## Halogenated arenes in the Duff reaction at high pressures 1. The effect of reaction conditions on the reactivity of fluorobenzene

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The reaction of fluorobenzene with urotropine in trifluoroacetic acid (TFAA) at high pressures and temperatures affords predominantly fluorobenzaldehydes and N-(fluorophenylmethyl)trifluoroacetamides. The yields of these products depend considerably on the reaction conditions. The rates of their formation have the maximum values at the moment of the phase transition (PT) of TFAA. A new efficient cyclic (dynamic) regime is proposed for the synthesis at high pressures. The regime involves periodically occurring PT of the solvent. The change in the relative rate of product formation with the degree of fluorobenzene conversion is wave-like.

Key words: high pressure, phase transition, cyclic regime, relative rate, Duff reaction, fluorobenzene, fluorobenzaldehydes, *N*-(fluorophenylmethyl)trifluoroacetamides.

The reactions of aromatic hydrocarbons with urotropine in protic acids to afford aldehydes (the Duff reaction)<sup>1</sup> is applicable only to sufficiently activated compounds (derivatives of aromatic amines, phenols, etc.). The methods known to introduce halogenated benzenes into the Duff reaction suffer some drawbacks. Poor reproducibility of the results and low yields of aldehydes are typical of the reaction, which is carried out in polyphosphonic acid.<sup>2</sup> Satisfactoty yields have been reported for the reaction in liquid HF at a high pressure,<sup>3</sup> but this method needs special equipment for the reaction and for handling HF. We propose a method for the introduction of halogenated arenes and hexamethylenetetramine (HMTA) into the reaction at high pressures (p) and temperatures (T) in trifluoroacetic acid (TFAA), which makes it possible to obtain the corresponding aldehydes and/or N-(arylmethyl)trifluoroacetamides.<sup>4</sup> Aldehydes are normal products of the Duff reaction, but we are the first to report the formation of amides.

In the present work we investigate in detail the influence of certain factors on the conversion of fluorobenzene (1). The GC/MS analysis of reaction (1) showed that the formation of isomers of aldehydes (2, 3) and amides (4, 5), was accompanied by side reactions affording, in particular, benzylamines (6) (see Experimental):

$$FC_{6}H_{5} \xrightarrow{\text{TFAA, HMTA}} FC_{6}H_{4}CHO +$$

$$1 \xrightarrow{P} FC_{6}H_{4}CH_{2}NHCOCF_{3} + FC_{6}H_{4}CH_{2}NRR'$$

$$4, 5 \qquad 6$$

$$(1)$$

Based on special experiments, we chose a molar reagent ratio HMTA : 1 : TFAA = 1 : 1 : 20 which permits one to obtain both sufficiently high absolute (molar) yields and satisfactory relative yields (with respect to unit volume). Special attention to the latter values is necessary because the reaction at high pressures is carried out in reactors of small volume.

As phase transitions of the solvents and the components of the reaction often significantly influence the rate of the reaction and yield of the products under high pressures (e.g., see Refs. 5 and 6), it seemed reasonable to investigate the reaction mixture from this point of view. The data obtained are presented in Fig. 1. A phase transition at 90 °C was observed only for pure TFAA. The obscured phase transition for the reaction mixture may result from a "blur" of crystallization due to the intensely occurring reaction (the yield of the aldehyde alone is about 30 % in one separate measurement) and/or partial separation of the solvent.

Figure 1 illustrates two methods of bringing the system to the working conditions. The first one involves preliminary heating of the reaction mixture at 20 MPa followed by an increase in pressure (T, p, dashed line), while the second one consists of increasing the pressure at ~20 °C followed by heating (p, T, dash-dot line). For example, when the reaction conditions (76 °C and 600 MPa) are attained by the (T, p) method, the reaction mixture will always be in the liquid state, whereas the (p, T) method will bring the system into the frozen state at ~300 MPa and the increase in temperature to ~70 °C will again result in melting. Thus, one can predict the phase state of the system depending on the reaction conditions and the methods for their attainment.

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Fig. 1. Phase diagram of trifluoroacetic acid and its mixtures: *1*, values of phase transitions for TFAA; *2*, the same for the reaction mixture. I, liquid phase; II, crystalline state.

