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Kinetics of the Conformer Reactions: II.[1] Significance of Media in the Electrophilic addition Reactions

Yu. G. Shtyrlin, G. R. Shaikhutdinova, E. N. Klimovitskii

Butlerov Research Institute, Kazan State University, Kazan, Tatarstan, Russia

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Abstract — The kinetics of electrophilic addition reaction of bromine to a multiple bond in a series of conformationally unhomogenous 2-substituted 1,3-dioxa-5-cycloheptenes was studied. We found that the compounds with *trans* structure are formed. The partial reaction rate constant for *chair* and *twist* forms and the reaction susceptibility parameters to the substituent electronic effect at the C^2 atom are obtained. Relative reactivity of the alternative steric structures is defined by the specific solvation of the substrate. The result obtained are compared with those achieved without accounting for conformational term.

The problem of conformer reactivity is the less studied area in the modern chemistry. Earlier [1,2] with the Dils–Alder model reaction of conformationally unhomogenous 2-substituted 1,3-dioxa-5-cycloheptenes with 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine were determined the susceptibility parameters in the reaction series to the electronic substituent effect and the values of partial rate constant of *chair* and *twist* forms in different solvents. It was concluded that the difference in the conformer reactivity and the reaction diastereoselectivity under the conditions of kinetic control are defined by the cooperation of medium effect and stereoelectronic orbital interaction of the conformers in the reaction transition state.

For the further investigation of the factors controlling the reactivity of the conformers in the reactions of various type we decided to study electrophilic addition reactions proceeding via the transition state with significant charge separation rather than synchronous reactions.

Among such reactions, the essentially classic bromination seems the most attractive. Mechanism of olefin bromination in polar solvents is commonly accepted now as reversible formation of a π-complex (olefin–Vr_2) followed by reversible transition into a bromonium ion which then is attacked by the Br^- nucleophile or by the solvent molecule to form bromination or solvolisys products, respectively [3–6]. However, study of the reaction kinetics in nonpolar solvents is a nontrivial task due to the possible contribution of a homolytic process and the influence of several other factors. Thus, the bromine addition to olefins in nonpolar solvents is very sensitive to the presence of polar surface and soluble polar additives such as hydrogen halides and water [7, 8].

In this communication, we choose as the model of conformationally unhomogenous olefins a series of 2-substituted 1,3-dioxa-5-cycloheptenes (**Ia**–**If**) successfully used earlier in diene synthesis [1, 2]. These compounds obey the ordinary requirements to the substrates (a substantial distance between a substituent and reaction center and wide scale of conformation equilibrium appropriate for the quantitative control), and some of compounds of this series easily enter bromination at the double bond with a high yield [9–11]. Note that 5-methylene-1,3-dioxans isomeric to the acetals **Ia**–**If** also smoothly react with bromine at the multiple bond, but are not appropriate for our aims due to their conformational homogenity [12–14].

The scheme of the bromination of acetals **Ia**–**If** under the conditions of pseudo first order reaction is given below.

Analysis of reaction mixtures showed that bromination of acetals **Ia**–**If** proceeds stereospecifically. The *trans* structure of the compounds obtained was proved by the method of ^{13}C NMR spectroscopy, in the case of 2-substituted compounds **IIb**–**IIf** by nonequivalence of the atoms C^4 and C^7, C^5 and C^6 (Table 1) and ^1H NMR spectroscopy in the case of the acetal **IIa**, by the presence of a singlet for geminal hydrogens at C^2. We found that study of the bromine addition to 2-substituted 1,3-dioxa-5-cycloheptanes **Ia**–**If** in polyar acetonitrile and water by common kinetical methods is impossible due to high reaction rate. Therefore we used for the investigation the solvents

[1] For communication I, see [1].

