

STEREOCHEMICAL STUDIES. XVI*

Cyclic Aminoalcohols and Related Compounds. VIII** Examination of the Hammett Relation in the N → O Acyl Migration of *cis*- and *trans*-2-Aminomethylcyclohexanol and *cis*- and *trans*-2-Hydroxymethylcyclohexylamine Derivatives***

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Kinetics of the N → O acyl migration reaction of *m*- and *p*-substituted N-benzoyl derivatives of *cis*- and *trans*-2-aminomethylcyclohexanol (1a—1, 2a—g) and of *cis*- and *trans*-2-hydroxymethylcyclohexylamine (3a—j, 4a—1) was studied in abs. dioxane in the presence of an excess of 0.5 mole HCl at 100 ± 0.3 °C. The reaction rate is increased by electron-releasing groups, diminished by electron-attracting ones. In the case of *p*-nitrobenzoyl derivatives, the reaction rate markedly exceeds that expected on the basis of linear Hammett relation, while for *p*-methoxybenzoyl derivatives it is lower than expected. It follows that in the formation of the bicyclic transition state of the N → O acyl migration reaction, especially in the case of *p*-nitrobenzoyl derivatives, the bond-making part process is in a more advanced state than the bond-breaking one.

Though, in the compounds studied, the linear Hammett relation is fairly well fulfilled with the exception of *p*-nitro derivatives, deeper analysis shows that better fitting of the straight lines can be reached by plotting $\log k/k_0$ vs. σ for *meta* and *para* substituted compounds separately; the reaction constant of the *p*-substituted derivatives is less negative.

Earlier we dealt with kinetic investigations of the N → O acyl migration reaction of N-benzoyl derivatives of *cis*- and *trans*-2-aminomethylcyclohexanol and *cis*- and *trans*-2-hydroxymethylcyclohexylamine [1, 2] as well as of the corresponding cyclopentane and cycloheptane analogues [3—8]. The reaction mechanism of the N → O acyl migration, as well as earlier work on this topic, was reviewed [2] in connection with our studies on the N → O acyl migration reaction of the N-benzoyl cyclohexane derivatives [9].

The first step of the acyl migration reaction (Fig. 2) is the protonation of the acid amides taking place at the carbonyl oxygen, as indicated by NMR measurements [14, 15]. This is followed by intramolecular nucleophilic attack of the alcoholic hydroxyl group on the carbon atom of the carboxyl group, resulting in the formation

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of a bicyclic transition state. As shown [2], this step takes place on the quasi-carbonium ion of the protonated amide group, at right angles to the plane of the three substituents attached to it. This perpendicular attack, permitting maximum overlap between the nucleophile and the carbonyl π -orbital, is energetically the most favoured. The bicyclic transition complex rearranges to the O-acyl product by protonation, deprotonation and carbon-nitrogen bond cleavage.

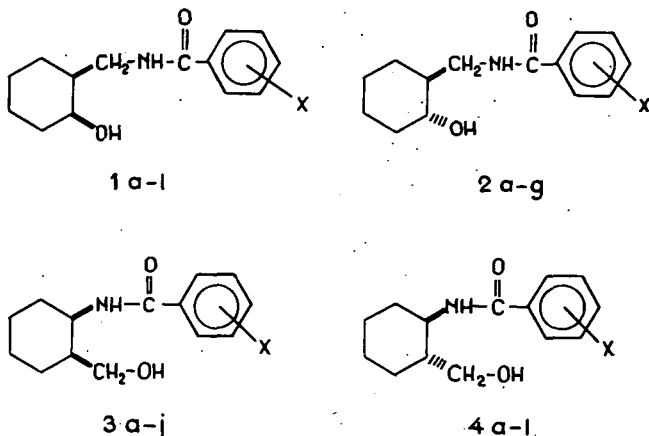


Fig. 1

In the acyl migration reaction of the N-benzoyl derivatives of 1,3-aminoalcohols with cyclohexane skeleton, we found [1, 2] that the process is accelerated by the *p*-methyl group and hindered by the *p*-nitro group. An electron donating group in *p*-position facilitates protonation of the carbonyl oxygen and stabilizes the bicyclic transition state.

