Carbohydrate Research, 214 (1991) 169–177
Elsevier Science Publishers B.V., Amsterdam

Kinetic and mechanistic studies on the rearrangement of 1-(substituted phenyl)-1,3-dimethoxy-2-propanones*

Guo-qiang Chen, Zhi-fen Li, and Pang Zhang[†]
Department of Chemistry, Peking University, Beijing 100871 (Peoples' Republic of China)

(Received August 13th, 1990; accepted December 10th, 1990)

ABSTRACT

The mechanism of rearrangement of 1-(substituted phenyl)-1,3-dimethoxy-2-propanones to give substituted benzylglyoxal dimethyl acetals (**5**) was studied by kinetic measurements, by the effects of acid catalysis, by rearrangements in the absence of acid and in the presence of base, by solvent effects, by effects of temperature, and by mass spectroscopy. It is concluded that the title ketones rearrange by a sigmatropic rather than an SN1′ allylic shift.

INTRODUCTION

Our previous paper[1] reported a novel rearrangement[2] of 1-R-substituted-1,3-dimethoxy-2-propanones, where R denotes hydrogen, an alkyl, or a substituted phenyl group, effected by acid catalysis, to yield the respective 3-substituted methylglyoxal dimethyl acetals. When R is a methoxycarbonyl or alkanoyl group, the ultimate rearrangement products were respectively 4,5-dimethoxy- and 5-alkyl-3-methoxy-2(5*H*)-furanones, formed by cyclization subsequent to a methoxyl-group shift, whereas when R is a substituted benzoyl group, scission at C-2–C-3 occurred instead of rearrangement, giving ω-methoxyacetophenone derivatives. Fedoroňko and coworkers[3] suggested that the formation of methylglyoxal from 1,3-dimethoxyacetone on heating in dilute hydrochloric acid proceeded by an SN1′ allylic rearrangement. This paper reports our findings concerning the mechanism involved in the rearrangement.

RESULTS

Kinetic measurements. — The rates of rearrangement of 1-(substituted phenyl)-1,3-dimethoxy-2-propanones (**1**) were monitored by n.m.r. and the specific rate-constants listed in Table I indicate a resultant Hammett reaction constant ρ (Eq. *1*) of practically zero*. It is believed that the methoxyl shift proceeds most probably from an allylic position and thus the rearrangement consists first of a tautomeric shift from H-3

---

* Presented at the 15th International Carbohydrate Symposium, Yokohama, Japan, August 12–17, 1990.

[†] To whom inquiries should be directed.

* A similar measurement in 0.13M p-toluenesulfonic acid solution of deuterated chloroform at 60 ±0.5°C yielded the following specific rate-constants ($k \times 10^3$ min^{-1}): X = H (7.3), p-Me (6.7), p-Cl (11), m-Cl (6.9), and p-NO$_2$ (6.0) which again give a ρ value of near to zero.

0008-6215/91/$ 03.50

TABLE I

The specific rate constants of the rearrangement of 1-(substituted phenyl)-1,3-dimethoxy-2-propanones (**1**)[a]

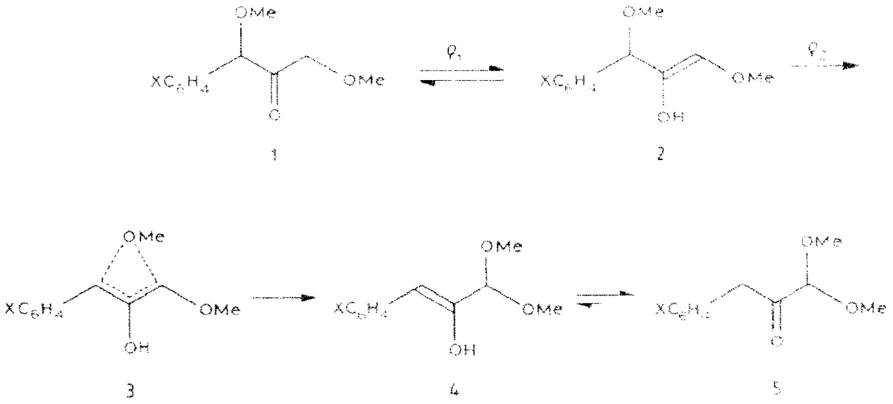
X	*H*	p-*MeO*	p-*Me*	p-*Cl*	m-*Cl*	p-NO_2
$k \times 10^3\ \text{min}^{-1}$	1.3	1.7	1.2	1.3	1.1	1.2
$\log(k_X/k_H)$	0	+0.12	−0.04	0	−0.07	−0.04

[a] 0.067M TsOH in CD_3CN at 69 ±0.5 .