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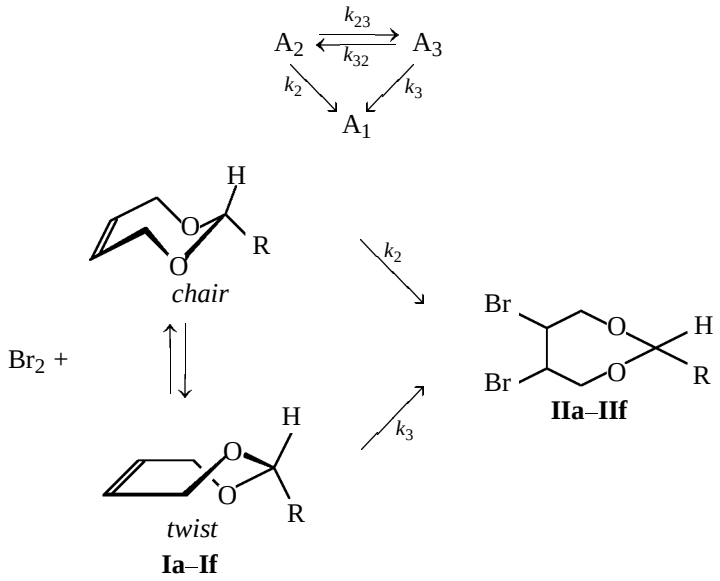

R = H (**a**), CH_3 (**b**), C_2H_5 (**c**), $(CH_3)_2CH$ (**d**), $(CH_3)_3C$ (**e**), C_6H_5 (**f**).

such as nonpolar aprotic dioxane and proton donor chloroform.

We found that the reaction rate (1) depends substantionally on the presence of trace amount of mineral acid in the chloroform distilled over P_2O_5 and (2) on the presence in the solvents of residual air oxygen that in the case of dioxane induces formation of peroxides and in the case of chloroform of acidic admixtures. We overcome these problems by means of additional refluxing of chloroform over potassium carbonate and dioxane over copper(I) bromide followed by distillation in an inert gas atmosphere just prior to the experiments. Only with such a procedure we were able to obtain reproducible results for the bromine addition to acetals **Ia**–**If**, except compound **Ie**, where side-chain bromination probably takes place.

We found that reaction of bromine addition to the acetals double bonds is of overall second order and partial first order on each reagent.

$$v = k_{W-H}[Br_2]\cdot[\text{olefin}].$$

Here k_{W-H} is observed Winstein–Holness constant.

Bromine addition rate constant are listed in Table 2, together with mole fractions of the *chair*

Table 1. ^{13}C chemical shifts in the spectra of 2-R-*trans*-5,6-dibromo-1,3-dioxacycloheptanes (**IIa**–**IIf**) (δ_C,ppm, CCl_4)

Comp. no.	C^2	C^4, C^7	C^5, C^6	R
IIa	94.66	68.04	55.08	–
IIb	99.96	64.80, 67.33	55.57, 55.83	20.73
IIc	104.50	65.15, 67.66	55.60, 55.89	10.04 27.39
IId	108.14	66.06, 68.24	56.15, 56.44	19.39 32.76
IIe[a]	109.86	68.12, 68.37	55.42, 55.70	25.81 37.50
IIf [a,b]	99.95	64.44, 65.10	54.80, 54.92	–

[a] Solvent $CDCl_3$. [b] The signals of phenyl carbon atoms are omitted.

Table 2. Rate constant of bromine addition to the double bond of 2-R-1,3-dioxa-5-cycloheptenes *Ia–Ic*, *Ie*, *If* at 298 K (k_{W-H}, l mol^{-1} s^{-1}), molar fractions of the *chair* form (α_2), inductive substituent constant (σ^*) and vertcal ionization potentials of double bond (IP_1)

Comp. no.	$k_{W-H}\times 10^3$		α_2		σ^{*a}	IP_1[b]
	chloro-form	di-oxane	chloro-form	di-oxane		
Ia	7.9	8.2	0.11	0.12	0.49	9.54
Ib	9.9	25.2	0.17	0.18	0	9.41
Ic	10.0	32.3	0.17	0.18	–0.10	9.26
Id	39.8	54.3	0.82	0.80	–0.30	9.23
Ie	6.5	–	0.09	0.07	0.60	9.61

Table 3. Reaction rate constant for bromine addition to acetals **Ia**–**Ic**, **Ie**, and **If** calculated by iterations with equation (1) (k_{calc}, l mol^{-1} s^{-1}), and relative deviations from experimental parameters (Δ)[a]

Comp. no.	$k_{calc} \times 10^3$		Δ, %	
	chloroform	dioxane	chloroform	dioxane
Ia	7.7	8.1	2.5	1.2
Ib	10.0	26.0	–1.0	–3.2
Ic	9.9	33.0	1.0	–2.2
Ie	39.8	53.0	0.0	2.4
If	6.7	–	–3.1	–

[a] $\Delta = (k_{exp} - k_{calc})/k_{exp}$.

form, values of induction constant σ^* and vertical ionization potential of the doublei bond (IP_1).

