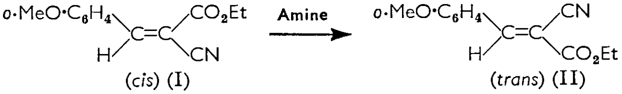
861. *Nucleophilic Attacks on Carbon–Carbon Double Bonds. Part VI.*[1] *Amine-catalysed* cis–trans-*Isomerisation of Ethyl α-Cyano-*β-o-*methoxyphenylacrylate through a Zwitterionic Carbanion in Benzene.*

By Zvi Rappoport, Chemda Degani, and Saul Patai.

The nucleophilic isomerisation of ethyl *cis*-α-cyano-β-*o*-methoxyphenylacrylate to the *trans*-isomer by various secondary and tertiary amines in benzene has been studied. The reactions followed overall second-order kinetics, first-order in both the substrate and the catalytic amine. The observed very low activation energies are explained by the composite nature of the measured rate coefficients. The order of reactivity of the amines was $Bu^n_2NH > Pr^n_2NH > Bu^i_2NH > Bu^n_3N > Pr^i_2NH > Et_3N >$ pyridine > 2,6-lutidine. This order and the detailed mechanism of the isomerisation process are discussed.

Relatively few kinetic studies have been conducted on the large group of nucleophilic reactions on activated carbon–carbon double bonds, and in only a few of these was the effect of different nucleophiles studied with the same substrate.



(*cis*) (I) (*trans*) (II)

The isomerisation of ethyl *cis*-α-cyano-β-*o*-methoxyphenylacrylate (I) to the *trans*-ester (II) was previously shown to be catalysed by oxygen-, nitrogen-, and carbon-containing nucleophiles.[2] As isomerisations give information both on the relative reactivities of the various nucleophiles and on the mechanism of the common primary step of all nucleophilic attacks on activated carbon–carbon double bonds, we have studied the isomerisation of (I) to (II) with a variety of amines.

Results

The rate of the isomerisation in the presence of eight amines was studied spectrophotometrically. In ethanol, dioxan, tetrahydrofuran, and acetonitrile, solvent-catalysed isomerisation took place and therefore the solvent chosen was benzene, the only one in which the rate of the reaction was negligible compared to the rate of the catalysed one, and complications did not arise from formation of new nucleophilic species (*e.g.*, formation of alkoxide ions in alcohols). Most of the reactions were conducted with a constant concentration (10^{-4} mole $l.^{-1}$) of the *cis*-ester, but one or more runs with each amine were conducted with a different ester concentration, showing the reaction to be first-order in the ester. The amine concentrations were varied up to five-fold, and in all cases the reaction was first-order in the amine (Table 1). The differences in the optical densities of the *cis*- and the *trans*-isomers are relatively small, and the error in the individual rate coefficients in the Table may be as much as 5%, as judged by the reproducibility of the experiments and the sensitivity of the spectral measurements. The order of the reactivity of the amines was: $Bu^n_2NH > Pr^n_2NH > Bu^i_2NH > Bu^n_3N > Pr^i_2NH > Et_3N >$ pyridine > 2,6-lutidine.

Activation parameters were calculated from the rate coefficients of Table 1. The activation energies (E_A) are unusually low (2·7—5·0 kcal. mole^{-1}) for all the amines studied. The entropies of activation ($\Delta S^‡$) have high negative values, increasing from ~ -45 e.u. with the most reactive amines to ~ -65 e.u. with the least reactive ones (Table 2).

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[1] Part IV, Rappoport, preceding paper.

[2] Patai and Rappoport, *J.*, 1962, 396.

TABLE 1.

First-order (k in sec.$^{-1}$) and second-order rate coefficients ($k_{\text{exp}} = k/[\text{amine}]$ in sec.$^{-1}$ l. mole^{-1}) for the *cis–trans*-isomerisation of ethyl α-cyano-β-*o*-methoxyphenylacrylate (10^{-4} mole l.$^{-1}$) by various amines in benzene at different temperatures.