Taking into account the ways described for reaching the working conditions of the system, we studied the effect of pressure on the formylation of 1 (Fig. 2). When the (p, T) method at 76 °C was used (Fig. 2, curve I), the yield reached its maximum at 500-600 MPa, while at ≥900 MPa aldehydes were not found at all. Taking into consideration the phase diagram (Fig. 1), one may conclude that the reaction proceeds extremely slowly in the region where TFAA is in the crystalline state. A comparison of curves 1 and 2 (76 °C, the (T, p) method) shows that the yields are close up to the region of crystallization. However, at pressures >600 MPa a difference between the two methods appears. This fact allowed us to propose that in the latter case, the reaction at p > 600 MPa proceeds mainly at the moment of the phase transition of TFAA. This proposal is supported, for example, by the results of experiments at 1000 MPa (T, p). In this case, when the system was brought to the working regime (reference point for the reaction time, t = 0), 6 % aldehydes 2, 3 were obtained, while the subsequent reaction resulted in a 10 % overall yield of aldehydes after 10 min and 12 % after 50 min. Increasing the reaction time to 8 h afforded only 16 % 2 and 3, whereas side processes were insignificant.

At 90 °C (Fig. 2, curves 3 and 4), the maximum yields are also shifted towards higher pressures than those of the same dependences at 76 °C. However, unlike the latter case, curves 3 and 4 nearly coincide if the yields obtained as the system was being brought to the working parameters (8-12 % at 800-1000 MPa for)



**Fig. 2.** Plot of the yield of benzaldehydes (2, 3) vs. pressure. The reaction time was 1 h. 1, 76 °C (p, T); 2, 76 °C (T, p); 3, 90 °C (p, T); 4, 90 °C (T, p).

the (T, p) method and about 0 % for the (p, T) method) are subtracted.

We found that, for the (T, p) method, a noticeable portion (at 90 °C) or even the main portion (at 76 °C) of the product was formed as the pressure was increasing. This fact prompted us to investigate the reaction in a dynamic (cyclic) regime with regard to pressure. After heating to a required temperature, one cycle of the regime involves increasing the pressure to a chosen value, holding it there for 1 min, then decreasing the pressure to 20 MPa and holding it there for 1 min.

As can be seen from the data in Table 1, the dynamic regime allows us to obtain equal yields in significantly shorter time intervals (cf. experiments 4 and 7, 9; experiments 10 and 16, 19). At comparable reaction times (~30 min) and maximum pressure (1000 MPa), the static regime afforded yields several times smaller than the dynamic regime (cf. experiments 4 and  $\delta$ ; experiments 10 and 17, 18). This result can be explained by the decrease in the reaction rate in the region of the crystalline state of TFAA (see above). At the minimum pressure (20 MPa), the reaction proceeds extremely slowly (cf. experiments 4 and 5; experiments 10 and 13). However, at intermediate pressure values, when the reaction rate in the static regime is close to maximum (see Fig. 2), the dynamic regime invariably gives better results (cf. experiments 4 and 6; experiments 10 and 15). However, the dynamic regime did not always offer advantages over the static one (cf. experiments 10-12, Table 1). An increase in the yields was observed only in

Experi- ment	p/MPa (regime)	Reaction time, t	<i>Т</i> /°С	Fluorobenzene 1 recovery (%)	Yield of aldehydes 2+3 (%)	Yield of amides 4+5 (%)
1*	20÷1000 (1 cycle)	2 min	90	*	12	
2	20÷1000 (5 cycles)	12 min	90	52	24	4
3	20÷1000 (7 cycles)	15 min	90	38	32	4
4	20÷1000 (10 cycles)	30 min	90	10	44	12
5	20 (p, T)	30 min	90	96	2	0
6	600 (p, T)	1 h	90	52	30	2
7	600 (p, T)	8 h	90	8	46	8
8*	1000 (T, p)	30 min	90		22	2
9	1000 (T, p)	8 h	90	26	28	12
10	20÷1000 (10 cycles)	30 min	76	54	28	2
11	20÷600 (10 cycles)	25 min	76	84	12	0
12	600÷1000 (10 cycles)	25 min	76	70	10	0
13	20 $(T, p)$	30 min	76	96	0	0
14*	20(T, p)	12 h	76		4	0
15*	600 (T, p)	1 h	76		16	_
16*	500 (p, T)	4 h	76		28	
17	1000 (T, p)	10 min	76	76	10	0
18*	1000 (T, p)	1 h	76		12	
19	1000 ( <i>T</i> , <i>p</i> )	8 h	76	74	16	4

