Table 1. $RH \rightarrow R + H$

Compound	Rate constant interpolated to 804° C. 10^5 sec.$^{-1}$
Toluene	3·8
m-Xylene*	4·4
p-Fluoro-toluene	3·4
m-Fluoro-toluene	3·1
o-Fluoro-toluene	3·3
γ-Picoline	4·3

* The rate is divided by the statistical factor of 2.

strongest argument in favour of the assumption of the constancy of the frequency factors in a series of similar decompositions.

Recent studies of the pyrolysis of substituted benzyl bromides[6] provide additional evidence supporting this argument. It was shown that the rate-determining step in the pyrolysis of benzyl-bromide and its derivatives is a unimolecular homogeneous dissociation process :

$$C_6H_5.CH_2Br \rightarrow C_6H_5.CH_2 + Br,$$

and it was found that the rate of decomposition is nearly constant (within 25 per cent) for benzyl bromide, *m*-xylyl bromide, *p*- and *m*-chloro-benzyl bromides, and *p*- and *m*-bromo-benzyl bromides (see Table 2).

Table 2. $RBr \rightarrow R + Br$

Compound	Rate constant interpolated to 527° C. 10^5 sec.$^{-1}$
Benzyl bromide	46
m-Xylyl bromide	47
m-Chloro-benzyl-bromide	52
p-Chloro-benzyl-bromide	60
m-Bromo-benzyl-bromide	56
p-Bromo-benzyl-bromide	56

Some observations might be regarded as a generalization of the above rules to other series of similar reactions. Thus C. K. Ingold and W. S. Nathan[7] estimated the activation energies for the hydrolysis of various substituted benzoic esters. The graph of the estimated activation energies versus log k (k being the rate constant of hydrolysis) gives a straight line, proving that the frequency factors remain constant throughout the whole series. These authors also directed attention to the results obtained by E. G. Williams and C. N. Hinshelwood[8] for the kinetics of benzoylation of various substituted anilines. A similar plot of E versus log k obtained by the latter authors gave a straight line which was parallel to that obtained by Ingold and Nathan. The idea of the constant frequency factors in a series of kindred reactions was developed further by L. P. Hammett[9], who devised a system of ρ- and σ-factors ; ρ represents an entropy change constant for the same type of reaction, and σ represents the change in activation energy characteristic for each member of the series. It has to be emphasized, however, that the regularities discussed above were observed in liquid-phase reactions, and one has to be careful in using them as a support for argument which applies to gas-phase reactions.

Attention must be directed to a relationship frequently assumed between the activation energy of a process and its frequency factor. This relationship is justified only for such series of reactions in which the variable parameter affects the reacting centre. For example, by varying the solvent in which some process takes place, one affects both the energy and the entropy of activation, and both are changed in the same direction. For the gas reactions, however, the relationship between the activation energy and the frequency factor seems to be fortuitous. Due to technical limitations, we are forced to measure rates of reactions in a comparatively narrow range ; in consequence, the accumulated experimental material sometimes indicates the existence of a relationship between two entities which has no real existence.

We conclude that the frequency factors of unimolecular dissociation processes occurring in the gas phase seem to be unaffected by the variation in the structure of a molecule which does not affect the reacting centre ; but that it depends on the type of reaction and on the structure of the reacting centre.

Thanks are due to Prof. M. G. Evans for helpful discussions.

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Modified Carbobenzyloxy Groups in Peptide Synthesis

The 'carbobenzyloxy' method of peptide synthesis[1] has proved its value in many important syntheses. Nevertheless, the practical difficulties still encountered in this field suggest that improved protecting groups should still be sought. We have recently been examining benzyl chloroformates substituted in the benzene ring, and other closely related compounds, in the hope that the amino-acid and peptide derivatives might crystallize more readily and that other properties, such as stability and ease of removal of the protecting group, might differ in such a way as to increase the scope of this method of synthesis.

α-Naphthyl carbinol reacted with phosgene to give a product which was coupled with glycine in the normal manner, giving carbo-α-naphthylmethoxyglycine (found : C, 65·2 ; H, 5·2 ; N, 5·3. $C_{14}H_{13}O_4N$ requires : C, 64·86 ; H, 5·02 ; N, 5·41 per cent), but this material began to decompose just below its melting point, liquefying at 136°. The theoretical amount of carbon dioxide was evolved on hydrogenation. The acid chloride was prepared by the action of phosphorus pentachloride and coupled with glycine ethyl ester, but difficulty was encountered in the purification of the product and of the carbo-α-naphthylmethoxyglycylglycine obtained by saponification, and no further derivatives were prepared.

p-Tolyl carbinol yielded a liquid chloroformate which was coupled in the normal manner to give carbo-*p*-tolyloxyglycine (m.p. 93°), and carbo-*p*-tolyloxyglycine ethyl ester (m.p. 38°) (found : C, 62·3 ; H, 6·9. $C_{13}H_{17}O_4N$ requires : C, 62·1 ; H, 6·8 per cent). Treatment of the ester with hydrazine gave carbo-*p*-tolyloxyglycyl hydrazide (m.p. 120°) (found : C, 55·7 ; H, 6·4. $C_{11}H_{15}N_3O_3$ requires : C, 55·7 ; H, 6·3 per cent). These compounds appear to offer little advantage over the corresponding carbobenzyloxy derivatives.