Amine	(mole l.$^{-1}$ × 10^3)	32°		40°		48°		56°	
		10^4k	k_{exp}	10^4k	k_{exp}	10^4k	k_{exp}	10^4k	k_{exp}
$\mathrm{Bu^n_2NH}$	0·03	1·78	5·9	2·24	7·5	2·84	9·4	3·30	11·0
	0·04	—	—	3·04	7·6	—	—	—	—
	0·05	—	—	3·75	7·5	4·60	9·2	5·60	11·2
	0·05 [a]	—	—	3·60	7·2	—	—	—	—
	0·06	3·62	6·0	4·46	7·4	—	—	—	—
	0·07	—	—	5·43	7·7	6·50	9·3	7·70	11·0
	0·10	5·94	5·9	7·35	7·4	—	—	—	—
		Average	5·9 ± 0·1		7·5 ± 0·1		9·3 ± 0·1		11·1 ± 0·1
$\mathrm{Pr^n_2NH}$	0·02	—	—	1·48	7·4	—	—	—	—
	0·03	1·90	6·3	2·32	7·4	2·54	8·4	2·84	9·5
	0·05	2·67	5·5	3·63	7·3	4·20	8·4	4·63	9·3
	0·07	3·74	5·7	5·04	7·2	5·82	8·3	6·52	9·3
	0·07 [a]	—	—	5·11	7·3	—	—	—	—
		Average	5·8 ± 0·3		7·3 ± 0·1		8·4 ± 0·1		9·4 ± 0·1
$\mathrm{Bu^i_2NH}$	0·1	—	—	1·50	1·50	—	—	—	—
	0·2	2·63	1·32	3·02	1·51	2·08	1·54	3·36	1·68
	0·2 [b]	—	—	2·94	1·47	—	—	—	—
	0·4	4·45	1·11	6·02	1·51	6·20	1·55	6·70	1·58
	0·4 [a]	—	—	6·05	1·51	—	—	—	—
	0·5	5·85	1·17	7·30	1·46	7·75	1·55	8·31	1·66
		Average	1·20 ± 0·08		1·49 ± 0·02		1·55 ± 0·01		1·67 ± 0·01
$\mathrm{Bu^n_3N}$	2	2·06	0·103	2·16	0·108	5·32	0·116	2·73	0·136
	3	2·72	0·091	3·15	0·105	—	—	—	—
	4	4·70	0·094	4·14	0·104	4·86	0·121	5·53	0·138
	5	—	—	5·35	0·107	6·00	0·120	6·70	0·137
	5 [a]	—	—	5·42	0·108	—	—	—	—
	6	—	—	6·30	0·105	—	—	—	—
		Average	0·096 ±0·002		0·106 ±0·002		0·116 ±0·002		0·136 ±0·001
$\mathrm{Pr^i_2NH}$	2	1·05	0·052	—	—	2·23	0·062	1·81	0·091
	3	—	—	1·75	0·058	—	—	—	—
	4	2·10	0·052	2·38	0·059	2·52	0·063	3·57	0·089
	5	2·60	0·052	2·84	0·057	3·20	0·064	4·24	0·085
	5 [a]	—	—	2·90	0·058	—	—	—	—
	6	—	—	3·44	0·057	—	—	—	—
	7	—	—	3·98	0·057	—	—	—	—
		Average	0·052		0·058 ±0·001		0·063 ±0·001		0·088 ±0·002
$\mathrm{Et_3N}$	2	0·56	0·028	—	—	—	—	—	—
	3	—	—	0·84	0·027	—	—	—	—
	4	0·93	0·023	1·07	0·027	—	—	—	—
	5	—	—	1·24	0·025	—	—	—	—
	6	—	—	1·60	0·027	2·08	0·035	2·38	0·040
	7	—	—	2·08	0·030	2·34	0·033	2·76	0·040
	7 [a]	—	—	2·08	0·030	—	—	—	—
	8	—	—	—	—	2·58	0·032	3·09	0·040
	10	2·12	0·021	—	—	—	—	—	—
		Average	0·024 ±0·003		0·028 ±0·002		0·033 ±0·001		0·040
Pyridine	10	—	—	1·08	0·0108	—	—	—	—
	20	1·83	0·0092	2·12	0·0106	2·38	0·0119	2·66	0·0133
	30	—	—	3·14	0·0105	—	—	—	—
	30 [a]	—	—	3·18	0·0106	—	—	—	—
	40	3·70	0·0092	4·20	0·0105	4·76	0·0119	5·40	0·0135
	50	4·60	0·0092	5·30	0·0106	6·90	0·0118	6·55	0·0131
		Average	0·0092		0·0106 ±0·0001		0·0119 ±0·0001		0·0133 ±0·0001

TABLE 1. (*Continued.*)

Amine	(mole l.$^{-1}$ × 10^3)	32°		40°		48°		56°	
		10^4k	k_{exp}	10^4k	k_{exp}	10^4k	k_{exp}	10^4k	k_{exp}
2,6-Lutidine	100	—	—	0·96	0·00096	—	—	—	—
	200	1·66	0·00083	1·84	0·00092	2·22	0·00111	2·55	0·00127
	300[a]	—	—	2·99	0·00099	—	—	—	—
	400	3·56	0·00089	3·62	0·00092	4·48	0·00112	5·0	0·00125
	500	—	—	—	—	—	—	6·2	0·00124
	600	5·0	0·00083	5·35	0·00089	7·20	0·00120	—	—
	Average		0·00085 ±0·00003		0·00094 ±0·00003		0·00114 ±0·00004		0·00125 ±0·00001

[a] Concentration of the ester is 5 × 10^{-5} mole l.$^{-1}$. [b] Concentration of the ester is 2 × 10^{-4} mole l.$^{-1}$.

TABLE 2.

Activation parameters for the *cis–trans*-isomerisation reaction in the presence of various amines.