Table 1. Formation of the products in the reaction mixture in different regimes

*Note.* The yields were calculated on the basis of GLC data for the reaction mixtures. Average values from several experiments are given with an accuracy of  $\pm 0.02$  %. \*The values were not determined.

the case of alternate melting-crystallization of the reaction mixture. In experiment 12, the yield remained constant after the phase transition (cf. experiment 17). The changes in pressure in the liquid phase region (experiment 11) did not give any significant advantages over the process at a constant pressure (cf. experiment 15). The overall yield in experiments 11 and 12 was lower than in experiment 10, in which periodic phase transitions of the solvent were observed. The conclu-

Fig. 3. Plot of the yield of fluorobenzaldehydes (2, 3) (X; I), according to the spline approximation method, number of discontinuity points N = 3, standard deviation S = 5.1 %) and the relative rate of their formation (v; 2), according to the spline approximation method) vs degree of fluorobenzene conversion (Z). a, yields under the conditions of static pressure; b, in the cyclic regime.

sions about the phase state of the reaction mixture during the experiments were made on the basis of the diagram shown in Fig. 1.

Hence, the moment of phase transition is accompanied by accelaration of the reaction of fluorobenzene, although a significant deceleration of the main and side reactions is observed after the phase transition.

The data obtained allow us to conclude that reaction (1) proceeds in several directions and that the relative



Fig. 4. Plot of the overall yield (X; I), according to the spline approximation method, N = 3, S = 4.2%) and the relative rate of formation of fluorobenzaldehydes (2, 3) and N-(fluorophenylmethyl)trifluoroacetamides (4, 5) (v; 2, according to the spline approximation method) vs degree of fluorobenzene conversion (Z). a, yields under the conditions of static pressure; b, in the cyclic regime; c, with the addition of 0.26 mol of 3 to the starting reaction mixture.

Experiment (Fig. 4)	Experiment (Fig. 3)	Consumpt of 1 (%)	ion Yield of 2+3 (%)	Yield of <b>4+5</b> (%)	Conditions: p/MPa, (regime), t/h, T/°C
1	1	4	2	0	600; ( <i>T</i> , <i>p</i> ); 0; 90
2	2	8	2	0	20; (p, T); 1; 90
3	3	10	4	0	500; (T, p); 10 min; 76
4	4	16	8	0	800; (T, p); 10 min; 76
5	5	16	12	0	20÷600; (10 cycles); 76
6	_	18	8	0	800; ( <i>T</i> , <i>p</i> ); 0; 90
7	6	22	10	0	200; (p, T); 1; 90
8	7	24	10	0	1000; (T, p); 10 min; 76
9	8	26	16	4	1000; (T, p); 8; 76
10	9	28	16	2	1000; (p, T); 8; 90
11	10	30	10	0	600÷1000; (10 cycles); 76
12	11	32	18	2	1000; (T, p); 10 min; 90
13		34	12	16	20; (p, T); 2; 130
14*		34	12 (38)	0	600; (p, T); 1; 90
15	12	38	28	0	20÷1000; (3 cycles); 90
16	13	40	34	4	600; $(p, T)$ ; 1; 90 after that
					the mixture was kept at 20;
				•	(T, p); 6; 90
17	14	46	28	2	$20 \div 1000; (10 \text{ cycles}); 76$
18	15	48	24	4	$20 \div 1000$ ; (5 cycles); 90
19	16	48	30	2	600; (p, T); 1; 90
20**		50	36	8	600; ( <i>p</i> , <i>T</i> ); 1; 90
21	17	62	32	4	$20 \div 1000$ ; (7 cycles); 90
22		64	16	24	20; (p, T); 12; 130
23	18	64	28	6	1000; (T, p); 2; 90
24	19	74	28	12	600; (p, T); 2; 90
25	20	74	26	12	600; $(p, 1)$ ; 1; 90 after that
					the mixture was kept at 1000;
				_	(T, p); 2; 90
26	21	78	36	8	1000; (p, T); 0; 130
27	22	78	34	8	$20 \div 1000$ ; (8 cycles); 90
28	23	82	34	12	500; (p, T); 3; 100
29	24	84	34	8	500; (T, p); 8; 80
30		86	28	10	800; ( <i>p</i> , <i>1</i> ); 8; 90
31	25	90	44	12	$20 \div 1000;$ (10 cycles); 90
32	_	92	38	12	700; ( <i>T</i> , <i>p</i> ); 8; 90
33	_	92	44	14	500; (p, T); 8; 90
34	26	92	46	8	600; (p, T); 8; 90
35*		100	34 (60)	18	600; (p, T); 1; 130

