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REACTIVITY OF AMBIDENT ANIONS—II

KINETICS OF ALKYLATION OF β-KETOESTER ALKALINE ENOLATES BY ETHYL TOSYLATE IN HEXAMETHYLPHOSPHOTRIAMIDE

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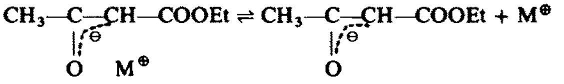
Abstract—The alkylation of K- and Cs-enolates of ethyl γ,γ-dimethyl-, ethyl γ,γ,γ-trimethylacetoacetates and also Cs-enolate of ethyl γ,γ,γ-trifluoroacetoacetate by ethyl tosylate in HMPT is reported. The degree of dissociation of β-ketoester Cs-enolates in the same solvent was measured by the conductometric method. The rates of both O- and C-ethylations of the enolate ion were measured. The p*Ka* of the corresponding β-ketoesters were measured in DMF. The reactivity of the enolates investigated was found to be proportional to their basicity.

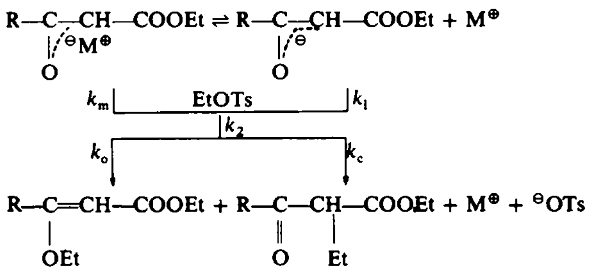
IN OUR previous paper[1] we reported the kinetic data for ethylation of ethyl acetoacetate alkaline enolates by ethyl tosylate in HMPT. We have shown that the reaction rate increases in the series: Li < Na < K < Cs while the ratio of C- and O-alkylation products (C/O) is constant for all enolates in studies of the initial concentrations. The observed second order rate constant k_2 did not vary when the ethyl tosylate concentration was changed but decreased with an increase in enolate concentration as a result of the change in the degree of dissociation of the latter. Also a certain decrease in k_2 due to the common ion effect has been observed in the course of kinetic measurements.



$$\mathrm{CH_3{-}\underset{\overset{\|}{O}\quad M^{\oplus}}{C}{\overset{\ominus}{\doteq}}CH{-}COOEt \rightleftharpoons CH_3{-}\underset{\overset{\|}{O}}{C}{\overset{\ominus}{\doteq}}CH{-}COOEt + M^{\oplus}}$$

The study of the dependence of the degree of enolate dissociation on both the cation nature and concentration enabled us to establish that only the free acetoacetate anion underwent ethylation. This fact is in good agreement with the observed constancy of C/O ratio for all enolates at different initial reagent concentrations.

It was of interest to clarify the mechanism that would accomodate all the observed facts for the series of γ-substituted ethyl acetoacetates and to establish the effect of changes in β-ketoester structure on the reaction rate and on the site of electrophilic attack by the agent. In the present paper the kinetics of ethylation of K- and Cs-enolates of ethyl γ,γ-dimethyl- and ethyl γ,γ,γ-trimethylacetoacetate and also that of caesium enolate of ethyl γ,γ,γ-trifluoroacetate with with ethyl tosylate were investigated in HMPT at 20·0°. The C/O ratio was determined. Ethylation of Cs-enolate of ethyl γ,γ,γ-trifluoroacetate gave only O-alkylation product.



$$R = (CH_3)_2CH—, (CH_3)_3C—, CF_3—$$

$$k_2 = k_c + k_o \qquad (1)$$

$$k_c/k_o = \frac{\%\ \text{C-alkylation}}{\%\ \text{O-alkylation}} \qquad (2)$$

$$k_2 = k_i\alpha + k_m(1 - \alpha) = (k_i - k_m)\alpha + k_m \qquad (3)$$

$$k_i = k_{c_i} + k_{o_i} \qquad (4)$$

where k_2 is the observed second order reaction rate constant, k_i and k_m are the ethylation rate constants for the enolate ion and ion pair respectively.

k_c and k_o are the observed rate constants of C- and O-alkylations.

k_{c_i} and k_{o_i} are the reaction rate constants of C- and O-alkylation reactions of the enolate ion.