	Bu^n_2NH	Pr^n_2NH	Bu^i_2NH	Bu^n_3N	Pr^i_2NH	Et_3N	Pyridine	2,6-Lutidine
E_A (kcal. mole^{-1})	5·06	4·00	2·76	2·71	4·60	4·60	3·08	3·22
$\Delta S\ddagger$ (e.u.)	−43	−46	−53	−58	−54	−55	−66	−63

DISCUSSION

For the correlation of nucleophilic reactivity the preferred method would be to calculate the "inherent nucleophilicity" from parameters such as polarisability, basicity, interaction energies in the transition states, etc., which are independent of rate measurement.[3-5] However, as these are only incompletely known, the usual way of correlating nucleophilicity is to choose a standard reaction, and to measure reaction rates with various nucleophiles.[6]

The relative reactivity of nucleophiles varies when atoms in different molecular environments are attacked [7] and each type of reaction has its "nucleophilic series" of reactivity. In isomerisation studies with a single substrate, regardless of the nucleophile, the reaction product is always the same, and no complications can arise from the intrusion of partial thermodynamic control. Several reagents (*e.g.*, tertiary amines, water, and alcohols), even in cases when they do not give substitution or addition reactions, still catalyse the isomerisation, and the nucleophilicity can, therefore, be determined in this manner. The reactivity series obtained in isomerisation could be used to correlate attacks on other doubly-bonded carbon systems, such as aromatic and carbonyl carbon atoms (see below).

Nucleophilic *cis–trans*-isomerisations were recorded in the literature mainly in relation to the stereochemistry of other reactions on activated double bonds, such as nucleophilic vinylic substitutions [8-10] or alkaline epoxidation.[11,12] Amine-catalysed isomerisations were described in the case of *cis*-4-nitrochalcone,[13] in the conversion of maleic into fumaric acid by ammonia [14] or pyridine,[15] and in the isomerisations of ethyl and methyl maleate to the fumarates, catalysed by primary and secondary but not by tertiary amines.[16] The last reaction was shown to be of first order in maleate and of second order in the amines.[17,18] The differences between these systems and the present one are summarised in Table 3.

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[3] Edwards, *J. Amer. Chem. Soc.*, 1954, **76**, 1540; 1956, **78**, 1819.

[4] Edwards and Pearson, *J. Amer. Chem. Soc.*, 1962, **84**, 16.

[5] Ogg and Polanyi, *Trans. Faraday Soc.*, 1935, **31**, 604; Evans and Polanyi, *ibid.*, 1938, **34**, 11; Baughan and Polanyi, *ibid.*, 1941, **37**, 648.

[6] Swain and Scott, *J. Amer. Chem. Soc.*, 1953, **75**, 141.

[7] Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, 1956, p. 142.

[8] Jones, Morris, Vernon, and White, *J.*, 1960, 2349.

[9] Miller and Yonan, *J. Amer. Chem. Soc.*, 1957, **79**, 5391.

[10] Modena, Todesco, and Tonti, *Gazzetta*, 1959, **89**, 878.

[11] House and Ro, *J. Amer. Chem. Soc.*, 1958, **80**, 2428.

[12] Payne and Williams, *J. Org. Chem.*, 1961, **26**, 651.

[13] Southwick and Shozda, *J. Amer. Chem. Soc.*, 1959, **81**, 3298.

[14] Tanatar, *J. Russ. Phys. Chem. Soc.*, 1911, **43**, 1742.

[15] Pfeiffer, *Ber.*, 1914, **47**, 1592.

[16] Clemo and Graham, *J.*, 1930, 213.

[17] Nozaki, *J. Amer. Chem. Soc.*, 1941, **63**, 2681.

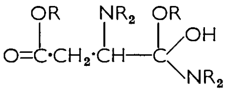
[18] Davies and Evans, *Trans. Faraday Soc.*, 1955, **51**, 1506.

TABLE 3.

Comparison between the amine-catalysed *cis–trans*-isomerisations in the fumarate–maleate and in the ethyl α-cyano-β-*o*-methoxyphenylacrylate systems.

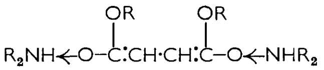
	Maleate ⟶ *Fumarate*	cis-*Ester* (I) ⟶ trans-*Ester* (II)
1.	Catalysed by primary and secondary, but not by tertiary amines.	Catalysed by all types of amines (partially cleaved by primary amines).
2.	Overall third order (second order in the amine).	Overall second order (first order in the amine).
3.	Correlation between base strength and rate coefficients.	No correlation between base strength and rate coefficients.
4.	$E_A = 9$—10 kcal. mole^{-1}, $\Delta S^{\ddagger} \sim -40$ e.u.	$E_A = 3$—5 kcal. mole^{-1}, $\Delta S^{\ddagger} \sim -45$ to -65 e.u.
5.	Amine addition product detected.	No amine addition product detected.

Various intermediates with a single C_α–C_β bond, enabling free rotation, were postulated. Intermediate (A) is based on Nozaki's original suggestion[17] as corrected by Davies and Evans[18] who, however, preferred (B). Intermediate (C), tentatively suggested by Eliel[19] as a product of 1,4-addition, explains neither the third-order kinetics nor the unreactivity of tertiary amines in the reaction, unless the mechanism is a concerted one, as otherwise a planar carbanion, capable of isomerisation should be formed in the first, nucleophilic, addition step of this mechanism.



