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INTRAMOLECULAR ACID-CATALYZED REACTIONS OF o-CARBOMETHOXY-ω-DIAZOACETOPHENONES

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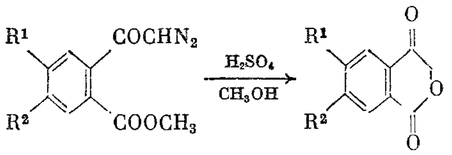
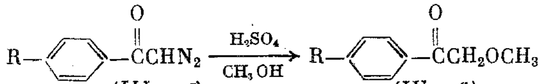
ω-Diazoacetophenones (DAP) are broadly applied as model compounds in studying the correlation between structure and reactivity of diazoketones in their acid-catalyzed decomposition reactions [1, 2].

In order to elucidate the intramolecular (anchimeric) effect of the o-CO_2CH_3 group on the rate and mechanism of acid-catalyzed DAP decomposition, we studied the decomposition kinetics of o-carbomethoxy-ω-diazoacetophenones (CMDAP) (Ia-h) and DAP (IIIa-f) in methanol on exposure to H_2SO_4.



(Ia–h) (IIa–h)

$R^1 = H$, $R^2 = OCH_3$ (a), $R^1 = R^2 = H$ (b), $R^1 = H$, $R^2 = Cl$ (c), $R^1 = CO_2CH_3$, $R^2 = H$ (d), $R^1 = Cl$, $R^2 = H$ (e), $R^1 = H$, $R^2 = CO_2CH_3$ (f), $R^1 = NO_2$, $R^2 = H$ (g), $R^1 = H$, $R^2 = NO_2$ (h).



(IIIa–f) (IVa–f)

$R = OCH_3$ (a), $R = CH_3$ (b), $R = H$ (c), $R = Cl$ (d), $R = Br$ (e), $R = NO_2$ (f).

The synthesis of (Ia-h) and (IIIa-f) was performed according to [3, 4] by acylation of diazomethane with the appropriate carbonic acid chloranhydrides. Thin layer chromatographic analysis of the CMDAP (Ia-h) acid conversion products showed that isochromane-1,4-diones (IIa-h) were formed exclusively. The structure of compounds (Ia-h) and (IIa-h) was confirmed by physicochemical methods (Tables 1 and 2). The properties of compounds (IIIa-f) correspond to the literature data [4].

The kinetics of the acid-catalyzed decomposition of (Ia-h) and (IIIa-f) were followed spectrophotometrically by the disappearance of the characteristic absorption bands of the diazocarbonyl group (Table 3). The reactions are of the first order with respect to diazoketone and acid. The k_{ef} values ($k_{ef} = k_{obs}/[H^+]$) are shown in Table 3.

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TABLE 1. Physicochemical Characteristics of o-Carbomethoxy-ω-Diazoacetophenones (Ia-h)

