- + HOCH_2OC_2H_5 \rightleftharpoons C_2H_5OH + {}^-OCH_2OC_2H_5$$
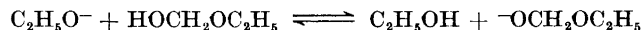
The hemiformal anion should be less basic and consequently less active as a catalyst than the ethoxide ion (*cf.* Ref. 8).

In Fig. 2 are given pseudo-first-order rate constants for the reaction between fluorene and formaldehyde at different concentrations of potassium

ethoxide. The direct proportionality between rate and catalyst concentration implies that the reaction is of first order also with respect to potassium ethoxide.

Sprinzak et al.[6,7], who studied base-catalyzed addition reactions between fluorene and aldehydes in pyridine [6] and ethanol [7] solutions, suggested for the reactions in ethanol a mechanism in which a concerted attack of the basic catalyst and the aldehyde on fluorene would account for the formation of the reaction products, i.e. no free carbanion would appear. This suggestion was based on the observation that in the presence of sodium ethoxide fluorene was tritiated in the 9-position by tritiated ethanol at a rate lower than the rate of its reaction with benzaldehyde in ethanol. Furthermore, no autoxidation of fluorene was found to take place in ethanol solution in the presence of base. The kinetics of the reaction of fluorene with benzaldehyde in ethanol were not studied, but apparently the concerted mechanism would imply third order kinetics, i.e. first order with respect to each one of the three reactants.

In the present investigation the kinetic results obtained are in accordance with the view that the proton abstraction from fluorene by ethoxide ions to form 9-fluorenyl anion (2) is rate-determining for the overall reaction. Addition of the anion (2) to the carbonyl group of formaldehyde thus is a very rapid reaction. The mechanism suggested by Sprinzak et al.[7] cannot be applicable in the present case.

Cram and co-workers [3,9] have shown that the rate of the methoxide-catalyzed racemization of 2-methyl-3-phenylpropionitrile, which proceeds via a rate-determining proton abstraction in the 2-position, in mixtures of methanol and DMSO varied considerably with solvent composition. In the present investigation the rate of the reaction between fluorene and formaldehyde was similarly found to be strongly dependent on the concentration of DMSO in the reaction medium, being five powers of ten greater at 90 % DMSO (by volume) than at 30 % DMSO. As shown in Fig. 3, there is a straight-
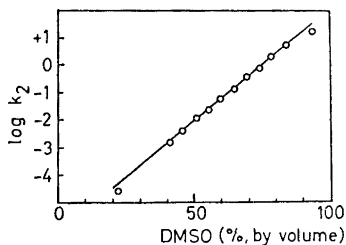

Fig. 3. Correlation between the logarithm of the second-order rate constant (k_2) for the base-catalyzed reaction of fluorene with formaldehyde in DMSO-ethanol, and the concentration of DMSO in the reaction medium. Temperature, $18.0° \pm 0.1°$.

line relationship between the logarithm of the second-order rate constant and the concentration of DMSO in the reaction medium. Since the logarithm of the rate constant is a linear function of the activation energy for the reaction, i.e. the proton abstraction, the figure also implies that the activation energy is a linear function of the concentration of DMSO in the reaction medium.

A similar linear dependence on the concentration of DMSO, within a broad concentration range, was reported by Cram et al.[3],[9] for the above-mentioned racemization of 2-methyl-3-phenylpropionitrile. As an explanation of this behaviour the authors suggested that the energy of the initial state for the reaction gradually increased with increasing concentration of DMSO in the reaction medium; the increased DMSO concentration caused a decreased solvation of the anionic catalyst. Within this linear range, the degree of solvation, and thus the energy, of the transition state for proton abstraction would remain practically unchanged. At very low concentrations of DMSO, however, there will be a deviation from the straight-line relationship, which, according to Cram et al.,[3],[9] may be due to changes in the solvation of the transition state. This interpretation would be directly applicable to the present reaction between fluorene and formaldehyde in mixtures of DMSO and ethanol.

EXPERIMENTAL

DMSO (purum) was dried over calcium hydride and distilled at 2 mm Hg through a 60 cm Vigreux column. Paraformaldehyde (98 % CH_2O) was supplied by Perstorp AB, Perstorp. Fluorene (purum) was recrystallized before use. Potassium ethoxide was prepared by reacting potassium with abs. ethanol. NMR spectra were recorded on a Varian A-60 spectrometer, and IR spectra on a Beckman IR-9 instrument. Vapour phase chromatography (VPC) was performed using a Perkin-Elmer 800 instrument.