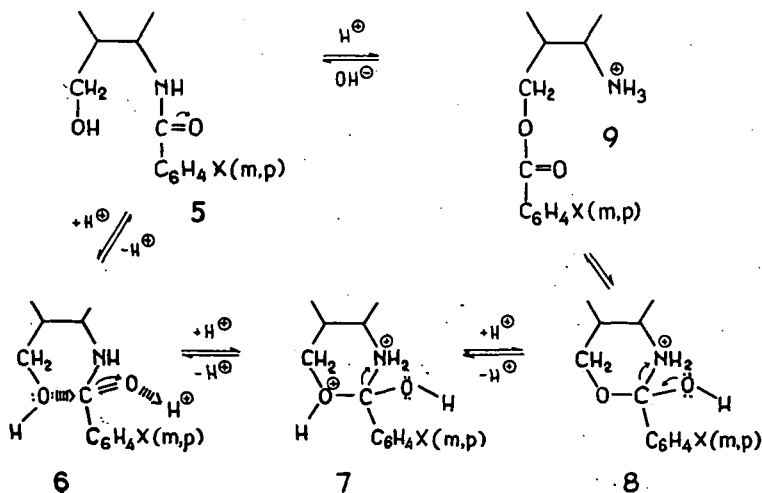


Fig. 2.

The N→O acyl migration reaction being a multistep process, deeper insight into the part processes of the reaction may be expected by determining the reaction rates for different *meta* and *para* substituents and evaluating the validity of the Hammett relation.

As well known, valuable conclusions regarding the part processes of the reactions can be drawn from the behaviour of the *meta* and *para* substituents, from the slope of the line obtained from the Hammett equation [16—19], especially from its deviation from linearity [20, 44, 45].

Therefore, it seemed reasonable to prepare a greater number of *m*- and *p*-substituted N-benzoyl derivatives of *cis*- and *trans*-2-aminomethylcyclohexanol (**1a—1**, **2a—g**) and *cis*- and *trans*-2-hydroxymethylcyclohexylamine (**3a—j**, **4a—1**) and to study the kinetics of their N→O acyl migration reaction.

The stereospecific synthesis of *cis*- and *trans*-2-aminomethylcyclohexanol and of *cis*- and *trans*-2-hydroxymethylcyclohexylamine was described earlier [9]. In connection with the starting aminoalcohols it is to be remarked that, as shown [9], the aminoalcohols considered as stereohomogeneous by earlier authors proved to be mixtures of the *cis*- and *trans*-isomers. Thus, the 2-aminomethylcyclohexanol obtained by reduction of 2-cyanocyclohexanol regarded as stereohomogeneous by MOUSSERON *et al.* [21] and supported to be a *trans* compound by MORICONI and MAZZOCCHI [22] is, in reality, a mixture of the *cis* and *trans* isomers. Our above finding is also supported by a very recent paper of SCHWARTZ *et al.* [23].

The N-benzoyl derivatives used were prepared by a modified Schotten—Baumann process described earlier [13]. M.p., analytical data of *m*- and *p*-substituted-N-benzoyl derivatives and rate constants of their N→O acyl migration reactions are summarized in Tables I—IV.

The synthesis of some analogous acid amides, containing aminomethylcyclohexane structural moiety, for pharmacological purposes, has been reported in our former communication [13] and is subject of patents [10—12].

Plots of $\log k/k_0$ vs. σ are shown in Figs. 3—6. Calculated ρ values are: —0.606; —0.588; —0.571 and —0.580 for the derivatives **1a—1**; **2a—g**; **3a—j**; and **4a—1**, respectively. An interesting common feature of the figures is that the reaction constants (ρ) are less than unity and negative in all four cases. The negative sign of ρ shows the importance of the first step of the acyl migration reaction (**5**→**6**), the protonation of the oxygen of the acid amide. This is facilitated by electron releasing groups and hindered by electron attracting substituents.