Let us consider the results obtained both accounting for and omitting the conformational term.

The data show that the expected picture is observed in the both solvents: increase in electron donor properties of substituents leads to growing of the reaction rate constant, which is typical of the process where inductive substituent effects predominates over stereochemical ones [17,18]. At the same time, transfer from dioxane (ε 2.21) into more polar chloroform (ε 4.70) the observed decrease in the reaction rate also can be explained by simple consideration, namely, favorable stabilization of polar form in chloroform is compensated by diminished donor properties of the multiple bond and increased steric hindrances in the H-complex.

Now let us consider the results of treatment of the observed reaction rate constant accounting for the conformational term introduced in [1], according to relation (1):

$$\frac{10^{\log k^{R_i}_{W-H} - \rho^*\sigma^*} = (k_2 - k_3)\alpha_2 + k_3}{10^{\log k^{R_j}_{W-H} - \rho^*\sigma^*} = (k_2 - k_3)\alpha_2 + k_3}. \qquad (1)$$

Here k_2 and k_3 are the reaction rate constant for *chair* and *twist* forms (see scheme), ρ^* is the parameter of the reaction susceptibility in respect of electronic substituent effect at the C^2 atom.

The parameters $k_2 \times 10^3$ (l mol^{-1} s^{-1}), $k_3 \times 10^3$ (l mol^{-1} s^{-1}), ρ are as follows: 26.0, 26.0, and 1.03 (dioxane); 50.6, 1.7, and 0.07 (chloroform).

Table 3 lists reaction rate constants for bromine addition to the series of acetals **Ia**–**Ic**, **Ie**, and **If** calculated by iterations with equation (1) and the values of relative deviations from experimental parameters (Δ). If errors in measuring of experimental parameters used in equation (1) is taken into account, one can conclude that the deviations, which are equal or less than 3%, confirn correctness of the applied approach to description of reactivity of the chosen series of acetals.

From the data obtained follows that the partial conformer rate constants and the susceptibility parameters in respect of inductive substituent effects depend considerably on the solvent used. Namely, in dioxane, the effect of a substituent at the acetal carbon atom infuences nucleophilicity of the double bond only and does not induce difference in reactivity of the structures differ in steric architecture. This is a special case in the reactivity of the conformatinally inhomogenous substrates, when the conformers react with the same rate and formally it does not differ from the case of conformationally rigid substrates. Note that the similar picture was earlier observed for the Diles–Alder reaction with the same substrates but in the other solvent (acetone).

In the case of proton donor chloroform the situation is quite opposite: the reaction susceptibility parameter in respect of the substituent inductive effects is near zero, while the difference in reactivity of *chair* and *twist* forms achieves 30-fold. It is obvious that this is absolutely another situation. The typical electrophilic process now is transformed into a reaction close to neutral type, and the conclusion about decrease in the reaction rate due to formation of H-complex with chloroform is valid for the *twist* form only.

Without going into detail, let us advance certain ideas concerning these interesting facts.

Earlier [19] using the method of IR spectroscopy in the framework of Kagaiya's approach with reference proton donor (monodeuteromethanol) we studied basicity of substrates **Ia**–**f**. We showed that within the series the basicity of the acetals is determined by electronic and steric substituent effects and by steric structure of the heterocyclic fragment of a molecule. Therewith, the *chair* form gives stronger complexes with the proton donors than *twist*. We can assume that higher reactivity of the *chair* form results from stereochemical features of the H-complex formed. Note that unlike the substituents at the C^2 atom which is distant from the reaction center, the CCl_3 fragment in H-complex is close to the multiple bond and will express strong screening effect (higher than that of *t*-butyl group. In the case of the *chair* structure (C_s symmetry) the steric requirements at the

attack of bromine on the different sides of double bond are very different, and the attack from the side opposite to coordinated chloroform molecule is much easier. At the samei time, the similar difference seems doubtful for the *twist* form (C_2 symmetry), and steric hindrancesf for the attack of bromine should be equal for both the sides. Such stereochemical consideration in our view allows understanding of the forces leading to diminished reactivity of the *twist* form in chloroform as compared with dioxane and great increase in the relative rate constant for the *chair* form in the former solvent. This also explains increase in reactivity of *chair*-like form with growing in the medium polarity.

