426. *Kinetic Solvent Isotope Effects in Spontaneous Hydrolysis Reactions of Acyl Derivatives.*

By A. R. Butler and V. Gold.

The effect of replacing solvent water by deuterium oxide on the rates of some spontaneous hydrolyses has been measured. The rates in water are depressed by the following factors at 25°: benzoic anhydride, 3·9; succinic anhydride, 2·5; β-propiolactone, 1·15. Similar effects have been studied for the hydrolyses of benzoyl chloride and mesitoyl chloride in dioxan–water mixtures. The mechanistic implications of the results are indicated.

The observation that the spontaneous hydrolysis of acetic anhydride is retarded by a factor of 2·9 on changing from ordinary water to deuterium oxide[1] has prompted a comparative study of the solvent isotope effects in some kindred reactions. These measurements,[2] relating to two further acid anhydrides, two aroyl chlorides, and a lactone, are reported in the present paper.

Experimental

Dioxan was purified and diluted as in previous work.[1b] Deuterium oxide was the Norsk Hydro product with a stated deuterium content of >99%.

Mesitoyl chloride was prepared by a standard procedure[3] and fractionally distilled under reduced pressure. Other organic substances were commercial specimens of which the solids were purified by crystallisation and the liquids by distillation. Their measured properties (b. p., m. p., acid equivalent) agreed with recorded values. The substances were stored in closed containers inside a desiccator.

Reaction Velocities.—These were determined by electrical-conductivity measurements, potentiometry, or spectrophotometry. The electrical methods were based on procedures used in earlier investigations of the same or similar reactions.[4] Methods of evaluation of rate constants from the observations depended on the nature of the hydrolysis products and are separately described below, together with the experimental details. The selection of a particular technique for a certain compound was, in some measure, a matter of taste or temporary expediency, and does not necessarily imply that alternative methods are less suitable.

Mesitoyl Chloride.—The reaction was followed by rapidly withdrawing 1 ml. samples of the reaction mixture and adding them (at timed intervals) to portions (*ca.* 20 ml.) of an aqueous reagent solution containing α-naphthylamine and sodium nitrite at the concentrations recommended for the determination of acetic anhydride.[5] The mixture was then made up to 25 ml. with the reagent solution and left in the dark for 20 min. The concentration of unhydrolysed mesitoyl chloride was determined by spectrophotometry. The relation between concentration and optical density at 470 mμ was established by observations on measured amounts of a 0·2% solution of mesitoyl chloride in dioxan added to the coupling medium. The hydrolysis was carried out at a single dioxan–deuterium oxide composition ($[D_2O]$ = 3·68M) and in four dioxan–water media. The rate at the corresponding molarity of water ($[H_2O]$ = 3·68M) was obtained by interpolation of the results in the four media. The rate constants are tabulated in Table 1.

Benzoyl Chloride.—In dioxan–water mixtures of low water content the reaction was followed by conductance measurements. To relate the concentration of reaction products (c) to the conductance, the solution remaining on completion of the hydrolysis was diluted successively with a series of known volumes of the solvent, and the conductance was measured after each dilution. From these figures a calibration graph of conductance against the ratio $\alpha = c/c_\infty$ was plotted (where c_∞ is the concentration of reaction products at complete hydrolysis). The conductance readings during a run were thus converted into values of α_t, representing the

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[1] Butler and Gold, (*a*) *Proc. Chem. Soc.*, 1960, 15; (*b*) *J.*, 1961, 2305.
[2] Butler and Gold, *Chem. and Ind.*, 1960, 1218.
[3] Barnes, *Org. Synth.*, 1941, **21**, 77.
[4] (*a*) Gold, *Trans. Faraday Soc.*, 1948, **44**, 506; (*b*) Archer and Hudson, *J.*, 1950, 3259.
[5] Lees and Saville, *J.*, 1958, 2262.

TABLE 1.

Results for mesitoyl chloride.