The second main step, the nucleophilic attack of the alcoholic hydroxyl on the quasi-carbonium carbon atom of the acid amide (**6**→**7**) is influenced, besides electrostatic effects by steric and conformational factors. The conformational factors influencing the formation of the bicyclic transition states of the acyl migration reaction were thoroughly discussed in our earlier paper [2]. Due to the above factors, the acyl migration of the *trans* derivatives (**2**, **4**) is faster than that of the corresponding *cis* derivatives (**1**, **3**), and the reaction rate of the hydroxymethyl derivatives containing primary alcoholic hydroxyl groups exceeds that of the derivatives with secondary hydroxyl group (**1**, **2**).

It is to be mentioned that the reaction constants of the acyl migration process studied are rather low compared with the ρ values of other reactions [16, 36]. The factors determining the reaction constant were discussed earlier [16, 35]. Low reaction constants generally indicate that the reaction is not very sensitive to substituents.

Table I

Melting points, analyses of *m*- and *p*-substituted-*N*-benzoyl derivatives of *cis*-2-aminomethylcyclohexanol (1a—l) and rate constants of their *N*-O acyl migration reaction

No.	X	Formula, molecular weight	M.p. (°C); Solvent of crystallization	Analysis (%)		$k_a \cdot 10^3$ sec ⁻¹ at 100±0.3°C	Note
				Calcd. C	Found H		
1a	<i>p</i> -Me	C ₁₅ H ₂₁ NO ₂ 247.35	132.5—133 ethanol/water			2.93	a)
1b	<i>m</i> -Me	C ₁₅ H ₂₁ NO ₂ 247.35	105—105.5 ethanol/water	72.84 72.66	8.56 8.70	1.35	
1c	H	C ₁₄ H ₁₉ NO ₂ 233.21	117—118 ethanol			2.02	a), b)
1d	<i>p</i> -F	C ₁₄ H ₁₅ O ₂ NF 251.30	126—127 ethanol/water	66.92 66.86	7.22 7.31	1.41	c)
1e	<i>p</i> -Br	C ₁₄ H ₁₅ NO ₂ Br 312.22	151.5—152 ethanol/water	53.86 54.26	5.81 5.94	1.18	
1f	<i>p</i> -Cl	C ₁₄ H ₁₅ O ₂ NCl 267.76	155—156 benzene	62.80 62.92	6.78 6.80	1.87	
1g	<i>m</i> -F	C ₁₄ H ₁₅ O ₂ NF 251.30	103—103.5 ethanol	66.92 66.96	7.22 7.23	0.91	c)
1h	<i>m</i> -Cl	C ₁₄ H ₁₅ O ₂ NCl 267.76	126—126.3 ethanol	62.80 62.87	6.78 6.89	1.15	
1i	<i>m</i> -Br	C ₁₄ H ₁₅ NO ₂ Br 312.22	132—133.5 ethanol	53.86 53.50	5.81 5.61	0.94	
1j	<i>m</i> -CF ₃	C ₁₅ H ₁₅ O ₂ F ₃ N 301.32	146.5—147 ethanol/water	59.79 60.08	6.02 6.17	0.908	
1k	<i>m</i> -NO ₂	C ₁₄ H ₁₃ N ₂ O ₄ 278.31	131—132 ethanol/water	60.42 60.71	6.52 6.56	0.62	
1l	<i>p</i> -NO ₂	C ₁₄ H ₁₃ N ₂ O ₄ 278.31	166—167 ethanol			1.17	a)

Note: a) For lit. m.p. (analysis) and k see: [9] and [2], respectively.

b) Lit. [21] m.p.: 116—117 °C.

c) Needles.