Compound	R_f	Yield, %	mp., °C	IR spectrum, (ν, cm⁻¹)			PMR spectrum (δ, ppm, J, Hz)		
				N≡N	C=O	Ar	$COCHN_2$	CO_2CH_3	Ar
(Ia)	0,34*	60	129–130	2110	1725, 1600	1555	5.64	3,86	3,92 s (3H, OCH_3), 6,98 q (1H, H^5, $J=8,1$ and 2), 7,20 d (1H, H^3, $J=2$), 7,41 d (1H, H^6, $J=8,1$)
(Ib)	0,30†	75	61–62	2130, 2100	1725, 1600	1585, 1560	5,55	3,88	7,37–7,75 m (4H, C_6H_4)
(Ic)	0,34†	50	109–110	2115, 2105	1730, 1620	1585, 1560	5,60	3,88	7,38 d (1H, H^6, $J=8,1$), 7,50 d (1H, H^5, $J=8,1$), 7,76 s (1H, H^3)
(Id)	0.64‡	27	–	2100	1705, 1600	1550	5.75	3,93	3,89 s (3H, CO_2CH_3), 7,83 d (1H, H^3, $J=8,3$), 8,05 d (1H, H^6, $J=2$), 8,16 q (1H, H^4, $J=8,3$ and 2)
(Ie)	0,40†	25	94–95	2115, 2090	1725, 1605	1570, 1560	5,54	3,88	7,32 d (1H, H^6, $J=1,5$), 7,39 q (1H, H^4, $J=8,1$ and 1.5), 7,73 d (1H, H^3, $J=8,1$)
(If)	0.53‡	30	–	2094	1705, 1600	1550	5.75	3,93	3,96 s (3H, CO_2CH_3), 7,52 d (1H, H^6, $J=8,1$), 8,16 d (1H, H^5, $J=8,1$), 8,48 s (1H, H^3)
(Ig)	0.45†	19	97–98	2130	1730, 1620	1605, 1570, 1530 (NO_2)	5,73	3.95	7,96 d (1H, H^3, $J=8,3$), 8,30 d (1H, H^6, $J=2,2$), 8,45 q (1H, H^4, $J=8,3$)
(Ih)	0,34†	20	64–65	2130	1730, 1620	1605, 1570, 1530 (NO_2)	5,73	3.95	7,65 d (1H, H^6, $J=8,1$), 8,38 d (1H, H^5, $J=8,1$), 8,62 s (1H, H^3)

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*Benzene/ethyl acetate, 3:1.

†The same, 9:1.

‡The same, 2:1.

TABLE 2. Physicochemical Characteristics of Compounds (IIa-h)

Compound	R_f*	Yield, %	mp., °C	IR spectrum (ν, cm⁻¹)		PMR spectrum (δ, ppm., J, Hz)	
				C=O	Ar	CH_2	Ar
(IIa)	0,49	95	173–174	1720, 1680	1590	5,13 s	4,02 s (3H, OCH_3), 7,41q (1H, H^5, $J=8{,}1$ and 1,7), 7,59 d (1H, H^3, $J=1{,}7$), 7,97 d (1H, H^6, $J=8{,}1$)
(IIb)	0,55	80	146	1730, 1680	1580	5,09 s	7,73–7,85m (2H, H^4, H^5), 8,02 d (1H, H^6, $J=8{,}1$), 8,21 d (1H, H^3, $J=8{,}1$)
(IIc)	0,63	80	137–138	1705, 1670	1565	5,13 s	7,73 q (1H, H^5, $J=8{,}1$ and 2), 7,96 d (1H, H^6, $J=8{,}1$), 8,18 d (1H, H^3, $J=2$)
(IId)	0,58	80	136–137	1725, 1705, 1680	1612, 1580	5,17 s	4,00 s (3H, CO_2CH_3), 8,35 d (1H, H^3, $J=8$), 8,49 q (1H, H^4, $J=8$ and 1,7), 8,69 d (1H, H^6, $J=1{,}7$)
(IIe)	0,65	90	131–132	1730, 1710	1600	5,13 s	7,82 q (1H, H^4, $J=8$ and 2), 8,02 d (1H, H^6, $J=2$), 8,23 d (1H, H^3, $J=8$)
(IIf)	0,55	80	100–102	1730, 1705, 1680	1600, 1580	5,15 s	4,00 s (3H, CO_2CH_3), 8,10 d (1H, H^6, $J=8$), 8,40 q (1H, H^5, $J=8$ and 2), 8,86 d (1H, H^3, $J=2$)
(IIg)	0,51	60	118–120	1700	1600 (C=C) 1530 (NO_2)	5,24 s	8,50 d (1H, H^3, $J=8$), 8,67 q (1H, H^4, $J=8$ and 2), 8,86 d (1H, H^6, $J=2$)
(IIh)	0,48	40	123–125	1720	1640, 1620, 1580 (C=C) 1530 (NO_2)	5,18 s	8,25 d (1H, H^6, $J=8$); 8,58 q (1H, H^5, $J=8$ and 2), 9,03 d (1H, H^3, $J=2$)

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*Benzene/ethyl acetate, 9:1.