(the more pronounced tautomeric shift from H-1 is not concerned with the rearrangement) to generate an enol, **2**, which rearranges sigmatropically as **3** or by an SN1′ allylic process to give **4**, which then ketonizes to yield 3-(substituted phenyl)methylglyoxal dimethyl acetals (**5**), as shown in Scheme I. The Hammett equation for the process takes the form[4] of Eq. *1*.

$$\log\left(\frac{k_X}{k_H}\right) = \sigma\rho_{obs} = \sigma(\rho_1 + \rho_2) \qquad (1)$$

in which the observed ρ value should be the sum of ρ_1 for acid-catalyzed enolization and ρ_2 for the rearrangement. The value of ρ_1 is not yet known, but following the practice of Bordwell and Scamehorn[5], it is possible to estimate it from the reaction constants of acid-catalyzed enolization of substituted acetophenones, which were reported[6] to range from −0.16 to −0.57, and thus the value of ρ_1 probably[7] lies between −0.1 and −0.3, which leads to a value of ρ_2 within an approximate range of 0.1–0.3. Such a low value of ρ_2 implies that there is very little electronic perturbation around the rearranging centre and is consistent with a methoxy [1,3] sigmatropic shift via an intermediate **3** to give **5** rather than via the intermediacy of a benzylic carbenium ion, which would yield a large negative value of the reaction constant, such as $\rho = -2.7$ for the acid-catalyzed rearrangement of *p*-substituted phenyl propenyl carbinols in 60% 1,4-dioxane as reported by Braude *et al.*[8], and $\rho = -2.37$ for the Favorskii rearrangement of 1-(substituted phenyl)-1-chloro-2-propanone[9].



Scheme I

The [1,3] sigmatropic rearrangement may proceed by either antara-retention or supra-inversion. This requirement makes [1,3] antarafacial hydrogen migration extremely difficult, but is feasible for other atoms and thus [1,3] sigmatropic shifts for carbon, sulfur, and silicon are known[9]. With regard to methoxy [1,3] sigmatropic migration, the present work is probably the first one reported.

Addition of a free-radical initiator such as benzoyl peroxide or irradiation with u.v. light did not alter the rearrangement rates, thus eliminating the possibility of free-radical or photochemical processes.

The effects of acid catalysis were studied with unsubstituted **1a** under the same conditions at different concentrations of *p*-toluenesulfonic acid. The results show plots with time that are linear and thus imply a first-order reaction up to at least 80% conversion. The rearrangement is accelerated by increase of acid concentration up to a limit (0.324M TsOH) beyond which no further speed-up is observed (Fig. 1). A similar study was carried out in methanol, and a constant rate of rearrangement is attained as low as at 0.15M *p*-toluenesulfonic acid. These results suggest that the apparent rate of sigmatropic rearrangement varies with acid concentration as a consequence of its acceleration of enolization, and the rate of enolization should be much faster than sigmatropic shift. Incidentally, the temperature necessary to effect rearrangement also points to a slower step of methoxy migration; it is known[6] that acid-catalyzed enolization may be very fast at room temperature, but the present sigmatropic shift is very slow under the same conditions.

1-Methyl-1-phenyl-1,3-dimethoxy-2-propanone (**6**) was synthesized by a similar route[1] and subject to acid-catalyzed rearrangement. The specific rate-constant was found to be 0.7×10^{-3} min^{-1}, about one half of that of **1a**. This result also seems to be consistent with the sigmatropic rearrangement, because the methyl group added to C-1 will very probably cause hindrance in a transition state such as **3** and thus retard the

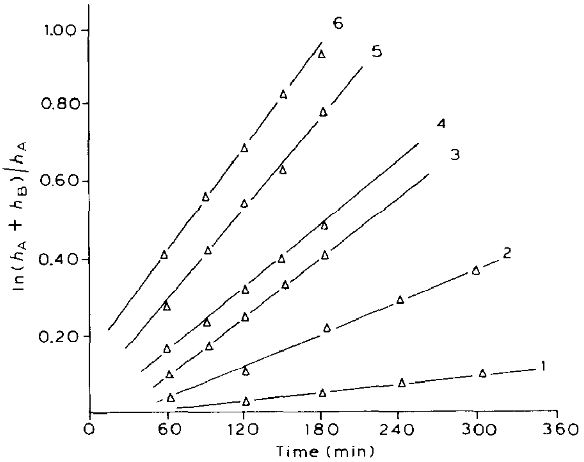


Fig. 1. The dependence of specific rate constants for the rearrangement of 1-phenyl-1,3-dimethoxy-2-propanone (**1a**) on the concentration of catalyzing acid.