Table II

Melting points, analyses of *m*- and *p*-substituted-*N*-benzoyl derivatives of *trans*-2-aminomethylcyclohexanol (2a—g) and rate constants of their *N*—O acyl migration reactions

No.	X	Formula, molecular weight	M.p. (°C); Solvent of crystallization	Analysis (%)		$k_2 \cdot 10^3$ sec ⁻¹ at 100±0.3 °C	Note
				Calcd. C	Found H		
2a	<i>p</i> -CH ₃	C ₁₅ H ₂₁ NO ₂ 247.35	100—100.5 benzene			4.83	a)
2b	H	C ₁₄ H ₁₉ NO ₂ 233.31	127.5—128 ethanol			2.02	a), b)
2c	<i>p</i> -F	C ₁₄ H ₁₆ O ₂ NF 251.30	127.5—128 ethanol/water	66.92 66.72	7.22 7.30	2.69	
2d	<i>p</i> -Br	C ₁₄ H ₁₈ NO ₂ Br 312.22	128—129 ethanol/water	53.86 53.60	5.81 5.92	3.01	
2e	<i>p</i> -Cl	C ₁₄ H ₁₈ O ₂ NCl 267.76	114—115 ethanol/water	62.80 65.09	6.78 6.56	3.87	
2f	<i>m</i> -NO ₂	C ₁₄ H ₁₈ N ₂ O ₄ 278.31	104—104.5 ethanol/water	60.42 60.38	6.53 7.00	1.55	
2g	<i>p</i> -NO ₂	C ₁₄ H ₁₈ N ₂ O ₄ 278.31	159.5—160 ethanol			2.14	a)

Note: a) For lit. m.p. (analysis) and k see: [9] and [2], respectively.

b) Lit [21] m.p.: 123—124 °C, (*trans/cis* mixture. See: [2] and [23]).

Of course, in the case of reactions analogous to that dealt with in the present paper, *i.e.* in the case of multistep processes, this may result from the fact that the part processes are influenced differently by the substituents, and therefore the analysis of the process requires deeper consideration. Thus *e.g.* it is known that in concerted displacement reactions the sign and magnitude of the reaction constant are determined by the relative importance of the electrophilic and nucleophilic reactions occurring simultaneously.

By comparing our reaction constants with those found in analogous processes, a very good accordance can be observed. *E.g.* in the acidic hydrolysis ($A_{Ac}2$) of aromatic acid amides in 60% ethanol $\rho = -0.483$, -0.298 and -0.222 at 52.4 °C, 79.5 °C and 99.6 °C, respectively [40]. The reaction constants of the acidic hydrolysis of phenol acetates ($A_{Ac}2$) in 60% acetone are $\rho = -0.198$, -0.203 , -0.232 and -0.277 at 25 °C, 40 °C, 60 °C and 80 °C, respectively [41].

Another very interesting common feature of Figs. 3—6 is the deviation from the straight line of the value corresponding to the *p*-NO₂ group.

It is known [25, 38, 39] that deviations from the Hammett relation are to be expected and indeed do occur in reactions where conjugation between the reaction center and the substituent may occur. In such reactions, *e.g.* in aromatic side chain reactions, in which an α -carbonium center is produced in equilibrium, such as in

Table III

Melting points, analyses of *m*- and *p*-substituted *N*-benzoyl derivatives of *cis*-2-hydroxymethylcyclohexanol (3a—j) and rate constants of their *N*-O acyl migration reactions