TABLE 3. Kinetic Characteristics of the Decomposition of Compounds (Ia-h) and (IIIa-f)

Compound	λ *,nm (log ε)	$k_{ef(H)}\cdot 10^2$, liter/mole·sec	H_2SO_4 †, $10^2\cdot M$	$k_{ef(D)}\cdot 10^2$, liter/mole·sec	H_2SO_4, $10^2\cdot M$	k_H/k_D
(Ia)	303 (4,17)	380	0,10–0,70	44	0,10–0,90	8,64
(Ib)	288 (4,27)	165	0,80–0,95	27,1	0,80–0,95	6,09
(Ic)	293 (4,17)	78	0,80–0,95	15,6	0,80–0,95	5,00
(Id)	290 (4,11)	65	0,80–0,95	13,3	0,80–0,95	4,89
(Ie)	292 (3,92)	62	0,80–0,95	12,7	0,80–0,95	4,88
(If)	292 (3,97)	48,3	0,80–4,95	11,6	0,80–4,95	4,16
(Ig)	291 Hz (4,03)	19,6	1,89–5,19	7,0	1,89–5,19	2,80
(Ih)	291 Hz (4,06)	15,6	1,89–5,19	6,1	1,89–5,19	2,56
(IIIa)	306 (4,32)	28,9	1,89–5,19	29,3	1,89–5,19	0,99
(IIIb)	300 (4,19)	12,2	1,89–5,19	12,5	1,89–5,19	0,98
(IIIc)	299 (4,15)	6,72	1,89–5,19	7,47	1,89–5,19	0,90
(IIId)	300 (4,10)	3,83	1,89–5,19	4,03	1,89–5,19	0,95
(IIIe)	299 (4,06)	3,33	1,89–5,19	3,56	1,89–5,19	0,94
(IIIf)	307 (4,02)	0,67	5,19–14,06	0,78	5,19–14,06	0,86

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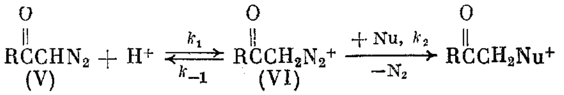
*Effective wavelength.

†Effective acid concentration interval.

According to [1], the acid-catalyzed decomposition of diazoketones consists of a pre-equilibrium protonation of the diazocarbonyl group and the subsequent decomposition of the methylenediazonium ion (VI).



$$\underset{(V)}{R\overset{O}{\overset{\|}{C}}CHN_2} + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{(VI)}{R\overset{O}{\overset{\|}{C}}CH_2N_2^+} \xrightarrow[-N_2]{+Nu,\ k_2} R\overset{O}{\overset{\|}{C}}CH_2Nu^+$$

We know that for primary diazoketones (V), including p- and m-substituted DAP, the limiting reaction step is the decomposition of ion (VI) [5]. However, in many cases the anchimeric effect of the functional groups in primary diazoketones leads to such a large increase in the acid-catalyzed decomposition rate of these ions that protonation may become the limiting step of the process (A-S_E2 mechanism) [6, 7].

Our study of the kinetic isotope effect of the solvent on CMDAP (Ia-h) decomposition in methanol on exposure to H_2SO_4 showed that the reaction rate in CH_3OH was significantly higher than in CD_3OD (see Table 3). These data, in accordance with [8], lead us to conclude that the rate-determining step in the decomposition of (Ia-h) is the protonation of the diazocarbonyl group. Obviously, the rate of this process will be determined only by the basicity of the azomethine C atom, at which protonation occurs [1]. Consequently, an increase in the electron donor properties of the CMDAP aromatic ring substituents should be accompanied by an increase in the reaction rate. Indeed, we found a linear correlation between the $\log k_{ef}$ values and Hammet's σ constants (σ_m and σ_p, respectively, were used for the R^1 and R^2 substituents [9]), with a negative value for the reaction constant ρ (Fig. 1).