Theoretical study of the processes of complex formation by *chair* and *twist* conformers of seven-membered unsaturated cyclic acetals **Ia**–**If** with various proton donor reagents will be described in a separate communication.

To conclusion, let us give a criticism of the publication [20] denoted to the study of a relative problem, namely, to the reactivity in a big series of diaryl-, dialkyl-, alkylaryl(chlormethyl)phosphine oxides which form in solution *gauche* and *trans* conformers [21]. These authors did not use common approach for the analysis of experimental Winstein-Holness constants [1, 22] and applied equation in the form (2):

$$\log k = a_0 + a_1\sigma^* + a_2P_{A(B)}. \qquad (2)$$

Here $P_{A(B)}$ is steric factor depending on the conformational state of the substrate in the A $\rightleftarrows$ B equilibrium. We suggest that such multiparametric equations have no physical meaning because applying of the principle of linearity of free energy to the reactions of conformers needs to combine the Taft type and Winstein–Holness equations {see the general form of the system of equations (1) in the publication [1]}.

EXPERIMENTAL

The ^{13}C NMR spectra of the adducts were registered on a Bruker WH-90 instrument with internal HMDS. The ^1H NMR spectrum was taken up on a Varian Unity-300 spectrometer with internal HMDS.

Spectrophotometric measurements were pereformed on a SF-46 spectrophotometer with termostated cell chamber, temperature fluctuations ±0.1°C. The reaction rate constants $k_{W–H}$ were determined under the conditions of pseudo first reaction order by measurement of decrease in absorption of bromine solution (λ 360–385 nm). The olefin concentration was varied in the range of $(3–60)\times10^{-3}$ mol l^{-1}, that of bromine in the range of $(2.7–4)\times10^{-3}$ mol l^{-1}.

Table 4. Boiling points, n_D^{20} and elemental analyses of 2-R-*trans*-5,6-dibrom-1,3-dioxacycloheptanes **IIb, IIc, IIe,** and **IIf**

Comp. no.	bp, °C (*p*, mm)	n_D^{20}
IIb	132 (30)	1.5290
IIc	124–126 (20)	1.5220
IIe	132 (20)	1.5110
IIf	54.5–55[a]	–

Comp. no.	Found, %		Formula	Calculated, %	
	C	H		C	H
IIb	26.67	3.64	¢6Æ10Br2O2	26.30	3.68
IIc	29.33	4.01	$C_7H_{12}Br_2O_2$	29.19	4.20
IIe	34.81	4.85	$C_9H_{16}Br_2O_2$	34.20	5.10
IIf	39.62	3.96	$C_{11}H_{12}Br_2O_2$	39.32	3.60

[a] mp.

In a special experiment we established that continuous passing of light beam through the cell does not affect the reaction rate. All measurements were repeated 3–5 times. Error in determination of the rate constants is not higher than 5%. The correlation coefficient for the kinetical curves anamorphoses was 0.999 or higher with the reaction propagation not less than 70%. The data were treated using a 586/7 PC computer using a STATISTICA-4.3 package (StatSoft, Inc., 1993).

The parent acetals and compounds **Ia**–**If** were prepared according to methods in [23].

Synthesis of dibromide **IIa** was described in [10], mp 36–37°C [10]. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.76–3.84 m (2H), 4.08–4.17 m (4H), 4.76 s (2H). Acetal **IId** was prepared by the procedure in [9], bp 134°C (20 mm), n_D^{20} 1.5067, {bp 94–96°C (15 mm) [9]}.

2-R-*trans*-5,6-Dibromo-1,3-dioxacycloheptanes (IIa–IIe). To a solution of 2 g of acetal **Ia**–**If** in 15 ml of tetrachloromethane equimolar amount of bromine was added dropwise in dark with continuous stirring at room temperature. The solvent was then removed and reaction product **IIb**–**IIe** was distilled in a vacuum. Compound **IIf** was crystallized from ethanol, yield (69–93%). Characteristics of the compounds obtained are listed in Table 4.

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