No.	X	Formula, molecular weight	M.p. (°C); Solvent of crystallization	Analysis (%)		$k_a \cdot 10^{-3}$ sec ⁻¹ at 100 ± 0.3°C	Note
				Calcd. C	Found H		
3a	<i>p</i> -CH ₃	C ₁₅ H ₂₁ NO ₂ 247.35	141—142 benzene			7.50	a)
3b	<i>m</i> -CH ₃	C ₁₅ H ₂₁ NO ₂ 247.35	122—122.5 ethanol/water	72.84 72.92	8.56 8.78	4.62	
3c	H	C ₁₄ H ₁₉ NO ₂ 233.31	115.5—116.5 ethanol			5.15	a)
3d	<i>p</i> -F	C ₁₄ H ₁₈ O ₂ NF 251.30	110.5—111 ethanol/water	66.92 66.64	7.22 7.36	4.17	
3e	<i>m</i> -F	C ₁₄ H ₁₈ O ₂ NF 251.30	102—103 ethanol/water	66.92 66.62	7.22 6.93	1.71	
3f	<i>m</i> -CF ₃	C ₁₅ H ₁₈ O ₂ F ₃ N 301.32	110—110.5 ethanol/water	59.79 60.08	6.02 6.29	2.85	
3g	<i>p</i> -NO ₂	C ₁₄ N ₁₅ N ₂ O ₄ 278.31	135—136 ethanol			3.67	a)
3h	<i>m</i> -NO ₂	C ₁₄ H ₁₈ N ₂ O ₄ 278.31	113—114 ethanol/water	60.42 60.20	6.52 6.44	2.12	
3i	3,5-NO ₂	C ₁₄ H ₁₇ O ₆ N ₃ 323.31	186—187 ethanol/water	52.00 52.14	5.30 5.47	0.69	
3j	<i>m</i> -Cl	C ₁₄ H ₁₈ O ₂ NCl 267.76	102—102.5 ethanol	62.80 62.40	6.78 6.66	2.90	

Note: a) For lit. m.p. (analysis) and *k* see: [9] and [2], respectively.

S_N1 solvolysis of aryl methyl esters, a very good correlation is found for different *meta* substituents; however, some *para* substituents show greater reaction rates than those expected from the linear relation. All these compounds having *para* substituents of -E or -I type, the deviations are to be attributed to conjugation between the *p*-substituents and the carbonium ion forming or formed.

Several attempts to explain the above deviations and to theoretical evaluation of the substituent constant (σ) were made [26—30, 37] and the theoretical analysis of Hammett's σ is the object of recent discussions [31—34].

In our case, the values found with all *meta* substituent give a straight line with very slight deviations. In the case of *p*-NO₂ group the reaction is considerably faster than that expected. This substituent effect shows markedly the role of the resonance effects in the stability of the bicyclic transition state (8) and in the formation of

Table IV

Melting points, analyses of *m*- and *p*-substituted *N*-benzoyl derivatives of trans-2-hydroxymethylcyclohexanol (4a—l) and rate constants of their *N* → *O* acyl migration reactions

No.	X	Formula, molecular weight	M.p. (°C); Solvent of crystallization	Analysis (%)		$k_2 \cdot 10^3$ sec ⁻¹ 100 ± 0.3°C	Note
				Calcd. C	Found H		
4a	<i>p</i> -CH ₃	C ₁₅ H ₂₁ NO ₂ 247.35	156.6—157.5 ethanol/water			24.04	a)
4b	<i>m</i> -CH ₃	C ₁₅ H ₂₁ NO ₂ 247.35	142—142.5 ethanol/water	72.84 72.96	8.56 8.79	19.23	
4c	H	C ₁₄ H ₁₉ NO ₂ 233.31	149—149.5 ether			20.28	a)
4d	<i>p</i> -F	C ₁₄ H ₁₈ O ₂ NF 251.30	143.5—144 ethanol/water	66.92 66.65	7.22 7.28	12.25	b)
4e	<i>p</i> -Cl	C ₁₄ H ₁₈ O ₂ NCl 267.76	152—152.5 ethanol	62.80 62.50	6.78 6.47	15.83	
4f	<i>m</i> -F	C ₁₄ H ₁₈ O ₂ NF 251.30	129—129.5 ethanol/water	66.92 66.90	7.22 7.02	10.73	
4g	<i>m</i> -Cl	C ₁₄ H ₁₈ O ₂ NCl 267.76	141—141.5 ethanol/water	62.80 63.03	6.78 6.75	10.00	c)
4h	<i>m</i> -Br	C ₁₄ H ₁₈ NO ₂ Br 312.22	152—153 ethanol	53.86 53.77	5.81 5.96	9.96	
4i	<i>m</i> -CF ₃	C ₁₅ H ₁₈ O ₂ F ₃ N 301.32	151—151.5 ethanol/water	59.79 59.66	6.02 5.86	8.91	
4j	<i>p</i> -NO ₂	C ₁₄ H ₁₈ N ₂ O ₄ 278.31	143 ethanol			13.17	a)
4k	<i>m</i> -NO ₂	C ₁₄ H ₁₈ N ₂ O ₄ 278.31	161—162 ethanol	60.42 60.20	6.52 6.50	8.32	
4l	3,5-NO ₂	C ₁₄ H ₁₇ O ₂ N ₃ 323.31	229.5—230.5 ethanol	52.00 52.06	5.30 5.08	2.82	d)