This correlation was also observed for DAP (IIIa-f) decomposition reactions in methanol on exposure to H_2SO_4 (Fig. 2). However, unlike the reactions with CMDAP (Ia-h), the DAP methanolysis reactions can best be described by using σ^+ substituent constants; concrete values for these constants were determined in [4, 10]. Thus, the observed difference in substituent constant values used to describe the decomposition reactions of CMDAP and DAP indicates a decrease in direct conjugation between the protonated diazocarbonyl group and the p substituent in the benzene ring of CMDAP as compared to DAP, due to intramolecular interactions of CO_2CH_3 and $COCHN_2$.

The presence of a linear correlation between $\log k_{ef}$ and σ (σ^+) for reactions of diazoketones (Ia-h) and (IIIa-f) allows the determination of the magnitude of ω-diazoacetophenone decomposition acceleration due to the anchimeric assistance of the CO_2CH_3 group. This can be done by comparing the appropriate decomposition rate constants for the given compounds, which can be measured directly or calculated from the correlation equations. Thus, from the data presented in Figs. 1 and 2 it can readily be shown that the acid-catalyzed decomposition rate of CMDAP (Ia-h) is higher than the decomposition rate of their o-unsubstituted analogs (IIIa-f) by 13-25 times.

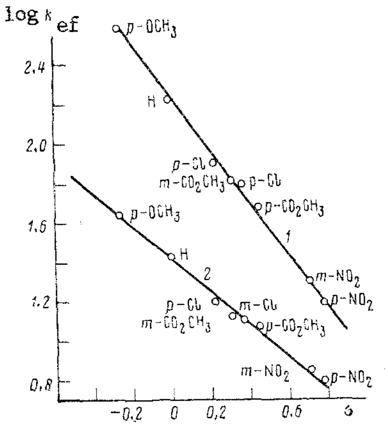


Fig. 1

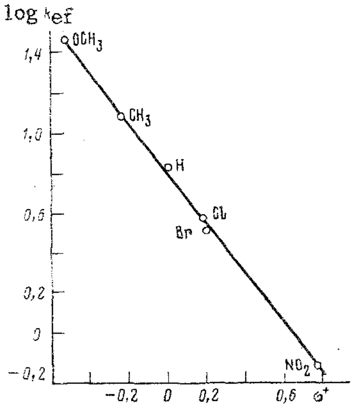


Fig. 2

Fig. 1. Dependence of the CMDAP (Ia-h) decomposition rates on Hammet's σ constants: 1) 20°C, CH_3OH, $\rho = -1.31$, $r = 0.998$, $s = 0.033$; 2) 20°C, CD_3OD, $\rho = -0.81$, $r = 0.997$, $s = 0.025$.

Fig. 2. Dependence of DAP (IIIa-f) decomposition rates on the electrophilic substituent constants σ^+ [4]: 20°C, CH_3OH, $\rho = -1.25$, $r = 0.999$, $s = 0.019$ (for an analogous dependence on Hammet's σ constants, the correlation equation parameters are: $\rho = -1.46$, $r = 0.986$, $s = 0.087$).

EXPERIMENTAL

PMR spectra were recorded on a Bruker WM-250 instrument (250 MHz) in $CDCl_3$ with TMS as internal standard. IR spectra were recorded on a Specord 75-IR instrument in petrolatum oil. Mass spectra were recorded on an MX-1303 mass spectrometer with direct feed of material into the ion source; ionizing electron energy, 70 eV; emission current, 150 μA; temperature, 40-120°C. Column chromatography was performed using silica gel $L_{40/100}$ and benzene–ethyl acetate as eluant. The purity of materials was determined by TLC in a benzene–ethyl acetate system on Silufol UV-254 plates. DAP (IIIa-f) were obtained according to [4].

2-Carbomethoxy-ω-diazoacetophenones (IIIa-f) (General Procedure). 4(5)-Substituted 2-carbomethoxybenzoic acid (0.1 mole) was boiled for 2-4 h with 0.3-0.4 mole $SOCl_2$. Excess $SOCl_2$ was removed at reduced pressure, and the residue was dissolved in dry ether or benzene. The resulting solution was added dropwise to a cold (–15°C) solution of diazomethane in ether, obtained from 100 g nitrosomethylurea in 900 ml ether. The temperature was then adjusted to ~20°C, excess diazomethane was removed by bubbling through N_2, the solvent was evaporated at reduced pressure, and the residue was chromatographed on a silica gel column. The characteristics of CMDAP (Ia-h) are shown in Table 1. The mass spectra of CMDAP (Ia-h) contained the following ions: $[M - N_2]^+$, $[M - CHN_2]^+$, $[M - N_2 - CH_3]^+$, $[M - N_2 - CO]^+$, $[M - CHN_2 - CH_2O]^+$.