TABLE 1. ETHYLATION OF ALKALINE ENOLATES OF $RCOCH_2COOEt$ BY ETHYLTOSYLATE IN HMPT AT 20·0°

R	Metal	$C.10^2$ mole/l	$\alpha.10^2$	$k_2.10^{5b}$ l/mole sec	k_c/k_o
CH_3[a]	Cs	1·00	70	1250	0·13
		1·92	60	1080	0·13
		4·01	48	870	0·13
		8·00	36	600	0·13
$(CH_3)_2CH$	K	2·04		550	0·14
		4·10		410	0·14
		7·84		230	0·15
	Cs	0·99	52	1000	0·14
		1·97	42	680	0·14
		4·08	32	530	0·14
		6·08	26	470	0·14
		8·25	22	330	0·14
$(CH_3)_3C$	K	2·02		230	0·16
		4·20		120	0·19
		7·80		64	0·25
	Cs	1·00	8·4	600	0·14
		2·02	6·4	250	0·14
		4·01	5·0	150	0·17
		7·90	3·6	70	0·21
CF_3	Cs	0·5	48	8·2	0
		2·0	32	5·4	0
		8·0	18	2·9	0

[a] See ref. 1.

[b] Constants are average of three (or more) independent runs, deviation ±10%.

The degrees of dissociation, α, was determined in HMPT for caesium enolates for the investigated β-ketoesters.

The ethylation rate constants obtained and also the observed ratio of C- and O-isomers (C/O) are shown in Table 1 (*c.f.* caesium acetoacetic ester). From these data it can be seen that as in the case of ethyl acetoacetate the reaction rate increases if Cs- instead of K-enolate is used. This effect is clearly observed for ethyl γ,γ-dimethylacetoacetate but it is less obvious in the case of ethyl γ,γ,γ-trimethylacetoacetate whose enolates are both weakly dissociated. The reaction rate increases with decreases in initial concentration, i.e. with increase in dissociation. This effect is stronger for ethyl γ,γ,γ-trimethylacetoacetate.

A drop in reaction rate constant was observed during measurements. As in the case of ethyl acetoacetate this was a result of the common ion effect which is more powerful than that of decreasing concentration. The common ion effect is essentially pronounced in reactions of ethyl γ,γ,γ-trimethylacetoacetate enolates. In this connection the value k_2 presented in Table 1 was found by extrapolation to zero time.

The general character of the dependences obtained allows us to assume that in ethylation of the γ-substituted ethyl acetoacetate enolates the free anion is again the reacting species. This is confirmed by the constancy of the C/O ratio in alkylation of both the K- and Cs-enolates of ethyl γ,γ-dimethylacetoacetate and also by the fact that the ratio does not depend on the initial concentrations (C/O = 0·14, *cf* 0·13 for ethyl acetoacetate). However for ethyl γ,γ,γ-trimethylacetoacetate the C/O ratio is not constant. The quantity of C-isomer increases if potassium enolate is used instead of caesium or if the initial concentration is increased. (The potassium enolate concentration being $7{\cdot}8 \times 10^{-2}$ mole/l, the C/O ratio varies from 0·25 at the beginning of the reaction to 0·34 at 38% conversion). The same effect is produced by introduction of a common cation into the mixture. These results are in agreement with the assumption that not only ions but also ion pairs participate in the reaction. The extent of ion participation increases with decrease in concentration. At the initial concentrations of $(1\text{–}2) \times 10^{-2}$ mole/l, the enolate ion probably is the only reacting species since under these conditions the ratio of C- and O-alkylation products remains constant.

As one can see from Table 1, structural changes in the enolate ion affect ethylation rates considerably. The enolate reactivity is determined by the following factors: (1) basicity of the ambident anion, (2) the degree of enolate dissociation, (3) the extent of ion and ion pair participations in the reaction. As a result the observed reactivity depends upon the relative changes of each factor.

Taking into account that the observed reaction rate constant $k_2 = \alpha k_i + k_m(1 - \alpha)$ the values of α being known, one can determine k_i and k_m. In the case of ethylation of caesium enolates of ethyl γ,γ-dimethyl- and γ,γ,γ-trifluoroacetoacetate, as in the case of ethyl acetoacetate, the plot k_2 vs. α passes through the centre of coordinates (Figs 1 and 2), which means that for the enolates in question free enolate ions are the only reacting species. For alkaline enolates of ethyl γ,γ,γ-trimethylacetoacetate as already mentioned, one may assume the participation of both the ion and ion pair in the reaction.