In dioxan–deuterium oxide:

$[D_2O] = 3{\cdot}68$M. $10^3k = 3{\cdot}67, 3{\cdot}59$ sec.$^{-1}$; mean: 3·63 sec.$^{-1}$

In dioxan–ordinary water:

$[H_2O]$ (M)	2·56	3·31	3·68	3·94	4·36
10^3k, sec.$^{-1}$	1·55	3·84	(5·55) *	7·13	10·9

* By interpolation.

fractional progress of the reaction after time t. Rate constants were evaluated graphically from plots of log $(1 - \alpha_t)$ against t. The analysis assumes that non-electrolyte molecules at the concentration of the substrate (*ca.* 0·02M) have no effect on the conductance.

In the experiments at high water concentration the formation of hydrogen chloride during a run was followed by measuring the e.m.f. between a glass electrode (Cambridge Yellow Cap) and a silver–silver chloride electrode, both inserted in the reaction medium. Rectilinear calibration graphs of $(E_t - E_\infty)$, the difference between the e.m.f.'s of the cell after times t and infinity, respectively, against log α_t were constructed from measurements on successively diluted solutions of completely hydrolysed benzoyl chloride, where α_t expresses the instantaneous concentration of chloride ion after time t as a fraction of the final concentration (c_∞), *i.e.*, $\alpha_t = 10^x$, where $x = (E_t - E_\infty)/m$. The slope m of these graphs was found to have the values $-0{\cdot}104$, $-0{\cdot}104$, and $-0{\cdot}106$ at water concentrations of 23·5, 24·6, and 25·6M, respectively, and a value of $-0{\cdot}103$ in 24·1M-deuterium oxide. These slopes are in good agreement with theoretical predictions, as will now be shown.

On the assumption that hydrogen and chloride ions are formed in equivalent amount during hydrolysis, the e.m.f. after time t should be given by the expression

$$E_t = E^\circ - 2{\cdot}303\,\frac{2\boldsymbol{RT}}{\boldsymbol{F}}\log\,[\mathrm{Cl}^-]\gamma_\pm$$

where $\gamma_\pm$ is the stoicheiometric mean ionic activity coefficient of hydrogen chloride relative to infinite dilution in the solvent concerned. Since the dissociation constant of benzoic acid in the solvent mixtures employed will be of the order of 10^{-7} or less, the degree of dissociation of benzoic acid at concentrations (of both benzoic acid and hydrogen chloride) exceeding 10^{-4}M will be less than 0·1%, so that our initial assumption is justified. Inspection of available values of activity coefficients for solutions of hydrogen chloride in dioxan–water mixtures[6] shows that, over short ranges of acid concentration, log $\gamma_\pm$ can reasonably well be represented as a linear function of the logarithm of that concentration, *i.e.*:

$$-\log\gamma_\pm = \beta\log\,[\mathrm{Cl}^-] + \text{constant};$$

so that (writing $[\mathrm{Cl}^-] = \alpha_t c_\infty$)

$$E_t = E^\circ - 2{\cdot}303(1-\beta)(2\boldsymbol{RT}/\boldsymbol{F})\log\alpha_t c_\infty,$$

and

$$E_\infty = E^\circ - 2{\cdot}303(1-\beta)(2\boldsymbol{RT}/\boldsymbol{F})\log c_\infty,$$

whence

$$E_t - E_\infty = -2{\cdot}303\,(1-\beta)\,(2\boldsymbol{RT}/\boldsymbol{F})\log\alpha_t.$$

The slope m should therefore be given by $-2{\cdot}303(1-\beta)2\boldsymbol{RT}/\boldsymbol{F}$. By interpolation from determinations on dioxan–water mixtures at other compositions, the values of β in mixtures with 23·5, 24·6, and 25·6M-water (appropriate to the hydrogen chloride concentration range covered in the kinetic runs) are estimated to be 0·14, 0·13, and 0·12, respectively, leading to corresponding theoretical values of m of $-0{\cdot}102$, $-0{\cdot}103$, and $-0{\cdot}104$, in good agreement with the experimental ones. An error of as much as 5% in m produces only an insignificant change (<1%) in rate constants of runs over the first half-life evaluated by our usual procedure of plotting log $(1 - 10^x)$ against t. A specimen evaluation is given in Table 2.