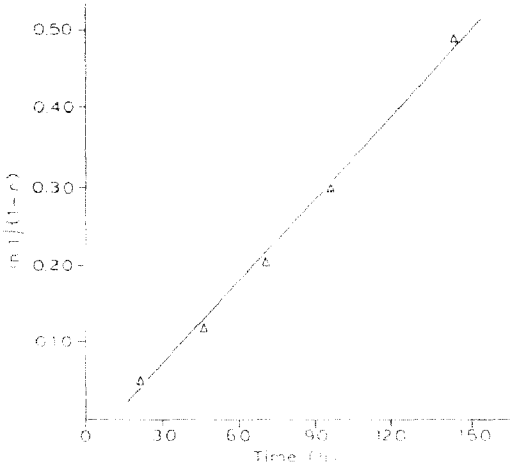


Fig. 2. Linear plot for the rearrangement of 1-phenyl-1,3-dimethoxy-2-propanone (**1a**) in methanol in the absence of acid (r = fraction rearranged).

rearrangement, whereas an allylic shift of analogous allyl alcohols usually leads to an increase in rates[10].

Rearrangement in neutral media and in the presence of bases. It was shown that **1a** indeed undergoes rearrangement to give **5** at moderate temperature, alone or in various organic solvents, without addition of an acid as catalyst. Thus, Fig. 2 shows that **1a** in methanol alone at 55° rearranges to give **5a** just as it does under acid catalysis (Table I). Table IIa shows that methanol is better than acetonitrile in promoting the rearrangement, probably because of the fact that a hydroxylated solvent tends to facilitate enolization. Acetonitrile seems to exert no effect on the rearrangement, as the

TABLE II

Rearrangements of 1-phenyl-1,3-dimethoxy-2-propanone (**1a**) in the absence of acid and in the presence of amines

a. **1a** *for 10 days at 55*				
Solvent:	none	MeCN	MeOH	
Yield:	19%	13%	59%	
b. **1a** *for 21 h at 80*				
Media:	Me_2SO	3.8M EtOH in Me_2SO	2.6M H_2O in Me_2SO	0.7M Ph_2NH in Me_2SO
Yield:	29%	35%	45%	17%
c. **1a** *in methanol containing triethylamine for 40 h at 55°*				
Et_3N:	0.37M	0.17M	0.06M	0
Yield:	2.3%	3.0%	4.6%	9.7%

yield of **5a** is comparable to that obtained by rearranging **1a** alone. Table IIb also supports the idea that hydroxylated solvents facilitate rearrangement, but addition of diphenylamine in dimethyl sulfoxide evidently retards the formation of **5a**. It seems likely that the rearranging species is an enol rather than an enolate. The effect of base was further studied with addition of triethylamine in methanol, and again it was found to hinder the rearrangement (Table IIc).

These spontaneous rearrangements agree again with sigmatropic rather than allylic shifts, for it is known that allylic alcohols and ethers rearrange only in the presence of Lewis acids as catalysts[10].

Solvent effects. — The yields of benzylglyoxal *p*-nitrophenylosazone formed by the sigmatropic rearrangement of **1a** in 0.058M *p*-toluenesulfonic acid solutions in various solvents for 21 h at 55° showed that the maximum difference in yields is less than 4 fold (Table III), and this is again in agreement with a sigmatropic rearrangement.

Temperature effects. — Specific rate constants were measured for the rearrangement of **1a** in deuterated dimethyl sulfoxide at two concentrations, 0.076 and 0.33M, of *p*-toluenesulfonic acid and at five temperatures between 60° and 86° for 5 and 4 h respectively. The activation parameters obtained therefrom clearly demonstrate the pericyclic nature of the rearrangement, with a characteristically large negative entropy of activation (Table IV). The values of the entropy of activation for allylic alcohol isomerization, which proceeds by dissociation, are generally near zero[10].