Note: a) For lit. m.p. (analysis) and k see: [9] and [2], respectively.

b) Fine crystal needles which form a fluffy cluster.

c) Needles.

d) Well developed plates.

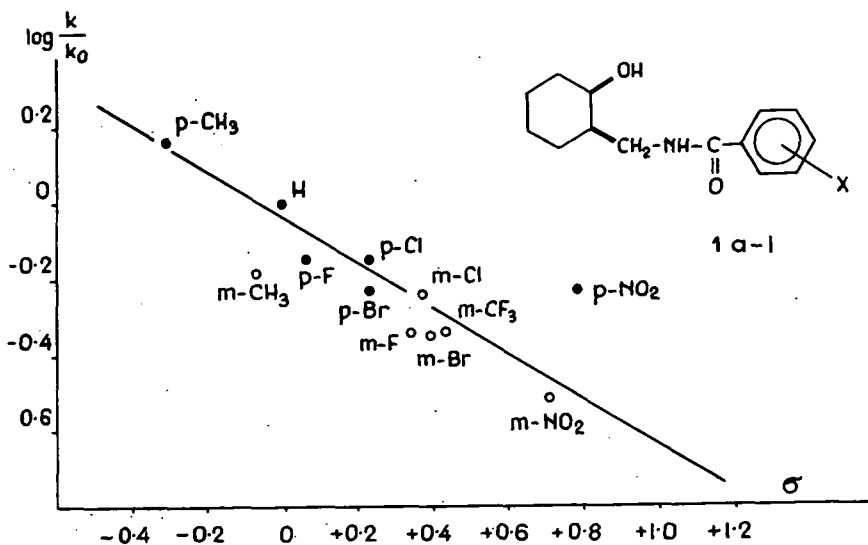


Fig. 3

the end-product (9). Namely, in the part process 8→9, splitting of the carbon-nitrogen bond and deprotonation of the oxygen occurs. This is influenced by *para* substituents exerting resonance effect more markedly than would follow from the substituent constants. The stability of the bicyclic transition state is obviously diminished by *p*-NO₂ in a higher degree than expected.