p-Bromobenzyl chloroformate was then prepared from *p*-bromobenzyl alcohol, as a stable low-melting crystalline solid. With glycine it gave carbo-*p*-bromobenzyloxyglycine (m.p. 139°) (found: C, 41·8; H, 3·3. $C_{10}H_{10}O_4NBr$ requires: C, 41·7; H, 3·5 per cent); treatment of the latter with phosphorus pentachloride followed by coupling with glycine ethyl ester gave carbo-*p*-bromobenzyloxyglycylglycine ethyl ester (m.p. 125°) in nearly theoretical yield (found: C, 45·3; H, 4·5. $C_{14}H_{17}O_5N_2Br$ requires: C, 45·04; H, 4·56 per cent). With hydrazine, carbo-*p*-bromobenzyloxyglycylglycyl hydrazide was obtained (m.p. 180°) (found: C, 40·5; H, 4·3. $C_{12}H_{15}O_4N_4Br$ requires: C, 40·12; H, 4·18 per cent). With glycine ethyl ester, *p*-bromobenzyl chloroformate gave carbo-*p*-bromobenzyloxyglycine ethyl ester (m.p. 74°), which yielded a hydrazide (m.p. 148°) (found: C, 39·9; H, 3·5. $C_{10}H_{12}O_3N_3Br$ requires: C, 39·7; H, 3·85 per cent). Hydrogenation removed the protecting group from carbo-*p*-bromobenzyloxyglycine in the normal manner. All these materials have melting points higher than the corresponding carbobenzyloxy compounds, and in general they crystallize with greater ease. Derivatives of other amino-acids are being prepared.

Other modifications of the carbobenzyloxy group are being examined, but meanwhile the use of *p*-bromobenzyl chloroformate may be found advantageous in peptide synthesis.

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Epidermal Mitotic Activity and Oxygen Tension

The effects of anaerobic conditions on mammalian epidermis were first studied by Medawar[1], who developed an elegant technique for showing that this tissue can survive by anaerobic glycolysis alone, but that cell movement and division depend on "respiratory activity in the narrow sense". These conclusions, which apply to the rabbit, have now been confirmed and elaborated in the case of the mouse. A technique has been devised, using standard Warburg equipment, for the maintenance of ear epidermis from adult male mice in a phosphate-buffered saline with added glucose.

Five fragments of ear epidermis (*c.* 2·5 mm. × 5·0 mm.) were immersed in 4 ml. saline medium in each flask, the side arm containing 0·016 mgm. colchicine in 0·04 ml. solution. The manometers were gassed with oxygen, nitrogen, or oxygen/nitrogen mixtures as required, and the flasks were maintained at 38° C. After one hour, when all the mitoses originally present were judged to have passed the metaphase, the colchicine was tipped into the main compartment. The incubation was then continued for a further four hours, when the tissue was fixed for sectioning. The results are shown in Table 1.

Table 1. The average numbers of mitoses arrested by colchicine in unit lengths (1 cm.) of sections (7 μ thick) of mouse ear epidermis after 4 hr. incubation at 38° C. in phosphate-buffered saline with added glucose. Each figure is the average of 10 observations

Gas phase:					
100% N_2	80% N_2/20% O_2	60% N_2/40% O_2	40% N_2/60% O_2	20% N_2/80% O_2	100% O_2
0·4 ± 0·10	2·2 ± 0·26	3·9 ± 0·27	5·5 ± 0·33	6·8 ± 0·34	8·3 ± 0·49

These figures indicate a direct linear relationship between epidermal mitotic activity and oxygen tension, and coincident observations on oxygen uptake (without colchicine) have confirmed that with increased oxygen tensions increased quantities of oxygen are absorbed (Table 2).

Table 2. $Q(O_2)$ of mouse-ear epidermis determined during 4 hr. incubation at 38° C. in phosphate-buffered saline with added glucose ($Q(O_2)$ = μl. oxygen consumed/mgm. dry wt./hr.). Each figure is the average of 8 observations

Gas phase:		
80% N_2/20% O_2	40% N_2/60% O_2	100% O_2
1·18 ± 0·05	1·52 ± 0·06	1·83 ± 0·07

Evidently a direct linear relationship also exists between oxygen consumption and oxygen tension.

Confirmation is thus provided for the theory already advanced that epidermal mitotic activity depends on the energy derived from the aerobic metabolism of glucose[2,3]. If this is so, then by adding to the saline medium known catalysts of the tricarboxylic acid cycle, it should be possible to increase the oxygen consumption and hence the mitosis rate. The results of an experiment in which 0·02 *M* sodium glutamate was present in the saline medium are shown in Table 3.

Table 3. The influence of 0·02 *M* sodium glutamate on the numbers of mitoses arrested by colchicine in 4 hr. and on the $Q(O_2)$ of mouse-ear epidermis incubated at 38° C. in phosphate-buffered saline with added glucose and a gas phase of oxygen

Numbers of mitoses (5 observations)		$Q(O_2)$ (8 observations)	
without glutamate	with glutamate	without glutamate	with glutamate
6·7 ± 0·60	10·0 ± 0·75	1·83 ± 0·07	2·40 ± 0·13

It has already been established that glucose and oxygen exert their action on mitosis at a time immediately prior to the prophase, and that they are without effect once the prophase has begun[4]. This pre-prophase is evidently a critical time in the physiology of mitosis, and the name of 'antephase' has been suggested for it. The evidence so far available suggests that the energy required for mitosis must be built up in the antephase, and that once a division begins it can continue to completion in almost any circumstances short of the death of the cell. On one hand, the numbers of mitoses developing can be increased by stimulating the rate of energy production from glucose oxidation, while, on the other, they can be depressed by anaerobic conditions and by such known inhibitors of cellular metabolism as cyanide, fluoride, and dinitrophenol[5]. However, none of those substances which stimulates or depresses mitotic activity in this way appears to have any substantial effect on the course of a cell division once it has begun.

A full account of the techniques devised for this work and of experiments with catalysts and inhibitors will be published in due course.

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