Mass-spectroscopic studies. — Neither **1a** nor its rearrangement product **5a** yield molecular ions in their mass spectra, but give characteristic *m/z* 121 and 75 peaks, respectively. Compound **1a** was rearranged in 0.058M *p*-toluenesulfonic acid solution in ethanol at 55° for 26 h to 2/3 completion, and the resultant product mixture was subjected to mass spectroscopic examination (Table V). Fragment *a* originates from the remaining **1a** and fragments *c*, *d*, and *e* from the rearranged product **5a** and its

TABLE III

Yields of benzylglyoxal *p*-nitrophenylosazones from the rearrangements of 1-phenyl-1,3-dimethoxy-2-propanone (**1a**) in various solvents[a]

Solvents:	*MeOH*	*Me_2SO*	*MeCN*	*$CHCl_3$*	*CCl_4*	*C_6H_6*	*AcOH*	*AcOEt*	*THF*
Yield, %	55	36	35	32	28	25	25	23	16

[a] 0.055M TsOH for 21 h at 55°.

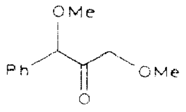
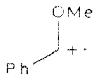
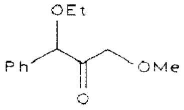
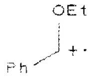
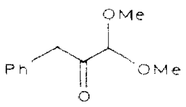
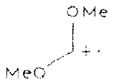
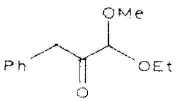
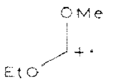
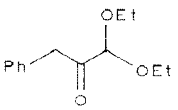
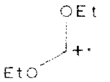
TABLE IV

Activition parameters for the rearrangement of 1-phenyl-1,3-dimethoxy-2-propanone (**1a**)

TsOH	ΔE^*, J mol^{-1}	ΔS^*, J mol^{-1} K^{-1}
0.076M	76.1×10^3	−88.9
0.33M	66.1×10^3	−107.6

TABLE V

Masses of ions from partial rearrangement of 1-phenyl-1,3-dimethoxy-2-propanone (**1a**)

	Components	*Characteristic fragments*		m/z	% *Composition*
1.			*a*	121	32.7
2.			*b*	135	0.6
3.			*c*	75	22.7
4.			*d*	89	6.1
5.			*e*	103	37.9

transacetalization products, respectively. Identification of a minor fragment (*b*) is noteworthy and indicates that a small fraction of **1a** may suffer solvolytic dissociation and yield a small proportion of component **2** by internal return, which gives rise to fragment *b* in the mass spectrum. This result was used to explain the slightly higher rate of rearrangement of compound **1b** (section 1).

DISCUSSION

The migration of a methoxyl group in **1** to give **5** was shown by the evidence of kinetic studies, effects of acid catalysis, rearrangement in neutral media and in the presence of an organic base, solvent effects, effects of temperature, and mass spectroscopic analysis, to be a [1,3] sigmatropic rearrangement. It was concluded that only acids are responsible for catalyzing the enolization. A small extent of S_N1' disscociation may still contribute to the rearrangement. As neither 1- nor 3-methoxypentane-1,3-diones showed any tendency to undergo methoxyl-group shift,[1] it is believed that a 1,3-dimethoxyalkan-2-one structural unit is necessary for a sigmatropic methoxyl shift. It seems that no steric congestion is involved, because the migrating methoxyl group has almost the same steric environment at C-3 and at C-1. The reverse rearrangement is therefore unfavorable on steric grounds. Further work on synthetic application of this rearrangement is underway.

EXPERIMENTAL

Except that the kinetic measurements were made on a Jeol-FX-90Q spectrometer, the general experimental details are as given in the preceeding paper[1].

Kinetic materials and methods. — Chromatographically pure 1-phenyl- (**1a**) and 1-(substituted phenyl)-1,3-dimethoxy-2-propanones (**1b–f**)[1] were used. Compounds **1a–f** and their rearranged products (**5a–f**) exhibit distinct methine-proton n.m.r. signals at approximately δ 4.82 and δ 4.53 p.p.m. respectively, and their rates of rearrangement were monitored by n.m.r. with 5–10% experimental errors. The integrated values h_A and h_B for **1** and **5**, respectively, are related to their concentrations A and B by $A = rh_A$ and $B = rh_B$ where r is a proportionality constant, and thus the first-order rate equation for the rearrangement takes the form of: $\ln[(A+B)/A] = \ln[(h_A + h_B)/h_A] = kt$.