The deviations from linearity found in our case can be related with those found

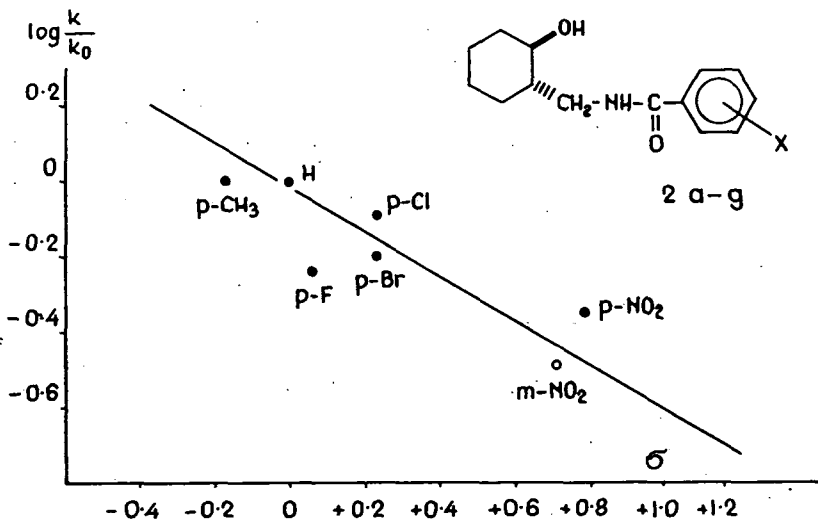


Fig. 4

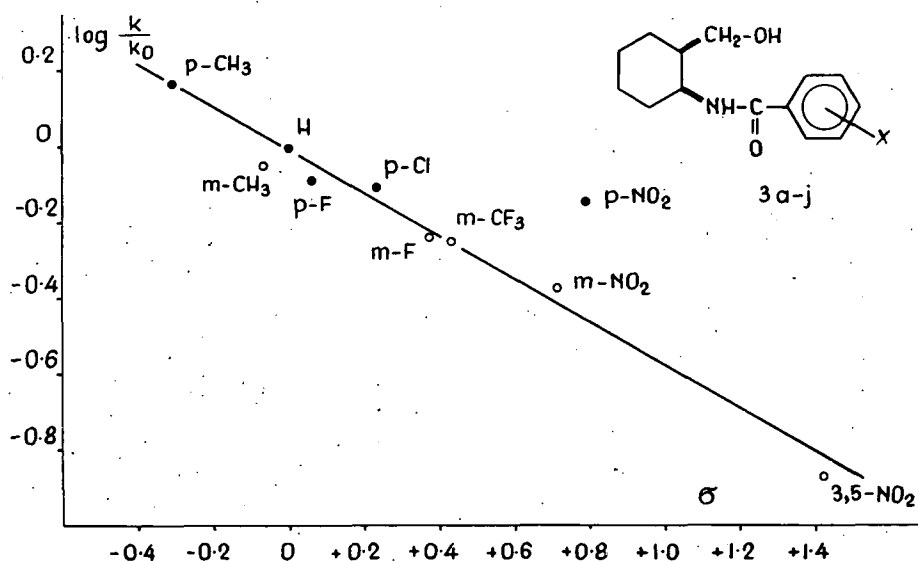


Fig. 5

earlier in some other reactions [43, 44]. Namely, as JAFFÉ pointed out [42], reactions such as acidic hydrolysis of esters [43] seem to fit least satisfactorily to the Hammett equation. These reactions involve both bond-breaking and bond-forming steps, neither of which alone is rate-determining. The balance of these steps as well as their concerted or subsequent occurrence will depend to some extent on the nature of the substituent, and plots of the same type as ours can be expected.