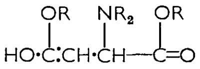
$$O{=}\overset{OR}{\overset{|}{C}}\cdot CH_2\cdot \overset{NR_2}{\overset{|}{C}H}—\overset{OR}{\overset{|}{C}}\!\begin{smallmatrix}OH\\ NR_2\end{smallmatrix}$$

(A)



$$R_2NH\leftarrow O–\overset{OR}{\overset{|}{C}}{:}CH\cdot CH{:}\overset{OR}{\overset{|}{C}}–O\leftarrow NHR_2$$

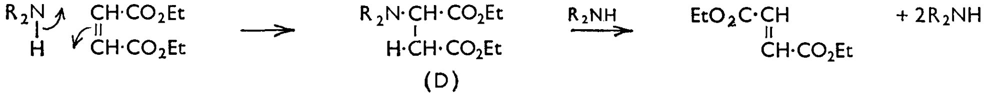
(B)



$$HO\cdot \overset{OR}{\overset{|}{C}}{:}CH\cdot \overset{NR_2}{\overset{|}{C}H}—\overset{OR}{\overset{|}{C}}{=}O$$

(C)

We believe that a similar mechanism operates in both reactions, and that the differences shown in Table 3 can be adequately explained by assuming quantitative differences in the rate coefficients of the different stages, determined mainly by the different electrophilicity of the β-carbon atom in the two systems. In the maleate system, with the attacked carbon atom activated only by one ethoxycarbonyl group, and with even this effect diminished by the symmetry of the molecule, direct nucleophilic attack by amines is difficult. The attack can be easier when a four-centre αβ-addition can take place, as with primary and secondary amines. Formation of a planar carbanion is not required in the first step of this mechanism and stereoselective elimination of the amine from the adduct (D) gives the fumarate. However, the tertiary amino-group in (D), bound to a carbon atom bearing an electron-withdrawing group, cannot compete seriously for the proton with free amine molecules, the necessary presence of which in the rate-determining step gives the overall third-order kinetics. Owing to the correlation between hydrogen basicity and hydrogen nucleophilicity,[20] an experimental relation of the rate coefficient with the p*K* values for the amines is obtained.



$$\begin{matrix}R_2N\\ |\\ H\end{matrix}\;\begin{matrix}CH\cdot CO_2Et\\ \|\\ CH\cdot CO_2Et\end{matrix} \longrightarrow \underset{(D)}{\begin{matrix}R_2N\cdot CH\cdot CO_2Et\\ |\\ H\cdot CH\cdot CO_2Et\end{matrix}} \xrightarrow{R_2NH} \begin{matrix}EtO_2C\cdot CH\\ \|\\ CH\cdot CO_2Et\end{matrix} + 2R_2NH$$

In comparison, the electrophilicity of the β-carbon atom in ethyl *cis*-α-cyano-β-*o*-methoxyphenylacrylate is much higher owing to the additional strong activation by the cyano-group on the α-carbon atom and to the unsymmetrical structure of the system. Hence, it can be attacked by weak nucleophiles[2] as well as by tertiary amines to give the carbanion (III, *cis*).

No adduct of the type (IV) could be detected experimentally in our reaction mixture. Anyhow, its participation in the rate-determining step can be excluded by the high acidity of the α-hydrogen atom and the lack of correlation between the basicity of the catalysts and the rate coefficients.

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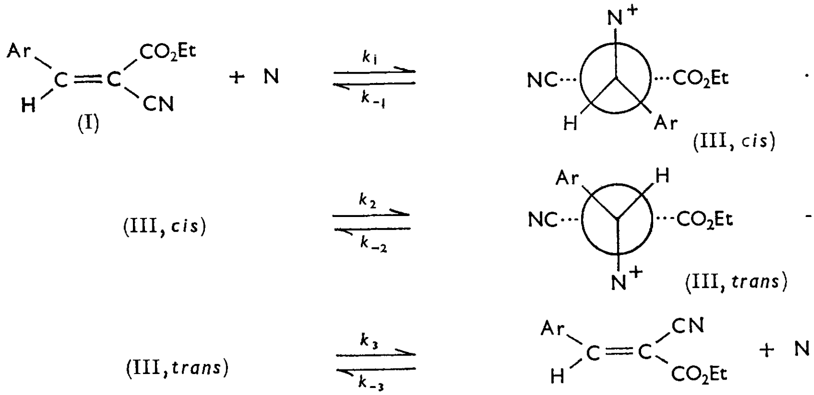
[19] Eliel, " Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., New York, 1962, p. 344.

[20] Bell, " The Proton in Chemistry," Cornell University Press, Ithaca, New York, 1959, p. 160; Pearson and Dillon, *J. Amer. Chem. Soc.*, 1953, **75**, 2439.

The following three-step mechanism is suggested for the isomerisation of (I) in the presence of various nucleophiles: (1) reversible addition of the nucleophile to the *cis*-isomer forms the "*cis*-carbanion" (III, *cis*) defined as the conformer immediately obtained by



.... (1)

.... (2)

.... (3)

attack of the nucleophile on the *cis*-isomer, followed by (2) internal rotation around the C_α–C_β bond to give the "*trans*-carbanion" (III, *trans*), defined analogously, giving the *trans*-isomer (II) after elimination of the nucleophile (3).