Due to the low degree of dissociation of caesium ethyl γ,γ,γ-trimethylacetoacetate and the difficulties in the determination of the real value of k_2, given by the drastic fall of the constants in the course of the kinetic graph, there is no linear

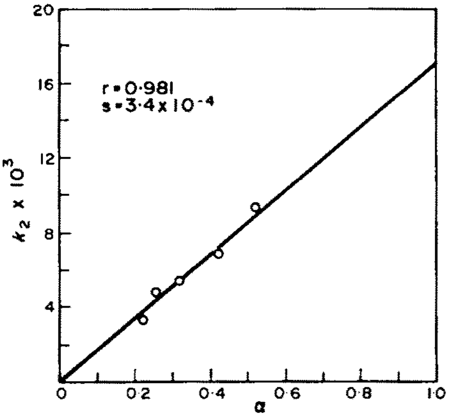


FIG 1. Plot of k_2 vs. α for ethylation of caesium enolate of ethyl γ,γ-dimethylacetoacetate by ethyltosylate in HMPT.

dependence of k_2 on α. For this reason only the k_i value is able to be estimated. Table 2. It follows that the enolate ion reactivity decreases in the series of β-ketoesters as follows

It follows that the enolate ion reactivity decreases as follows

$$(CH_3)_3CCOCH_2COOEt > (CH_3)_2CHCOCH_2COOEt > CH_3COCH_2COOEt > CF_3COCH_2COOEt.$$

This order is also preserved if one compares the alkylation rate constants for every enolate ion reaction centre (k_{o_i} and k_{c_i}). As it follows from the substituents inductive effects the enolate ion basicity should decrease in the same order.

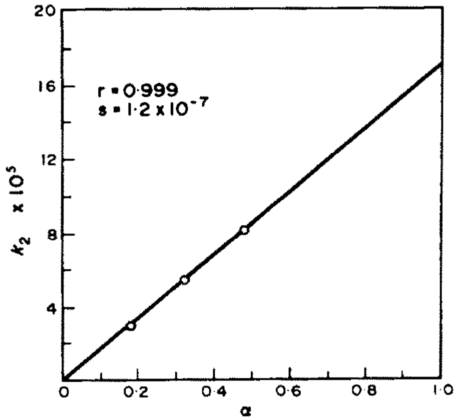


FIG 2. Plot of k_2 vs. α for ethylation of caesium enolate of ethyl γ,γ,γ-trifluoroacetoacetate by ethyltosylate in HMPT.

TABLE 2. RATE DATA FOR THE ETHYLATION OF β-KETOESTER ENOLATE IONS BY ETHYLTOSYLATE IN HMPT AT 20·0°

R in $RCOCH_2COOEt$	$k_i{}^a \times 10^5$	$k_{o_i}{}^a \times 10^5$	$k_{c_i}{}^a \times 10^5$
CF_3	17	17	—
$CH_3{}^b$	1800	1590	210
$(CH_3)_2CH$	1900	1670	230
$(CH_3)_3C$	8000	7000^c	1000^c

[a] In l mole^{-1} sec^{-1}.

[b] Ref. [1].

[c] The separation of k_i into k_{o_i} and k_{c_i} was provided with the minimal value of k_c/k_o obtained in the ethylation of the caesium enolate within the concentration range 1×10^{-2}–2×10^{-2} mole/l (Table 1).

For a quantitative comparison, the p*Ka* of the corresponding β-ketoesters were determined in DMF* (Table 3). It was shown that log k_0 and p*Ka* change simbathically. But it would be more reasonable to compare the values of log k_{o_i} and log k_{c_i} (log k_{o_m} and log k_{c_m}) with the basicity of each centre in the ambident system.