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[6] Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd edn., Reinhold Publ. Inc., New York, 1958, pp. 717—718.

TABLE 2.

Specimen evaluation of k for benzoyl chloride.

$[H_2O] = 23{\cdot}5\text{M}$; $[BzCl]_0 \simeq 6 \times 10^{-3}\text{M}$.

Time, t (min.)	$E_t - E_\infty$ (v)	$1 + \log(1 - 10^x)$ * Found	Calc.†	Time, t (min.)	$E_t - E_\infty$ (v)	$1 + \log(1 - 10^x)$* Found	Calc.†
3·0	0·0387	0·760	0·758	5·0	0·0232	0·604	0·598
3·5	0·0332	0·716	0·718	5·5	0·0202	0·556	0·557
4·0	0·0292	0·678	0·678	6·0	0·0182	0·521	0·517
4·5	0·0255	0·635	0·638	6·5	0·0159	0·473	0·477

$k = 3{\cdot}08 \times 10^{-3}$ sec.$^{-1}$.

* $x = (E_t - E_\infty)/m$.

† Calculated from the equation

$$1 + \log(1 - 10^x) = 0{\cdot}758 - (60 \times 3{\cdot}08 \times 10^{-3}/2{\cdot}303)t$$

(The measure of agreement between the found and calc. columns reflects the conformity to a first-order law and the reliability of the velocity constant.)

Table 3 summarises the rate constants for benzoyl chloride.

TABLE 3.

Results for benzoyl chloride.

In dioxan–deuterium oxide

$[D_2O]$ (M)	10^4k (sec.$^{-1}$)	Method
10·9	3·42	Conductivity
24·1	18·6	E.M.F.

In dioxan–ordinary water

$[H_2O]$(M)	10^4k (sec.$^{-1}$)	Method	$[H_2O]$(M)	10^4k (sec.$^{-1}$)	Method
10·6	4·91	Conductivity	23·5	30·8	E.M.F.
10·9	(5·13)	Interpolation	24·1	(35·1)	Interpolation
11·1	5·29	Conductivity	24·6	38·8	E.M.F.
11·5	5·68	,,	25·6	46·2	,,
12·2	6·64	,,			

Benzoic Anhydride.—The hydrolysis was studied conductometrically in a pipette-shaped cell into which the anhydride solution was drawn up through a sintered-glass filter stick (in order to prevent undissolved solid from entering the cell). The product is a weak acid and the resistance (r) of the cell obeys the dilution law which we may state in the form [4a]

$$cr = \frac{B^2}{K\Lambda_0^{\,2}} \cdot \frac{1}{r} + \frac{B}{\Lambda_0}, \qquad (1)$$

where K is the dissociation constant and Λ_0 the limiting conductance (regarded here as disposable parameters so as to ensure the best fit of the data). c is the concentration of acid and the constant B is 1000 times the conventional cell constant. If $B/K\Lambda_0 r \gg 1$, c is proportional to $1/r^2$; otherwise c is proportional to $q = \left\{\frac{1}{r^2} + \left(\frac{K\Lambda_0}{B^2}\right)\frac{1}{r}\right\}$. First-order rate coefficients for the hydrolysis were evaluated from linear plots of $\log(q_\infty - q)$ against time. The constant B was determined directly; values for K and Λ_0 for benzoic acid in ordinary water and deuterium oxide were taken from tables. Over the concentration range employed the calculated rate constant was quite insensitive to the value of $K\Lambda_0/B$.

The above treatment of conductometric measurements for the determination of reaction velocity was checked by measurements on acetic anhydride.

Duplicate determinations in ordinary water gave the rate constants $4{\cdot}1_1 \times 10^{-4}$ and $4{\cdot}2_0 \times 10^{-4}$ sec.$^{-1}$ (mean: $4{\cdot}16 \times 10^{-4}$ sec.$^{-1}$; cf. $3{\cdot}62 \times 10^{-4}$ sec.$^{-1}$ reported by Wilsdon and Sidgwick [7]), and the rate constant of a single run in deuterium oxide was found to be $1{\cdot}07 \times 10^{-4}$ sec.$^{-1}$.