It was suggested previously [2] that a tetrahedral *cis*-carbanion is formed in the primary attack and isomerises to a tetrahedral *trans*-carbanion by rapid inversion of its configuration. However, the insensitivity of the reaction to acidity,[2] brought as an argument in favour of rapid inversion, is also in agreement with rotation in a planar carbanion intermediate. From the mechanistic point of view there is little difference between the two alternatives but, as (III, *cis*) is formed from a planar molecule and is stabilised by resonance, it is more reasonable to suppose that it retains the planar structure and gives (III, *trans*) by rotation.

Steady-state treatment of the above scheme gives equation (4) for the rate of formation of the *trans*-isomer,

$$\frac{d[T]}{dt} = \frac{k_1k_2k_3[C][N] - k_{-1}k_{-2}k_{-3}[T][N]}{k_{-1}k_{-2} + k_{-1}k_3 + k_2k_3}, \quad . \; . \; . \; . \; . \; . \quad (4)$$

where $[C]$, $[T]$, and $[N]$ are the concentrations of the *cis*- and *trans*-isomers and of the nucleophile, respectively. The equilibrium favours overwhelmingly the *trans*-isomer, as shown by the practically complete *cis* ⟶ *trans*-isomerisation and by the fact that the *trans*-isomer gave no measurable reaction with any of the nucleophiles studied. Hence the second term of the numerator can be neglected in comparison with the first. As the reaction is of first order in both the amine and the *cis*-ester, the experimental rate coefficient, k_{exp}, is given by equation (5). From equation (4) and from the fact that the reaction is practically irreversible, equation (6) is obtained. In most systems the rate of nucleophilic attack on a pair of *cis*–*trans*-isomers is only slightly different.[8,11,21] In our case, the *o*-methoxy-group reduces the electrophilicity of the β-carbon atom [resulting from structures such as, *e.g.*, (V)] by the resonance contributions of structures such as (VI). This effect is smaller in the *cis*-isomer, in which steric interactions disturb more the coplanarity of the aryl group, resulting in a relatively higher electrophilicity of the β-carbon atom, and indeed it was shown that the rate of nucleophilic hydrolysis of the *cis*-isomer by water

$$k_{\text{exp}} = k_1/[1 + (k_{-1}/k_2)(1 + k_{-2}/k_3)] \quad . \; . \; . \; . \; . \; . \; . \quad (5)$$

$$k_1k_2k_3 > k_{-1}k_{-2}k_{-3} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (6)$$

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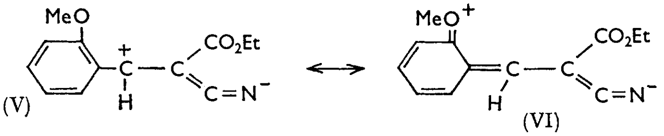
[21] Modena and Todesco, *Gazzetta*, 1959, **89**, 866; Campagni, Modena, and Todesco, *ibid.*, 1960, **90**, 694.

$ArCH(NR_2)\cdot CH(CN)CO_2Et$
(IV)



(V) (VI)

molecules is higher, although only slightly so, than that of the *trans*-isomer. Hence, k_1 and k_{-3} are not very different and equation (6) reduces to (7). We estimate that 1% of

$$k_2k_3 > k_{-1}k_{-2} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (7)$$

the *cis*-isomer would be detectable at equilibrium and that, from the above analogies, the value of k_1 is not more than twice that of k_{-3}. Therefore, we can safely assume that $k_2k_3 > 50k_{-1}k_{-2}$. By inserting equation (7) into (5) and neglecting $k_{-1}k_{-2}/k_2k_3$ compared

$$k_{\text{exp}} = k_1/(k_{-1}/k_2 + 1) \quad . \; . \; . \; . \; . \; . \; . \; . \quad (8)$$

to unity, equation (8) is obtained. We have to examine three possible situations: (a) $k_2 > k_{-1}$, *i.e.*, elimination of the nucleophile from the " *cis*-carbanion " is slow compared to its rotation, giving equation (9)

$$k_{\text{exp}} = k_1 \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (9)$$

(b) $k_{-1} > k_2$, *i.e.*, rotation is slower than elimination, giving equation (10)

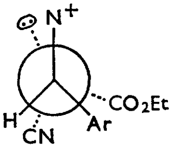
$$k_{\text{exp}} = k_1k_2/k_{-1} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (10)$$

(c) $k_{-1} \sim k_2$, *i.e.*, elimination and rotation have comparable rates, and the unchanged equation (8) applies.

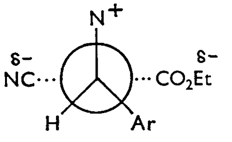
Equation (9) is immediately rejected, as it implies $E_{\text{exp}} = E_1$. The very low values of the activation energies of Table 2, which would fit a diffusion-controlled reaction,[22] cannot be the actual activation energies for a nucleophilic attack involving bond formation. Equation (8) with the condition (c) can be excluded by the same reasoning, as in this case k_{exp} still cannot be very different from k_1 and the reaction will still largely be controlled by step (1) and again does not fit the low activation energy.