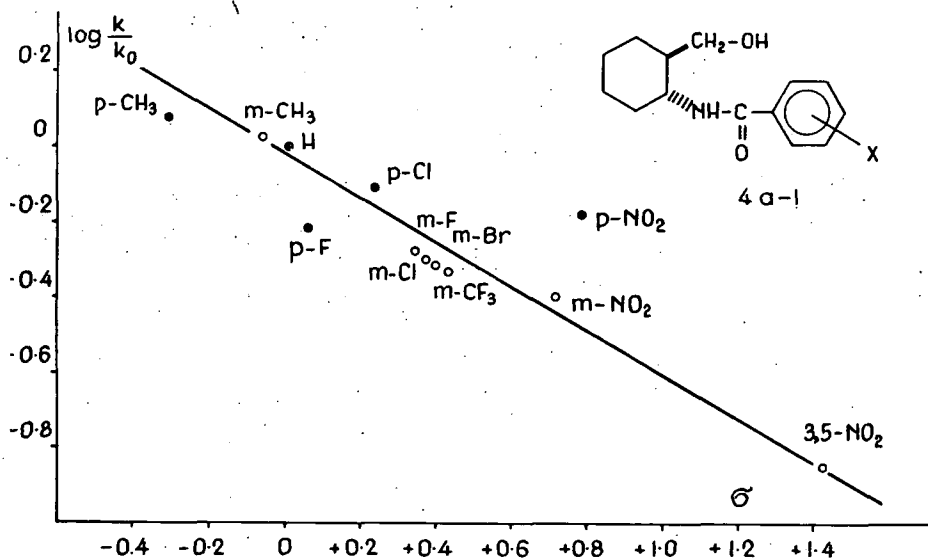


Fig. 6

As shown by SWAIN and LANGESDORF [44], in the transition state of polar displacement processes, either of both main steps: breaking of the old bond or forming of the new one may precede the other. The partial positive charge on the central carbon atom may be greater or less than in the ground state, depending on the circumstance, whether the bond-forming or bond-breaking part process is in more advanced state.

The reaction constant ρ can be related to the extent of bond-breaking compared with bond-formation and is a measure of the changes in charge, being determined by the deviation from perfect synchronism. The greater the increase of the partial positive charge of the central carbon atom in the transition state, the more expressed the accelerating effect of the electron releasing substituents (ρ will be more negative); and the greater the decrease in positive charge, the more the electron withdrawing substituents will exert their influence (ρ will be more positive).

In the acyl migration reaction studied in the present paper, similarly to the hydrolysis of benzoyl chlorides [46], on the plot of $\log k/k_0$ vs. σ a positive curvature (concave up) is observed. It follows that bond-making and bond-breaking processes are not synchronous in the transition state. In case of the *p*-nitro compound bond-making is in a more advanced state than bond-breaking. It is worth mentioning that in a very recent publication [45] the substituent effect on the kinetics of pyridine catalysed hydrolysis of aromatic sulphonyl chlorides was discussed with the result that the Hammett plots for the reaction of pyridine derivatives with different sulphonyl chlorides are curved owing to an abnormal low reactivity of *p*-nitro compounds.

In addition, a deeper analysis of our plots enables us to draw some further conclusions regarding the importance of the resonance effects; namely, lower rate constants were obtained with *meta* than with *para* substituents. Though in our case the slopes of the curves determined by *meta* and *para* substituents are not so different as in some other instances [44] studied earlier, the trend seems to be rather unambiguous. Two different straight lines can be drawn through the points of the *para* and *meta* substituted compounds, and the value of ρ is less negative in the case of *p*-substituted ones.

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СТЕРЕОХИМИЧЕСКИЕ ИССЛЕДОВАНИЯ. XVI.
ЦИКЛИЧЕСКИЕ АМИНОСПИРТЫ И РОДСТВЕННЫЕ СОЕДИНЕНИЯ. VIII.Исследование соотношения Гаммета в ацил миграции производных *цис*- и *транс*-2-аминометилциклогексанола и *цис*- и *транс*-2-гидроксиметилциклогексиламина

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Изучена кинетика реакции N–O ацил миграции для *m*- и *p*-замещённых N-бензоил-производных *цис*- и *транс*-2-аминометилциклогексанолов (1a–l, 2a–g), и *цис*- и *транс*-2-гидроксиметилциклогексиламинов (3a–l, 4a–l) при температуре 100 ± 0.3 °C в среде абсолютного диоксана с избытком 0.5 мол. HCl. Показано, что скорость реакции увеличивается в присутствии электроно-донорных групп и уменьшается при наличии электроно-акцепторных. В случае *p*-нитробензоилпроизводных скорость реакции значительно возрастает, что и предполагалось исходя из линейности соотношения Гаммета, в то время как для производных *m*-метоксibenzoила она ниже ожидаемого значения. Следовательно, в образовании бициклического переходного состояния реакции N–O ацил миграции, особенно в случае *p*-нитробензоилпроизводных, процесс образования связи является более предпочтительным, чем её разрыв.

Хотя в изучаемых соединениях линейность соотношения Гаммета довольно хорошо выполняется, за исключением *p*-нитропроизводных, более глубокий анализ показывает, что наиболее подходящим для прямолинейной зависимости отдельно для *мета* и *пара*-замещённых соединений является график зависимости $\log k/k_0$ vs. σ , константа реакции для *p*-замещённых производных менее отрицательна.