A specimen calculation (for the run in deuterium oxide solution) is given in Table 4.

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[7] Wilsdon and Sidgwick, *J.*, 1913, **103**, 1959.

TABLE 4.

Specimen evaluation of conductometric rate measurements (benzoic anhydride in D_2O).

Time, t (min.)	$10^5/r$	$10^{10} K\Lambda_0/Br$	$10^{10}/r^2$	q	$q_\infty - q$	$\log (q_\infty - q)$ Found	Calc.†
0 *	2·48	6·82	6·15	12·97	21·44	1·335	1·329
5	2·60	7·15	6·76	13·91	20·50	1·312	1·315
14	2·75	7·56	7·56	15·12	19·29	1·285	1·290
23	2·85	7·84	8·12	15·96	18·45	1·266	1·265
30	2·95	8·11	8·70	16·81	17·60	1·246	1·245
45	3·10	8·52	9·61	18·13	16·28	1·212	1·204
59	3·30	9·07	10·89	19·96	14·45	1·160	1·165
68	3·38	9·30	11·42	20·72	13·69	1·136	1·139
89	3·53	9·71	12·46	22·17	12·24	1·088	1·081
104	3·65	10·03	13·32	23·35	11·06	1·044	1·039
119	3·77	10·38	14·21	24·59	9·82	0·992	0·997
134	3·85	10·64	14·82	25·46	8·95	0·952	0·955
161	4·00	11·00	16·00	27·00	7·41	0·870	0·880
∞	4·65	12·79	21·62	34·41	—	—	—

$k = 1{\cdot}07 \times 10^{-4}$ sec.$^{-1}$.

* Time of first observation. † Calculated from the equation $\log (q_\infty - q) = 1{\cdot}329 - (60 \times 1{\cdot}07 \times 10^{-4}/2{\cdot}303)t$. (See also second footnote in Table 2.)

β-*Propiolactone*.—The dissociation constant of the product, β-hydroxypropionic acid, is $3{\cdot}1 \times 10^{-5}$ and it can be shown that the last term in equation (1) for the evaluation of rate constants by the conductometric method (at an initial lactone concentration of *ca.* 0·1M) is entirely negligible. When this method was used, two determinations in ordinary water gave identical rate constants of $5{\cdot}68 \times 10^{-5}$ sec.$^{-1}$ (cf. $5{\cdot}5 \times 10^{-5}$ sec.$^{-1}$ reported by Long and Purchase [8]); two determinations in deuterium oxide gave values of $4{\cdot}88 \times 10^{-5}$ and $4{\cdot}95 \times 10^{-5}$ sec.$^{-1}$ (mean: $4{\cdot}92 \times 10^{-5}$ sec.$^{-1}$).

Succinic Anhydride.—At *ca.* 0·1M-concentrations the hydrolysis product, succinic acid, can for present purposes be treated as a weak monobasic acid and it can again be shown that the last term in equation (1) is negligible at all concentrations of acid at which observations were taken during a run. Conductometrically observed rate constants were in this instance evaluated by Guggenheim's procedure,[9] duplicate determinations yielding the values $2{\cdot}89 \times 10^{-3}$ and $2{\cdot}99 \times 10^{-3}$ sec.$^{-1}$ (mean: $2{\cdot}94 \times 10^{-3}$ sec.$^{-1}$) in ordinary water, and $1{\cdot}20 \times 10^{-3}$ and $1{\cdot}15 \times 10^{-3}$ sec.$^{-1}$ (mean: $1{\cdot}17 \times 10^{-3}$ sec.$^{-1}$) in deuterium oxide. Previously reported values of the rate constant in ordinary water at 25° are $2{\cdot}82 \times 10^{-3}$ (Voerman [10]), $2{\cdot}66 \times 10^{-3}$ (Rivett and Sidgwick [11]), $2{\cdot}65 \times 10^{-3}$ sec.$^{-1}$ (Vles [12]).