Case (b) (eqn. 10) seems to fit the available data. In some examples described in the literature, the rate of a hindered rotation is slower than the rate of elimination from the same intermediate, *e.g.*, in the reaction of labelled iodine atoms with 1,2-di-iodoethylene, in which the rate of iodine exchange is much higher than the isomerisation rate,[23] showing that elimination from the intermediate may be much faster than internal rotation in it.

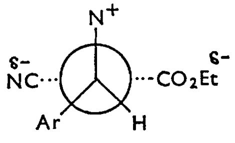
Our system contains a zwitterionic intermediate which may necessitate the introduction of rather special assumptions both as to its rotation and as to the *E*1*cB* elimination from it. Apart from the usual steric considerations relating to rotation, we may have to consider also the electrostatic interaction between the positive amino-nitrogen and the negative charge on the carbanionic entity of the molecule. Whether the negative charge appears localised on the α-carbon [in the tetrahedral carbanion (VII)] or distributed on the two substituents [in III, *cis* and III, *trans*, possibly with preference to charge development on the carbonyl oxygen of the ethoxycarbonyl group, stabilised by the formation of a



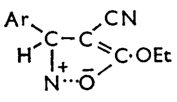
(VII, *eclipsed*)



(III, *cis*)



(III, *trans*)



(VIII)

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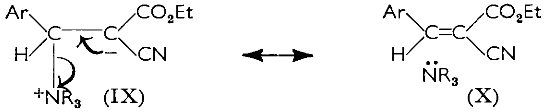
[22] Benson, " The Foundations of Chemical Kinetics," McGraw-Hill Book Co., New York, 1960, p. 499.

[23] Noyes, Dickinson, and Schomaker, *J. Amer. Chem. Soc.*, 1945, **67**, 1319.

quasi-five-membered ring (VIII)], it can be assumed that the rotation (or inversion) of the intermediate requires electrostatic work for the separation of opposite charges. The same conclusion (*i.e.*, enhanced hindrance to rotation) can be reached by assuming, in the zwitterionic intermediate, a partial double-bond character of the C_α–C_β bond. Accordingly, the rate of rotation (or inversion) leading from one intermediate to the other will be lowered. Moreover, the rate of the elimination will be enhanced as it is a favoured formation of two neutral molecules from a single zwitterionic intermediate. Indeed, this process can be depicted as a form of no-bond resonance with contributing structures (IX) and (X). When these considerations are taken into account, the condition $k_{-1} > k_2$ seems to be acceptable.


(IX) (X)

For case (b), following use of the equation $k = Ae^{-E_A/RT}$, the experimental activation energy is given by equation (11).

$$-E_{\text{exp}} = E_{-1} - E_1 - E_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where the *E*'s are the activation energies of the corresponding single-rate processes. Rough estimation of E_1 from the values of activation energies of other nucleophilic attacks on activated double bonds, *e.g.*, Michael reaction,[24] cyanoethylation,[25] and cleavage,[26,27] gives $E_1 = 13 \pm 3$ kcal. mole^{-1}. E_{exp} was 4 ± 1 kcal. mole^{-1} and therefore $E_{-1} - E_2 = E_1 - E_{\text{exp}} = 9 \pm 4$ kcal. mole^{-1}. The values of E_{-1} and E_2 are not known, but E_{-1} for our case is probably much lower than the values given for normal *E*1c*B* eliminations (30 kcal. mole^{-1} for activated,[28] 31—37 kcal. mole^{-1} for less active system [29]) and that of E_2 is higher than the value for only sterically and not electrostatically hindered rotations (2—6 kcal. mole^{-1}).[30] The value for the difference $E_{-1} - E_2$ is therefore reasonable. It should be noted that overall activation energies of composite processes may be very low or even negative, as, *e.g.*, in cationic [31] and anionic [32] polymerisations.

By an analogous treatment the experimental entropy of activation is given by equation (12). $\Delta S_2^\ddagger$ is relatively small compared with $\Delta S_{-1}^\ddagger$ (which has a positive value

$$\Delta S^\ddagger = \Delta S_1^\ddagger + \Delta S_2^\ddagger - \Delta S_{-1}^\ddagger \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

owing to the formation of two neutral molecules from a zwitterion), and also compared with $\Delta S_1^\ddagger$ (which has a high negative value as a result of the formation of a charged molecule from two uncharged ones). As k_1/k_{-1} is the equilibrium constant for step (1), ΔS° of the process has to be similar to that of ionisations and of quaterisations. These, *e.g.*, the ionisation of acetic acid in 82% dioxan,[33] or the quaternisation of *p*-bromodimethylaniline with allyl bromide in chloroform [34] have values of —50 to —60 e.u. Unfortunately, equation (12) cannot be used to correlate the trend in the activation entropies for the different amines, as in such comparisons $\Delta S_2^\ddagger$ cannot be neglected.

The foregoing analysis shows that our original intention of determining a scale of nucleophilicity for various amines cannot be carried out in the present system. Neither could the nucleophilic attack as such be isolated in other reactions, in which the first step

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[24] Kamlet and Glover, *J. Amer. Chem. Soc.*, 1956, **78**, 4556.

[25] Schmidt and Kubitzek, *Chem. Ber.*, 1960, **93**, 866.

[26] Patai and Rappoport, *J.*, 1962, 383.