Table 2. Consumption of fluorobenzene and formation of products under different conditions

Note. The yields and consumption were calculated on the basis of GLC data for the reaction mixtures. Average values from several experiments are given with an accuracy of  $\pm 0.02$  %. \* With the addition of 0.26 mol of 3 into the starting mixture. \*\* Molar ratio 1 : HMTA : TFAA = 1 : 1 : 23.

rates of the accumulation of aldehydes and amines change periodically as the degree of fluorobenzene conversion increases, and do not depend on the method of reaching this degree of conversion.

Table 2 summarizes the experiments carried out under different conditions, which served as the basis for plotting the yields of products vs. degree of conversion. Curves 1 and 2 (Figs. 3 and 4) were obtained by splineapproximation<sup>8</sup> of these experimental points. Curve 1 was constructed using the spline-approximation with respect to the least sum of the squared deviations of the points from the curve. The condition of the continuity of the derivative of this curve was met (curve 2).

In our case, the derivative of curve 2 is equal to the yield of aldehydes (or the overall yield for amides) with

respect to 1 % of the reacted fluorobenzene at any degree of its conversion.

Curves 1 and 2 (see Fig. 3) can be interpreted in the following way. In the interval below 40 % conversion of 1, the reaction proceeds towards the formation of aldehyde, then, up to 70 % conversion, the relative rate (v) of aldehyde formation decreases sharply. After 80 % conversion, the rate increases again. Thus, the formy-lation reaction seems to be "revived" twice in the course of the conversion of 1, *i.e.*, it has two impulses.

The corresponding plot of the overall yield of aldehydes and amides (see Fig. 4) is more stable since practically all experimental results are in agreement with it. The comparison of curves 1 in Fig. 3 and 4 shows that the latter curve is based on the "aldehyde" compo-

nent and both curves are synchronous. The latter dependence is more general due to the fact that the formation of amides alone was noted for some arylhalides under the conditions studied.<sup>4</sup>

Previously, a similar wave-like dependence was found in an investigation of some reactions of homolytic decomposition.<sup>7</sup> At this time, the reasons for the existence of phenomena of this type are obscure. They manifest themselves as a periodic redistribution of free energy in different directions within an overall chemical process.

## Experimental

Melting points were determined on a Kofler hot stage. <sup>1</sup>H NMR spectra were recorded on a Bruker WM-250 instrument using HMDS as the standard ( $\delta = 0.055$ ). Qualitative GC/MS analysis of the reaction mixtures was carried out on a Finnigan MAT INCOS-50 quadruple chromato-mass spectrometer (ionization by electron impact of 70 eV, capillary column 0.25 mm × 30 m with grafted 0.25  $\mu$  polydimethylsiloxane phase). Quantitative GLC analyses were carried out on a Biokhrom 1 M gas-liquid chromatograph (glass column 2 mm × 3 m, Chromaton N AW DMCS as the carrier, 5 % XE 60 phase). Normal hydrocarbons were used as the standards for calibration.

The reaction was carried out in teflon tubes on a testing unit.<sup>9</sup> The values of the phase transitions were determined from changes in the volumes of the reaction mixtures.<sup>10</sup>

"Chemically pure" fluorobenzene was used without additional purification.