DISCUSSION

As the summary of isotope effects (Table 5) shows, the four hydrolyses in which fission of an acyl–X bond occurs are subject to appreciable solvent isotope effects. Although none of these results applies precisely to the experimental conditions of measurements

TABLE 5.

Kinetic solvent isotope effects.

Compound	Solvent	k_0^H/k_0^D	Compound	Solvent	k_0^H/k_0^D
Benzoic anhydride	Water	3·9	Mesitoyl chloride	Dioxan–water	
Succinic anhydride	Water	2·5		(3·68M water)	1·5
Benzoyl chloride	Dioxan–water		β-Propiolactone	Water	1·15
	(24·1M water)	1·9			
	(10·9M water)	1·5			

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[8] Long and Purchase, *J. Amer. Chem. Soc.*, 1950, **72**, 3267.

[9] Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

[10] Voerman, *Rec. Trav. chim.*, 1904, **23**, 279.

[11] Rivett and Sidgwick, *J.*, 1910, **97**, 732.

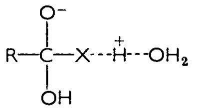
[12] Vles, *Rec. Trav. chim.*, 1933, **52**, 809.

reported in a preliminary communication by Bunton, Fuller, Perry, and Shiner,[13] there appears to be fair agreement between the two sets of results.

By contrast, there is only a small effect in the spontaneous hydrolysis of β-propiolactone, a compound closely related to the others on structural grounds but differing in the mechanism of its hydrolysis. This is known to involve alkyl–oxygen fission in the rate-controlling step of the process,[14] and therefore represents a nucleophilic replacement at a saturated carbon atom, a class of reaction known to be but slightly affected in rate by the change from ordinary water to deuterium oxide as solvent.[15] The observed difference between β-propiolactone and the other compounds now studied supports the inference that large isotope effects indicate a different reaction mechanism from that applying to substitutions at a saturated centre. If the isotope effect had been associated mainly with the structure of the hydrolysing substrate, rather than that of the transition state as well, β-propiolactone would have been expected to fall in line with the other acyl derivatives.

The two results for dioxan–water mixtures are not directly comparable with the values for water as solvent. As has previously been shown for acetic anhydride [1b,2] (cf. ref. 13), the ratio $k_0^{\mathrm{H}}/k_0^{\mathrm{D}}$ falls with increasing dioxan content of the medium. The same trend is noticeable in our two results for benzoyl chloride and in the comparison between our value for benzoic anhydride in water and that communicated by Bunton *et al.*[13] for the same compound in 60 : 40 (v/v) dioxan–water (at 35°: 3·45). The isotope effects for the hydrolysis of aroyl chlorides in water would therefore probably be greater than the values in Table 5. If only for this reason, the discussion of the mechanism of these reactions in relation to isotope effects appears to be premature.

An isotope effect in a reaction of this type indicates that there is a weakening of O–H bonds on formation of the transition state. If we generalise the model proposed for the transition state of the hydrolysis of acetic anhydride to include other spontaneous hydrolyses of acyl compounds, its structure may be written as (I). The formula is derived from the view that the spontaneous hydrolysis is to be regarded as a special case of a reaction subject to general base-catalysis, and we have previously shown [1b] that the formation of this transition state can be represented by a sequence of reasonable bimolecular steps. There are other models of transition states which satisfy the requirement of O–H bond-weakening and general base-catalysis. In the present state of understanding of the theory of solvent isotope effects and knowledge of experimental facts, a distinction between transition states (II—V) for the hydrolysis of an acid anhydride does not seem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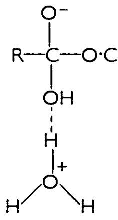
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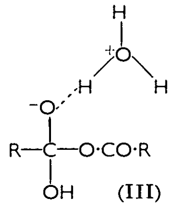
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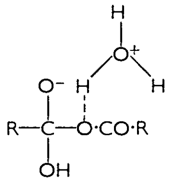
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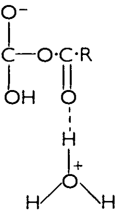
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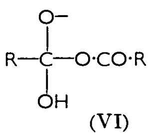
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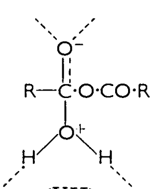
(VII)

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[13] Bunton, Fuller, Perry, and Shiner, *Chem. and Ind.*, 1960, 1130.