[27] Patai and Rappoport, *J.*, 1962, 392.

[28] Patai, Weinstein, and Rappoport, *J.*, 1962, 1741.

[29] Hine, Wiesboeck, and Ramsay, *J. Amer. Chem. Soc.*, 1961, **83**, 1222.

[30] Douben and Pitzer in Newman's " Steric Effects in Organic Chemistry," John Wiley and Sons, New York, 1956, p. 57.

[31] Plesch, *J.*, 1950, 543; Dainton and Tomlinson, *J.*, 1953, 151.

[32] Vofsi and Katchalsky, *Ricerca Sci.*, 1955, **25**, 165.

[33] Frost and Pearson, " Kinetics and Mechanism," John Wiley and Sons, New York, 1961, p. 135.

[34] Davies and Cox, *J.*, 1937, 614.

was reversible, with $K = k_1/k_{-1}$ having a low value.[35,36] Even so, our experimental rate coefficients can be used for the comparison of nucleophilic activities.

The rate coefficient $k_{\text{exp}} = k_1k_2/k_{-1}$ would be a measure of nucleophilicity in the case where k_2/k_{-1} is constant for a series of attacking reagents or where k_2/k_{-1} is strictly proportional to k_1. As the three single steps described by the rate coefficients k_1, k_{-1}, and k_2 are different in character and subject to different (steric, electronic, and electrostatic) influences it is hardly probable that any of the above two conditions would hold. Our data show no correlation between the pK's of the various amines used and k_{exp}, and this result is expected from the lack of correlation between carbon nucleophilicity and hydrogen basicity.[37]

As k_1/k_{-1} is the equilibrium constant, K, of the first reversible step of the reaction, $k_{\text{exp}} = Kk_2$ will be a measure of the " carbon basicity " [37] of the nucleophile if k_2 is either constant or proportional to K within a series of nucleophiles. Constancy or near constancy of k_2 for various nucleophiles is reasonable in a series with the same nucleophilic atom, becoming charged in the intermediate. In the latter the size and number of substituents bound to the attacking nucleophilic atom may play only a relatively minor part, except possibly with amines of excessive steric requirements. Alternately, the second, in itself sufficient, condition that k_2 should be proportional to K may be maintained in a series of amines of the same type, as the same steric effects which enhance k_2 will also increase K, and *vice versa.* Increasing reagent size hinders both the nucleophilic attack and the rotation in the intermediate formed (*i.e.*, lowers both k_1 and k_2) and at the same time enhances k_{-1} as the elimination of the nucleophile releases the steric compression in the intermediate. Hence, it is reasonable to suppose that the values of both $K(= k_1/k_{-1})$ and k_2 change in the same direction.

The " carbon basicity " of nucleophiles was determined recently in limited cases,[37] but not for amines. In a comparable case the nucleophilic attack of four secondary amines on the unsaturated carbon atom of 1-chloro-2,4-dinitrobenzene was studied.[38,39] The experimentally determined relative reactivities were: di-n-butylamine 1·00, di-n-propylamine 0·89, di-isopropylamine 0·32, and di-isobutylamine 0·005, *i.e.*, practically the same as in our case (1·00, 0·89, 0·17, and 0·008, respectively, for the same amines). The same order of reactivity of di-n-butylamine (1·00) and di-n-propylamine (0·84) was found in the aminolysis of phenyl acetate,[40] in which the amine attacks the unsaturated carbonyl carbon atom. Pyridine is more reactive than 2,6-lutidine in quaternisations [41] and also in our case, and similarly the equilibrium constants with various boron compounds [42] (which could be defined as " boron basicity ") are higher with pyridine than with 2,6-lutidine.

The reactivity of the various amines may be explained by taking into account both the electronic and steric factors operating concurrently, the first enhancing and the second lowering the reaction rates. The weakest catalysts are the tertiary heterocyclic and tertiary aliphatic amines. The fact that 2,6-lutidine, although a stronger base, is a weaker catalyst than pyridine, is clearly due to the steric hindrance exerted by the two α-methyl groups, while in the pair triethylamine–tri-n-butylamine the higher electron availability caused by the larger inductive effect of the butyl group ($\sigma^* = -0{\cdot}130$) [43] more than overcomes its steric hindrance compared to the ethyl group ($\sigma^* = -0{\cdot}100$).[43] Also, it should be noted that irregularities observed with n-butyl groups have been explained by postulating a " δ-effect." [44]

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[35] Crowell and Francis, *J. Amer. Chem. Soc.*, 1961, **83**, 591.
[36] Walker and Young, *J.*, 1957, 2045.
[37] Parker, *Proc. Chem. Soc.*, 1961, 371.
[38] Blanksma and Schreinemakers, *Rec. Trav. chim.*, 1933, **52**, 428.
[39] Brady and Copper, *J.*, 1950, 507.
[40] Arnett, Miller, and Day, *J. Amer. Chem. Soc.*, 1951, **73**, 5393.
[41] Brown, Gintis, and Podall, *J. Amer. Chem. Soc.*, 1956, **78**, 5375.
[42] Brown, Gintis, and Domash, *J. Amer. Chem. Soc.*, 1956, **78**, 5387.
[43] Taft in Newman's " Steric Effects in Organic Chemistry," John Wiley and Sons, New York, 1956, p. 591.
[44] Arnett, Miller, and Day, *J. Amer. Chem. Soc.*, 1950, **72**, 5635.