TABLE 3. p*Ka* OF β-KETOESTERS IN DMF AT 20–25°

β-ketoester	p*Ka*
Ethyl γ,γ,γ-trifluoroacetoacetate	7·4
Ethyl acetoacetate	12·6
Ethyl γ,γ-dimethylacetoacetate	12·9
Ethyl γ,γ,γ-trimethylacetoacetate	14·1
Ethyl α-ethylacetoacetate	12·5
Ethyl α-ethyl-γ,γ-dimethylacetoacetate	13·2
Ethyl α-ethyl-γ,γ,γ-trimethylacetoacetate	> 15·0

TABLE 4. CONDUCTIVITY DATA FOR CAESIUM ENOLATE OF ETHYL γ,γ,γ-TRIFLUOROACETOACETATE IN HMPT AT 20·0°

C.10^4 mole/l	*R* ohm	λ cm^2 equiv^{-1} cm^{-1}	α
800	47	2·13	0·187
400	71	2·82	0·247
200	108	3·70	0·315
100	166	4·80	0·393
50	263	6·04	0·482
25	422	7·52	
12·5	700	8·96	
6·25	1200	10·4	

$\lambda_0 = 14{\cdot}0$ cm^2 equiv^{-1} cm^{-1}

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* The choice of DMF was dictated by the fact that in the literature there is no information on the acidities of organic compounds in HMPT within the 5–12 p*Ka* range. Such data are available for DMF[2]—a dipolar aprotic solvent of the same class as HMPT and having similar properties.

As one can see (Table 1) for the enolate ion ethylation the C/O ratio is equal to 0·13 for ethyl acetoacetate and to 0·14 for ethyl γ,γ-dimethyl- and ethyl γ,γ,γ-trimethylacetoacetate. Thus the introduction of a Me-group does not noticeably change this ratio. However the ethylation of the ethyl trifluoroacetoacetate anion affords only the O-alkylation product.

TABLE 5. CONDUCTIVITY DATA FOR CAESIUM ENOLATE OF ETHYL γ,γ-DIMETHYLACETOACETATE IN HMPT AT 20·0°

$C.10^4$ mole/l	R ohm	λ $cm^2\,equiv^{-1}\,ohm^{-1}$	α
787	55	1·85	0·231
393·5	75·5	2·70	0·325
196·8	111	3·65	0·424
98·4	170	4·77	0·534
49·20	266	6·08	0·655
24·6	442	7·27	
12·3	767	8·30	
6·15	1460	8·65	

$\lambda_0 = 10{\cdot}9\,cm^2\,equiv^{-1}\,cm^{-1}$

It may be assumed that under the influence of the Me group the basicity of each centre alters equally. For the CF_3 group it is probable that along with a decreasing ambient ion basicity, the basicity of carbon decreases much faster than for oxygen. Thus a valid conclusion on the nucleophilic reactivity of ambient ions can be drawn only after a comparison of true rate constants k_i or k_m.

It follows from tables 1 and 2 that the relative reactivity of the alkaline enolates will be another when we compare the rate constants k_2, then when we compare the rate constants k_i.

TABLE 6. CONDUCTIVITY DATA FOR CAESIUM ENOLATE OF ETHYL γ,γ,γ-TRIMETHYLACETOACETATE IN HMPT AT 20·0°

$C.10^4$ mole/l	R ohm	λ $cm^2\,equiv^{-1}\,ohm^{-1}$	α
770	172	0·60	0·037
335	275	0·87	0·052
167·5	426	1·12	0·067
83·8	633	1·51	0·089
41·9	875	2·16	0·126
21·0	1230	3·08	
10·5	1670	4·54	
5·2	2230	6·75	
2·6	3350	8·89	
1·3	5400	10·9	

$\lambda_0 = 18{\cdot}2\,cm^2\,equiv^{-1}\,ohm^{-1}$

EXPERIMENTAL

IR spectra were measured on an UR-10 instrument, NMR spectra were obtained on a T-60 Varian Model spectrometer in CCl_4. Chemical shifts are given with respect to TMS as an internal standard, coupling constants (J) in Hz. GLC data were obtained on Chrom-2 instrument using 2 m column, diameter 4 mm, with apiezon L (17%) on chromosorb W. Hexamethylphosphotriamide, dimethylformamide and ethyltosylate were purified according to the methods described above.[1]

Ethyl γ,γ,γ-tritluoroacetoacetate (I) was obtained by condensation of ethyl trifluoroacetate with ethylacetate in presence of metallic Na,[3] with subsequent purification via its Cu derivative.[4]

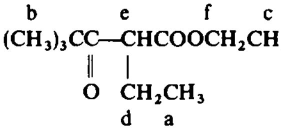
Ethyl γ,γ-dimethylacetoacetate (II) and *ethyl γ,γ,γ-trimethylacetoacetate* (III) were prepared by hydrolysis of hydrochloric iminoesters of isobutyrylacetic[5] and pivaloylacetic[6] acids respectively. The obtained γ-substituted ethyl acetoacetates were chromatographically pure.