The rate of rearrangement of **1a** was also monitored by pouring the mixture into a saturated solution of *p*-nitrophenylhydrazine in 1:1 AcOH–water followed by warming for a few minutes. The orange-red, solid *p*-nitrophenylosazone of **5a** was filtered off, washed with a little 95% EtOH, dried, and weighed.

Kinetic procedures. — *1.* Compounds **1a–f** (each 0.25 mmol) were weighed and dissolved in a 0.067M solution of anhydrous *p*-toluenesulfonic acid in CD_3CN (4.6 mL). The solution was introduced into an n.m.r. tube (no rearrangement was detected by n.m.r. at ambient temperature) and heated in a thermostat maintained at 69 ±0.5°. During an interval of 5 h, the tube was repeatedly taken out, cooled, and two methine-proton signals analyzed by n.m.r.. The results are summarized in Table I.

2. This was the same as in *1*, except that a 0.13M solution of anhydrous *p*-toluenesulfonic acid in $CDCl_3$ was used as the rearrangement medium.

1-Methyl-1-phenyl-1,3-dimethoxy-2-propanone (**6**). — 2-Methoxy-2-phenylpropanoic acid[11] (13.4 g, 74 mmol) was heated for 4 h at 60° with $SOCl_2$ (20 mL) and then processed by a general procedure[1] to give **6** (6.3 g) by distillation, b.p. 78–83°/0.2 mm. This product was chromatographed on a column of silica gel eluted with 1:10 EtOAc–CH_2Cl_2 to yield pure **6** (2.5 g, 16%), n_D^{15} 1.513; n.m.r. δ_H 3.28 (6 H, s, OCH_3), 4.35 (2 H, d, CH_2), 7.36 (5 H, s, PhH) (Found: *m/z* 208 (M^+). $C_{12}H_{16}O_3$ requires M^+ 208); 2,4-dinitrophenylhydrazone, m.p. 112–113° (DMF–EtOH) (Found: *m/z* 388 (M^+). $C_{18}H_{20}N_4O_6$ requires M^+ 388). The specific rate-constant measured for **6** by kinetic procedure *1* was 0.7×10^{-3} min.$^{-1}$.

Effects of acid concentrations. — *1.* Six portions of compound **1a** (419 mg, 2.2 mmol each) were dissolved separately in CD_3CN (4.0 mL each) and to each of solution was added different weights of anhydrous *p*-toluenesulfonic acid (16, 60, 104, 120, 225, and 290 mg). The mixtures were introduced separately into n.m.r. tubes and their methine signals monitored at 69 ±0.5° according to the kinetic prodedure *1* to give the results shown in Fig. 1, in which the respective acid concentrations are numbered consecutively.

2. Into each of six small test-tubes was weighed compound **1a** (~100 mg) and *p*-toluenesulfonic acid monohydrate (5, 10, 30, 50, 70, and 100 mg) and each mixture was separately dissolved in MeOH (1 mL). The test tubes were sealed and kept at 50 ±0.5° for 27 h and then cooled, opened, and analyzed as *p*-nitrophenylosazones; the respective yields were 23, 38, 59, 58, 56, and 58%.

Rearrangement of **1a** *in absence of acid catalyst.* — *1.* Five portions of **1a** (~100 mg each) were dissolved separately in MeOH (1.0 mL) in test tubes that were sealed, kept at 55 ±0.5° for 22, 45, 71, 95, and 140-h intervals, and the products analyzed by the *p*-nitrophenylosazone method to give 5.2, 10.6, 18.6, 25.7, and 38.3% yields of **5a**, respectively (Fig. 2).

2. Compound **1a** alone in a sealed tube was kept for 10 days at 55° and was shown to rearrange to an extent of 19%. Two portions of **1a** (~100 mg each) dissolved in MeCN (1 mL) and in MeOH (1 mL) separately in sealed tubes were kept at 55° for 10 days and the products analyzed as benzylglyoxal *p*-nitrophenylosazones (Table IIa).

3. Four portions of **1a** (~100 mg each) separately dissolved in Me_2SO (1 mL each) alone and with addition respectively of EtOH (175 mg, 3.8 mmol), of water (47 mg, 2.6 mmol), and of Ph_2NH (120 mg, 0.7 mmol) were sealed in test tubes, kept for 21 h at 80°, and analyzed as the benzylglyoxal *p*-nitrophenylosazones (Table IIb).