In the group of four secondary aliphatic amines, the two straight-chain derivatives both have similar steric requirements and electronic effects (σ^* for n-butyl = —0·130, and for n-propyl —0·115)[43] and also rather similar reaction rates, while the steric hindrance in the branched amines is much more important and lowers considerably the reaction rates even though the inductive effect is equal (for isobutyl, $\sigma^* = -0{\cdot}125$) or larger (for isopropyl, $\sigma^* = -0{\cdot}190$)[43] than that of the unbranched chains.

EXPERIMENTAL

Materials.—Benzene (Union Chimique Belge) was dried ($CaCl_2$ for 24 hr. and Na wire for 48 hr.). The fraction of b. p. 77°/720 mm. was used. The amines were pure commercial grades, distilled, dried, and stored over potassium hydroxide, and redistilled immediately before use.

Ethyl *trans*-α-cyano-β-*o*-methoxyphenylacrylate was prepared according to Baker,[45] and the *cis*-isomer by a modification of the methods described previously.[2,45] 3-Cyanocoumarin (11·4 g.) was dissolved in 1·25N-sodium hydroxide (360 ml.) with shaking for 10 min., and dimethyl sulphate (23 ml.) was added with continuous shaking during 45 min. at 0°. After an additional 1 hr. at 0°, the solution was acidified with 30% hydrochloric acid until precipitation ceased. The yellow solid was shaken with dilute sodium hydrogen carbonate solution, filtered from the unchanged 3-cyanocoumarin, and acidified again, giving the *cis*-acid (9·6 g., 69%), m. p. 159°. The acid was dissolved in the minimum quantity of sodium hydrogen carbonate solution and the silver salt, obtained by the addition of aqueous silver nitrate solution, was filtered off, and dried *in vacuo*. Ethyl iodide (31·2 g., 0·2 mole) and the silver salt (15·5 g., 0·05 mole) in methylene chloride (100 ml.) were stirred in the dark for 6 hr. and filtered. The solvent was evaporated *in vacuo*, and the residue was dissolved in a minimum quantity of methylene chloride, filtered, and kept at 0° for 24 hr.; the *cis*-ester (2 g., 17·4%) crystallised. Although the yield was lower, this method was reproducible, while those described previously[2,45] occasionally gave the *trans*-isomer.

The kinetic procedures and the treatment of data were described previously.[2] A stock solution of the *cis*-isomer in benzene was prepared daily. The reaction was followed spectrophotometrically at 360 and at 370 mμ, and the isosbestic wavelength of the *cis*- and the *trans*-isomers (333 mμ) was used occasionally to ascertain that isomerisation was the only reaction in the sytem. No indication of any side reaction was observed, even in reaction mixtures with the highest amine concentrations used. The values 4100 and 3900 at 360 and at 370 mμ, respectively, were used for ($\varepsilon_{trans} - \varepsilon_{cis}$) as calculated from the data in the following paragraph. The reaction was quantitative and practically irreversible, giving, within the experimental error, 100% conversion of the *cis*- into the *trans*-isomer. The *trans*-isomer did not react in benzene with the amines studied.

Spectra.—Ultraviolet data and kinetic measurements were determined in a Beckman DU spectrophotometer. Data for the *cis*- (I) and the *trans*- (II) esters in benzene are: (I) $\lambda_{max.}$ 299 (ε 8950), λ 333 (ε 7300), $\lambda_{max.}$ 347 (ε 7950) λ 360 (ε 7050), λ 370 mμ (ε 5200); (II) $\lambda_{max.}$ 299 (ε 12,200), $\lambda_{max.}$ 357 (ε 11,300), λ 360 (ε 11,150), λ 370 mμ (ε 9100).

A sample run is given in the annexed Table.

Isomerisation of *cis*-ester (10^{-4} mole $l.^{-1}$) in presence of di-n-butylamine (4×10^{-5} mole $l.^{-1}$).

Time (sec.)	60	150	210	300	420	660
log (I_0/I) at 360 mμ	0·720	0·735	0·745	0·755	0·775	0·810
Time (sec.)	105	180	260	360	480	570
log (I_0/I) at 370 mμ	0·545	0·555	0·570	0·585	0·602	0·615

$$\text{Initial rate coefficient} = (\text{Slope}/C_0\Delta\varepsilon)$$
$$\text{at } \lambda = 360 \text{ m}\mu,\ k = 3{\cdot}06 \times 10^{-4} \text{ sec.}^{-1};$$
$$\text{at } \lambda = 370 \text{ m}\mu,\ k = 3{\cdot}02 \times 10^{-4} \text{ sec.}^{-1};$$
$$\text{mean } k = 3{\cdot}04 \times 10^{-4} \text{ sec.}^{-1};$$
$$k_{exp} = k/[\text{amine}] = 7{\cdot}6 \text{ mole}^{-1} \text{ l. sec.}^{-1}.$$

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[45] Baker and Howes, *J.*, 1953, 119.