Hydrochloric iminoesters of isobutyryl and pivaloylacetic acids were obtained by the reaction of dry HCl with isobutyrylacetonitrile (IV)[5] and pivaloylacetonitrile (V)[7] respectively. IV and V were obtained by condensation of MeCN with ethylisobutyrate and trimethylacetic acid ethyl ester respectively, yield of V 32%, m.p. 68°.

Alkaline enolates of I, II *and* III were prepared from equimolar amounts of the corresponding alkaline metal tert-butylates and I, II and III in abs. ether as described for potassium ethyl acetoacetate.[8] Enolate purity was controlled by titration (not lower than 97%).

Ethyl α-ethyl- γ,γ-dimethylacetoacetate (VI) was prepared as chromatographically pure sample by alkylation of sodium enolate of II with 1·5 fold excess of EtBr in EtOH. VI was washed from II at 0–5° with 8% KOH. Yield 50%, b.p. 82–83°/6 mm, n_D^{21} 1·4262. IR spectrum: C=O 1719, 1747 cm^{-1}. (Found: C, 64·78; H, 9·67. $C_{10}H_{18}O_3$. Calc: C, 64·49; H, 9·74%).

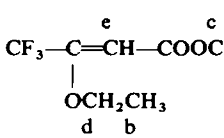
Ethyl α-ethyl-γ,γ,γ-trimethylacetoacetate (VII) was obtained analogously to VI. Yield 81%, b.p. 89–90°/6 mm, n_D^{21} 1·4305. IR spectrum: C=O 1712, 1748 cm^{-1}. PMR spectrum



$$\begin{array}{l}\quad\;\; b \qquad\qquad e \qquad\; f \qquad\quad c\\ (CH_3)_3CC{-}CHCOOCH_2CH_3\\ \qquad\quad\;\; \| \quad\; |\\ \qquad\quad\;\; O \;\; CH_2CH_3\\ \qquad\qquad\quad\; d \quad\; a\end{array}$$

(a) 0·9 (3H, t); (b) 1·15 (9H, s); (c) 1·25 (3H, t); (d) 1·80 (2H, quintet); (e) 3·65 (1H, t); (f) 4·08 (2H, q). (Found: C, 66·56; H, 9·98. $C_{11}H_{20}O_3$. Calc: C, 65·96; H, 10·07%).

Ethyl β-ethoxy-γ,γ,γ-trifluorocrotonate (VIII). A soln of 1·5 g (0·075 mole) of ethyltosylate in hexamethyltriamidophosphate (25 ml) was added dropwise with stirring in dry argon to 2·14 g (0·068 mole) of caesium enolate of I in the same solvent (25 ml). The mixture was stirred at 60–70° until neutral, poured in H_2O, extracted with Et_2O, dried over $MgSO_4$ and solvent evaporated. Distillation afforded 0·9 g of VIII (60%), b.p. 41–45°/35 mm, n_D^{23} 1·3912. IR spectrum: C=C 1671, C=O 1732 cm^{-1}. PMR spectrum

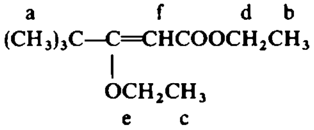


$$\begin{array}{l}\qquad\quad\;\; e \qquad\;\; c \qquad\;\; a\\ CF_3{-}C{=}CH{-}COOCH_2CH_3\\ \qquad\quad |\\ \qquad\; OCH_2CH_3\\ \qquad\quad d \quad\; b\end{array}$$

(a) 1·30 (3H, t); (b) 1·38 (3H, t); (c) 4·18 (2H, q); (d) 4·35 (2H, q); (e) 5·70 (1H, s). J_{ac} 7 Hz. (Found: C, 44·93; H, 5·40. $C_8H_{11}O_3F_3$. Calc: C, 45·28; H, 5·23%).