4. Four portions of **1a** (~100 mg each) dissolved separately in MeOH (1 mL), and in 0.06, 0.17 and 0.37M solutions of Et_3N in MeOH (1 mL each) were kept at 55 ±0.5° for 40 h in sealed tubes. These were cooled, opened, and analyzed as the benzylglyoxal *p*-nitrophenylosazones (Table IIc).

5. Two portions of **1a** (~100 mg each) dissolved in Me_2SO (1 mL each) with separate addition of benzoyl peroxide (10 mL) and 4-hydroxy-tetramethylpiperidinyloxy (5 mg) were kept for 21 h at 80 ±0.5°. In both cases, the yields of benzylglyoxal *p*-nitrophenylosazones were 24%.

Rearrangement of **1a** *in various solvents.* — To nine test tubes containing separately MeOH, Me_2SO, MeCN, $CHCl_3$, CCl_4, benzene, AcOH, EtOAc, and tetrahydrofuran (10 mL each) were dissolved **1a** (~100 mg each) and *p*-toluenesulfonic acid monohydrate (10 mg each). They were sealed, kept for 21 h at 55 ±0.5° and the products analyzed as *p*-nitrophenylosazones (Table III).

Rearrangement of **1a** *at different temperatures.* — The specific rate constants ($k \times 10^3$ min^{-1}) measured in Me_2SO-d_6 at two concentrations, 0.076 and 0.33M, of *p*-toluenesulfonic acid and at five temperatures T K = 333, 340, 347, 354, and 359 ±0.5 K for intervals of 5 and 4 h, respectively, according to kinetic procedure *1* were respectively 0.47, 1.75, 0.98 and 3.52, 1.70 and 6.00, 2.39, 9.08, 4.21 and 12.5 (Table IV).

Mass-spectroscopic studies. — See text.

ACKNOWLEDGMENTS

The authors thank Natural Science Foundation and National Commission of Education for financial grants, Professor Qi-feng Shen (Institute of Agricultural Applied Chemistry, Beijing Agricultural University) for providing the facilities and discussions related to spectroscopic matters, and Professor Hui-tong Tang and Dr. I-ling Huang also for the latter.

REFERENCES

1 Y. Yu, G.-Q. Chen, J. Zhu, X.-S. Zhang, S.-X. Chen, H.-T. Tang, and P. Zhang, *J. Chem. Soc., Perkin Trans. 1*, (1990) 2239–2243.
2 For a general reference see J. C. Speck, Jr., *Adv. Carbohydr. Chem.*, 13 (1958) 63–103.
3 M. Fedoronko, P. Temkovic, V. Mihalov, and I. Tvaroska, *Carbohydr. Res.*, 87 (1980) 51–62 and references cited therein.
4 C. D. Johnson, *The Hammett Equation*, Cambridge University Press, Cambridge, 1973, pp. 33–35.
5 F. G. Bordwell and R. G. Scamehorn, *J. Am. Chem. Soc.*, 90 (1968) 6751–6758.
6 J. Toullec, in V. Gold and B. Bethell (Eds.), *Adv. Phys. Org. Chem.*, Academic Press, New York, 1982, Vol. 18, pp. 1–77; R. P. Bell, *The Proton in Chemistry*, 2nd edn, Cornell University Press, Ithaca, New York, 1973, p. 172.
7 Reference 4, p. 8 and reference 5, p. 6753.
8 E. A. Braude and E. S. Stern, *J. Chem. Soc.*, (1974) 1096–1101.
9 C. W. Spangler, *Chem. Rev.*, 76 (1976) 187–217; H. Kwart and D. A. Benko, *J. Am. Chem. Soc.*, 101 (1979) 1277–1279; T. Mandai, K. Mori, K. Hasegawa, M. Kawada, and J. Otera, *Tetrahedron Lett.*, 25 (1984) 5225–5226; M. Aso, K. Hayakawa, and M. Kanematsu, *J. Org. Chem.*, 54 (1989) 5599–5603.
10 R. H. Dewolfe, in C. H. Bamford, C. F. H. Tipper, and R. G. Compton, (Eds.), *Comprehensive Chemical Kinetics*, Elsevier Amsterdam, 1973, Vol. 9, Chapter 5, pp. 417–487.
11 W. Reeve and E. L. Compere, *J. Am. Chem. Soc.*, 87 (1961) 2755–2761.