[14] Olson and Miller, *J. Amer. Chem. Soc.*, 1938, **60**, 2687; Olson and Hyde, *ibid.*, 1941, **63**, 2459.

[15] Robertson and Laughton, *Canad. J. Chem.*, 1957, **35**, 1319.

possible on the basis of the isotope effects of the reactions. For the hydrolysis of acid chlorides, formula (I) (with X = Cl) is questionable on the ground that it implies acid-catalysed removal of a chloride ion. Jencks and Carriuolo,[16] who give the analogues of (II—IV) in their discussion of ester hydrolysis [structure (V) having no relevance in that case] prefer to regard the bond linking the carbonyl group to the neighbouring oxygen atom as being weakened in the transition state. This implies that the rate-controlling proton transfer to the anionic intermediate (VI) [which is the scheme that we apply to the formation of the family of structures (II—V)] is synchronous with the loosening of the $R{\cdot}CO^{-}(OH){-}O{\cdot}CO{\cdot}R$ bond. There is no experimental evidence relevant to this question. Jencks and Carriuolo also consider alternative structures in which the hydroxide attachment is incomplete in the transition state.

Experiments on oxygen exchange between the carbonyl groups of benzoic anhydride and the solvent and, in particular, the fact that hydrolysis is more rapid than exchange,[17] have been interpreted as implying that, if the mechanism involves addition of water (or hydroxyl) before elimination of the benzoate group, the transition state for the overall reaction must be passed in the addition step.[18] This interpretation is based on the implied assumption that the proton transfers required to establish equivalence between the oxygen atoms of the carbonyl group and of the entering hydroxyl group are very rapid relative to the reversal of the initial addition. If this assumption were shown to be correct in these reactions, then the incompleteness of oxygen exchange during the hydrolysis of benzoic anhydride would disprove the sequence of events given in the specific form[1b] of Butler and Gold's mechanism, but, as far as we are aware, no evidence concerning the relative velocities of the two processes exists.

Structure (V), closely akin to (II), has more recently been considered by Bunton and Shiner,[18] who have discussed our results on solvent isotope effects during the hydrolysis of acetic anhydride in the course of a more general survey of solvent isotope effects. In formula (V) the dotted lines represent hydrogen bonds to water molecules. We need not here consider the interesting suggestions contained in this work in detail. We would merely point out that their quantitative application to the solvent isotope effects in the hydrolysis of acid anhydrides requires intuitively derived values of otherwise unknown and unknowable numerical parameters used in the calculation (*viz.*, the acid and base strengths associated with the hydrogen atoms attached to the incoming water molecule and with the carbonyl oxygen atom, respectively). However reasonable these values appear to be, their use prejudices a fair test either of the general theory or of the assumed model of the transition state. Further limitations of this theory (or of the necessary approximations) are indicated by its prediction that the ratio k_0^H/k_0^D should be the same for different acid anhydrides. The four compounds in Table 6 have now been studied in water at 25°, and the spread of values appears to be outside the limits of experimental error. There is no obvious regularity about the values and relatively large specific effects seem to exist.

TABLE 6.

Solvent isotope effects for spontaneous hydrolyses of acid anhydrides in water at 25°.

Anhydride	Acetic	Benzoic	Succinic	Glutaric
k_0^H/k_0^D	2·9,* 2·84 †	3·9 ‡	2·5 ‡	2·84 †

* Ref. 1. † Ref. 13. ‡ This work.

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF LONDON,
KING'S COLLEGE, STRAND, W.C.2.

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[16] Jencks and Carriuolo, *J. Amer. Chem. Soc.*, 1961, **83**, 1743.

[17] Bunton, Lewis, and Llewellyn, *Chem. and Ind.*, 1954, 1154.

[18] Bunton and Shiner, *J. Amer. Chem. Soc.*, 1961, **83**, 3207.