Alkylation of potassium enolate of ethyl γ,γ-dimethylacetoacetate. A soln of 1·51 g (0·0076 mole) of EtOTs in HMPT was added dropwise with stirring (argon) to 1·53 g (0·0074 mole) of potassium enolate II in the same solvent. Mixture was left at room temperature until neutral, poured in H_2O, extracted with Et_2O and ethereal extracts dried over $MgSO_4$. The solvent evaporated and residue distilled to give 1·7 g (94%); b.p. 110–115°/10 mm. GLC showed the product a mixture of two substances, one identical with VI. We failed to separate mixture. After work up with 0·04 N HCl the second compound converted to II. IR spectrum: C=C 1620, C=O 1713, 1748 cm^{-1}. PMR shows a vinyl proton singlet $\delta = 4{\cdot}79$ ppm. (Found: C, 64·55; H, 9·42. Monoethylated derivative of II $C_{10}H_{18}O_3$ requires: C, 64·49; H, 9·74%). The second product of the reaction was ethyl β-ethoxy-γ,γ-dimethyl crotonate (IX). IX and VI ratio 3·8 : 1.

Ethyl β-ethoxy-γ,γ,γ-trimethylcrotonate (X). A mixture of VII and X obtained by alkylation of 1·65 g (0·0078 mole) of potassium enolate of III with 1·65 g (0·0082 mole) ethyltosylate in HMPT as described for the alkylation of potassium enolate of II was separated by prep. chromatography (Al_2O_3 II–III; hexane–ether 13:2). X was eluted with ether, evaporated, and the residue distilled. Yield 0·44 g (28%), b.p. 52–56°/5 mm, n_D^{21} 1·4400. IR spectrum: C=C 1624, C=O 1719 cm^{-1}. PMR spectrum



$$\overset{a}{(CH_3)_3}C-\underset{\substack{|\\ \underset{e}{OCH_2}\underset{c}{CH_3}}}{C}{=}\overset{f}{CH}COO\overset{d}{CH_2}\overset{b}{CH_3}$$

(a) 1·12 (9H, s); (b) 1·22 (3H, t); (c) 1·28 (3H, t); (d) 4·00 (2H, q); (e) 4·08 (2H, q); (f) 4·98 (1H, s).

Kinetic measurements for the reaction of the alkaline enolates of II and III with EtOTs in HMPT were performed as described for the alkylation of alkaline ethyl acetoacetate derivatives:[1] the reaction rate was measured by the method of back titration. The C/O ratio was determined by GLC (column temperature 110°, gas carrier rate (N_2) 100 ml/min). For quantitative GLC analysis the compounds mentioned above were prepared and used as standards. The alkylation rate for caesium enolate of I was determined by the quantitative GLC analyses of O-isomer, with *p*-xylene as internal standard (column temperature 70°, gas carrier (N_2) rate 90 ml/min).

In all the cases the alkaline ketoester derivative and EtOTs were taken in equimolar quantities.

Conductance measurements were carried out in HMPT at 20·0° as in the case of the ethyl acetoacetate enolates.[1] Results of measurements and calculations in Tables 4–6.

p*Ka determination for* β*-ketoesters.* The p*Ka* of β-ketoesters were measured in DMF at 20–25° by potentiometric titration using an automatic TTT-1c Radiometer (Denmark), Model titrator. Glass electrode G-2222B was used for the titration. 0·1 N tetrabutylammonium hydroxide in C_6H_6–MeOH (10:1) was used as a titrant. To remove CO_2 pure dry nitrogen was bubbled through the soln.

Using the half-neutralization potentials and p*Ka* obtained in DMF for 4-nitrophenol (10·9), 2,4-dinitrophenol (6·0), dichloroacetic (7·2), monochloroacetic (9·0), benzoic (10·2) and acetic (11·1) acids[2] it was found that in DMF

$$pKa = 6{\cdot}8 + 0{\cdot}013\,E_{\frac{1}{2}} \qquad (5)$$

where $E_{\frac{1}{2}}$ is a half-neutralization potential (mV).

p*Ka* of each β-ketoester was determined from equation (5) at an accuracy of 0·3 p*Ka* units.

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