Isochromane-1,4-diones (IIa-h) (General Procedure). H_2SO_4 (15%, 2 ml) was added to 5 mmoles of diazoketone (Ia-h) in 15 ml methanol; the solution was allowed to stand at ~20°C for 1-1.5 h, and was neutralized by adding $NaHCO_3$. The major portion of the solvent was evaporated at reduced pressure, and the residue was recrystallized from benzene. The characteristics of compounds (IIa-h) are shown in Table 2. The mass spectra of (IIa-h) contained the following ions: $[M]^+$, $[M - CH_2O]^+$, $[M - CH_2O - CO]^+$, $[M - CH_2O - 2CO]^+$.

Kinetic Measurements. Methanol was dried by evaporation over Na. Commerical CD_3OD contained 98% of the D isotope, with a molar fraction of 0.988 of the ground substance. A solution of H_2SO_4 in methanol was prepared gravimetrically. The residual water content of methanol (according to Fischer) was ~0.5%.

The kinetics of CMDAP (Ia-h) and DAP (IIIa-f) decomposition were examined spectrophotometrically by the disappearance of the characteristic absorption bands of the diazoketone diazocarbonyl group (till ~90% reaction completion; see Table 3). The initial diazoketone concentrations were ~10^{-4} M. Each experiment was repeated at least two times. The kinetic curves were linearized in semilogarithmic coordinates; the k_{obs} pseudo first-order rate constants were calculated graphically; the standard deviation in the determination of k_{ef} was 5% (the mean error was computed for a 95% confidence interval).

CONCLUSIONS

1. A variety of new o-carbomethoxy-ω-diazoacetophenones and isochromane-1,4-diones were synthesized.

2. The decomposition of o-carbomethoxy-ω-diazoacetophenones in methanol–H_2SO_4, in constrast to reactions of their o-unsubstituted analogs, takes place via the A-S_E2 mechanism. The intramolecular nucleophilic assistance of the o-CO_2CH_3 group increases the decomposition rate of ω-diazoacetophenones by 13-25 times.

3. A correlation was observed between the acid-catalyzed reaction rates of o-carbomethoxy-ω-diazoacetophenones and Hammet's σ constants for benzene ring substituents.

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ASYMMETRIC REDUCTION OF THE CARBONYL GROUP BY CHIRAL HYDRIDES.

1. STEREOCHEMICAL CONSIDERATIONS

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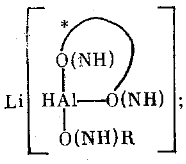
Asymmetric reduction of prochiral ketones by chiral hydrides readily affords alcohols. Chiral hydrides are obtained by partial decomposition of $LiAlH_4$, $LiBH_4$, $NaBH_4$, and BH_3 by R*OH or R_2*NH, where R* is a chiral substituent. Efficient hydrides for the asymmetric reduction of ketones (optical yields of product p > 75%) have the general structures



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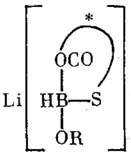

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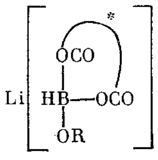

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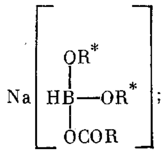

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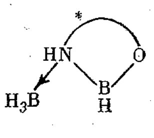

[9, 10]

Bearing in mind the similarities in the structure of chiral hydrides derived from $LiAlH_4$ and Na(Li)BH_4 (Al^- and B^- have the tetrahedral structure [1, 2]), it is reasonable to suppose that their enantioselective mode of action has common features. We propose a rule which takes into account this mechanism, and enables the reduction of ketones by chiral

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