Reaction of fluorene and paraformaldehyde in DMSO. A. To a chilled mixture of fluorene (2.0 g, 12 mmoles) and paraformaldehyde (1.5 g, 49 mmoles) in DMSO (50 ml) a solution of potassium ethoxide (0.13 mmole) in ethanol (0.5 ml) was added. The reaction mixture was well stirred and kept under N_2. After 1 min the reaction was interrupted by the addition of HOAc (0.5 ml). Water (150 ml) was added. The mixture was saturated with sodium chloride and extracted several times with ethyl acetate. The yellow extract was freed from polymeric material by filtration and diluted to 100 ml with ethyl acetate. After acetylation (5 ml of the extract was treated with 5 ml of acetic anhydride-pyridine 10:1 for 15 min at 70°) the yield of 9,9-bis(hydroxymethyl)fluorene (5) was found to be 1.08 g (41 %) by VPC. An additional reaction product with a retention time slightly longer than that of fluorene (stationary phase, silicone gum SE-30) was also detected.

B. In an experiment similar to A the reaction mixture was extracted with $CDCl_3$, after the addition of water (150 ml). VPC as well as thin layer chromatography of the yellow extract revealed the presence of a large amount of the unknown reaction product found in A. NMR spectrum of the extract showed, in addition to peaks from aromatic protons and from protons in the hydroxymethyl groups of 9,9-bis(hydroxymethyl)fluorene (5), a singlet at 5.92 ppm (downfield from tetramethylsilane), characteristic of a symmetrically substituted vinylidene group. IR spectrum showed bands at 3080 cm^{-1} (R'R''C=CH$_2$) and 1610 cm^{-1} (conjugated C=C bond). These findings indicate the second compound to be dibenzofulvene (6) Evaporation of the solvent gave a yellow oil which quickly polymerized.

C. A chilled mixture of fluorene (2.0 g, 12 mmoles) and paraformaldehyde (0.37 g, 12 mmoles) in DMSO (50 ml) was treated as described under A. A yield of 0.57 g (45 %) of 9,9-bis(hydroxymethyl)fluorene (5) was found by VPC, together with some dibenzofulvene (6) and 0.72 g of unchanged fluorene. In addition to compounds 5 and 6 a minor amount of a reaction product with a retention time between that of fulvene 6 and that of the diacetate of bis-hydroxymethyl compound 5 was observed. This product was assumed to be the acetate of mono(hydroxymethyl)fluorene (3).

Kinetic runs. Solutions (100 ml) of fluorene (2.0 g, 12 mmoles) and formaldehyde (added as a solution of paraformaldehyde in ethanol) in mixtures of DMSO and ethanol were kept with stirring under N_2 in a constant-temperature bath at 18.0±0.1°. A sample (5.0 ml) was removed and analyzed for fluorene by VPC. The reaction was initiated by

Table 1. Dependence of the pseudo-first-order rate constant on the initial concentration of formaldehyde. Concentration of potassium ethoxide, 12.8 mM; DMSO-ethanol, 55:45, by volume.

Concentration CH_2O (M)	$k_1 \times 10^4$ (s^{-1})
0. 125	3.0
0. 25	3.0
0. 50	3.4
1. 00	3.0
1. 50	2.9
2. 00	2.2
4. 00	1.4

addition of a solution of potassium ethoxide in ethanol (5.0 ml). Samples (10.0 ml) were removed at intervals, neutralized with acetic acid (2.0 ml), and analyzed for fluorene by VPC. Rate constants were calculated from the half-life of fluorene; the reactions were generally run for periods of $2-3$ half-lives. Results are given in Figs. 1, 2, and 3, and in Table 1.

REFERENCES

1. Parker, A. J. *Quart. Rev.* **16** (1962) 163.
2. *Dimethyl sulfoxide, Reaction Medium and Reactant,* Crown Zellerbach Corporation, Chemical Products Division, Camas, Washington, June 1962.
3. Cram, D. J., Rickborn, B. and Knox, G. R. *J. Am. Chem. Soc.* **82** (1960) 6412; Cram, D. J., Rickborn, B., Kingsbury, C. A. and Haberfield, P. *Ibid.* **83** (1961) 3678.
4. Wesslén, B. *Acta Chem. Scand.* **21** (1967) 713.
5. Wesslén, B. *Acta Chem. Scand.* **21** (1967) 718.
6. Ghera, E. and Sprinzak, Y. *J. Am. Chem. Soc.* **82** (1960) 4945.
7. Avramoff, M. and Sprinzak, Y. *J. Am. Chem. Soc.* **82** (1960) 4953.
8. Walker, J. F. *Formaldehyde,* 3rd Ed., Reinhold Publ. Corp., New York 1964, p. 232.
9. Cram, D. J. *Fundamentals of Carbanion Chemistry,* Academic, New York 1965, pp. 34−36.