2- and 4-Fluorobenzaldehydes (2 and 3). The excess TFAA was distilled off from the reaction mixture, and the residue was neutralized with a NaHCO<sub>3</sub> solution, extracted three times with ether, and the combined extracts were washed with an HCl solution. Aldehydes were isolated from ether as bisulfate derivatives. The salts obtained were decomposed. The products were identified by retention times (GLC). <sup>1</sup>H NMR of 2-fluorobenzaldehyde 2 (CDCl<sub>3</sub>), &: 7.85–8.00 (m, 4 H, Ar); 10.65 (s, 1 H, CHO) (~10 % of the isomer in the mixture). MS, [M]<sup>+</sup> = 124. <sup>1</sup>H NMR of 4-fluorobenzaldehyde 3 (CDCl<sub>3</sub>), &: 7.4–7.6 (m, 2 H, Ar); 8.05–8.15 (m, 2 H, Ar); 10.25 (s, 1 H, CHO) (~90 % of the isomer in the mixture). MS, [M]<sup>+</sup> = 124.

*N*-(2- and 4-Fluorophenylmethyl)trifluoroacetamides (4 and 5 with the ratio in the mixture 4 : 5  $\approx$  30 : 70). After extracting aldehydes, the ethereal solution was concentrated, and the residue was chromatographically separated on 40-60  $\mu$  silica gel previously eluted with hexane and then with a hexane-ether mixture (2 : 1) ( $R_f = 0.35$  on Silufol). Rerystallization from hexane afforded pure *N*-(4-fluorophenylmethyl)trifluoroacetamide (5), m.p. 75-77 °C. Found (%): C, 49.19; H, 3.21; F, 34.70; N, 6.25. C<sub>9</sub>H<sub>7</sub>F<sub>4</sub>NO. Calculated (%): C, 48.88; H, 3.19; F, 34.37; N, 6.33. <sup>1</sup>H NMR of compound 5 (CDCl<sub>3</sub>),  $\delta$ : 4.50 (d, 2 H, ArCH<sub>2</sub>); 6.7-7.0 (br, 1 H, NH); 7.0-7.1 (m, 2 H, Ar); 7.25-7.35 (m, 2 H, Ar). MS, [M]<sup>+</sup> = 221. Sedishev et al.

The GC/MS study of the mixtures is illustrated by the spectra of the compounds obtained in the experiment at 130 °C, (p, T), 1000 MPa, 2 h, addition of 2 gram-mol of water to the starting mixture (in this experiment, the maximum amount of side products was formed). MS, m/z (I (%)), nonidentified compound (6a): 203 [M]<sup>+</sup> (100), 183 (50), 109  $[CH_2C_6H_4F]^+$  (50), 83 (25), 75 (7), 63 (8), 57 (15), 39 (8), 28 (25); (4(2)-fluorophenylmethyl)ethylmethyl amine (6b) (for one of two isomers): 153  $[M]^+$  (100), 124  $[M-2CH_3+H]^+$ (25), 109  $[CH_2C_6H_4F]^+$  (52), 97 (20), 83 (12), 75 (8), 57 (12), 28 (80); (4(2)-fluorophenylmethyl)ethylmethyl amine (6c) (for one of two isomers): 167 [M]<sup>+</sup> (100), 152 [M-CH<sub>3</sub>]<sup>+</sup> (12), 138  $[M-C_2H_5]^+$  (6), 124  $[M-C_3H_7+H]^+$  (40), 109  $[CH_2C_6H_4F]^+$  (100), 97 (30), 83 (30), 57 (12), 42 (50), 28 (50); bis(4(2)-fluorophenylmethyl)ethyl amine (6d) (for one of three isomers): 261  $[M]^+$  (5), 152  $[M-CH_2C_6H_4F]^+$  (100), 124  $[M-CH_2C_6H_4F-C_2H_5]^+$  (65), 109  $[CH_2C_6H_4F]^+$  (80), 97 (30), 83 (25), 57 (10), 28 (55); N-(2-fluorophenylmethyl)trifluoroacetamide (4) (the spectrum is similar to that of 5): 221  $[M]^+$  (29), 132  $[M-89]^+$  (18), 109  $[CH_2C_6H_4F]^+$  $(100), 97 [COCF_3]^+ (9), 83 (19), 69 (29), 50 (10), 39 (7), 28$ (24): 2-fluorobenzaldehyde (2) (the spectrum is similar to that of 3): 124 [M]<sup>+</sup> (79), 95 [M-CO]<sup>+</sup> (54), 75 (26), 70 (13), 50 (21), 41 (8), 28 (49), 18 (100).

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