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Positive Halogen Compounds. X. Solvent Effects in the Reactions of *t*-Butoxy Radicals[1]

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Yields of *t*-butyl alcohol and acetone obtained on chlorinating dilute solutions of cyclohexane with *t*-butyl hypochlorite have been measured in some 14 solvents and relative rates of hydrogen abstraction and β-scission (k_a/k_d ratios) determined over the range 0–100°. Relative rates of attack on primary and tertiary hydrogen of 2,3-dimethylbutane (t/p ratios) have also been measured in many of the same solvents. The k_a/k_d ratios vary widely, as do their Arrhenius parameters, and smaller effects are observed on t/p ratios which show an isokinetic temperature within the experimental range. Effects roughly parallel solvent polarity and give little support to any role of charge-transfer phenomena between solvents and transition states. They are interpreted in terms of solvated *t*-butoxy radicals which lose much of their solvation in the transition states for hydrogen abstraction, but which have strongly solvated transition states for β-scission.

The major products of reaction of *t*-butoxy radicals in the presence of two potential hydrogen donors are determined by the competition

$$(CH_3)_3C{-}O\cdot \xrightarrow{k_d} CH_3COCH_3 + CH_3\cdot \quad (1)$$

$$(CH_3)_3C{-}O\cdot + R_1H \xrightarrow{k_{a1}} (CH_3)_3COH + R_1\cdot \quad (2)$$

$$(CH_3)_3C{-}O\cdot + R_2H \xrightarrow{k_{a2}} (CH_3)_3COH + R_2\cdot \quad (3)$$

In free-radical chlorinations utilizing *t*-butyl hypochlorite, reactions 1-3 alternate with

$$CH_3\cdot(R_1\cdot, R_2\cdot) + (CH_3)_3COCl \longrightarrow CH_3Cl\,(R_1Cl, R_2Cl) + (CH_3)_3C{-}O\cdot \quad (4)$$

to constitute a chain.[3] Under these conditions, the ratio of rate constants k_{a1}/k_{a2} may be determined *directly* by chlorinating mixtures of R_1H and R_2H and measuring either the disappearance of the two substrates or the formation of R_1Cl and R_2Cl. Similarly, k_{a1}/k_{a2} may be determined by chlorinating a single substrate and determining the ratio of *t*-butyl alcohol (or R_1Cl) to acetone produced. If such measurements are made on two separate substrates, the ratio of k_{a1}/k_d to k_{a2}/k_d should yield k_{a1}/k_{a2} *indirectly*, and this technique has frequently been used in the study of *t*-butoxy radicals derived from di-*t*-butyl peroxide.[4-6]

The purpose of the work described here has been to determine the effect of solvents on these various competitions, so as to be able to compare these direct and indirect techniques of determining substrate reactivities. We find solvent effects much more marked than the small ones reported previously.[3,6,7] These results are of great interest in themselves and indicate serious limitations on the indirect determination of substrate reactivities.

Determination of k_a/k_d Ratios.—In most of our work, cyclohexane was selected as a standard substrate. Mixtures of *t*-butyl hypochlorite and cyclohexane (1:5 mole ratio) were photolyzed at initial cyclohexane concentrations ranging from 0.01–0.50 *M* in each of several solvents at 0, 25, 40, 70, and 100°, and the resulting *t*-butyl alcohol:acetone ratios were determined by gas chromatography (g.l.c.). Results of experiments in chlorobenzene are shown in Fig. 1 in which alcohol:acetone ratios are plotted against initial cyclohexane concentration. If reactions 1–4 account for all of the products (*i.e.*, if chains are long and there are no additional side reactions), experimental points at each temperature should lie on a straight line with a slope equal to k_a/k_d, with any attack of *t*-butoxy radicals on solvent being measured by the intercept. The good linear relationship is evident from the figure (actually chlorobenzene yields the *poorest* linear relation of any of the solvents studied). Several other observations indicate that we are actually measuring k_a/k_d as intended. Even in quite polar solvents, reaction mixtures were stable in the dark or in the presence of air, indicating the radical chain nature of the reaction. Constant alcohol:acetone ratios were obtained over a tenfold range of hypochlorite:cyclohexane (1:2 to 1:20). Plots of cyclohexyl chloride:acetone *vs.* cyclohexane gave lines with the same slopes as those using alcohol:acetone ratios but with zero intercepts, and material balances were excellent. In systems in which there was little attack on solvent, yields of cyclohexyl chloride were 95–98% of those expected from the alcohol produced, and in four solvents where it was investigated—Freon 113 ($CFCl_2CF_2Cl$), chlorobenzene, acetic acid, and acetonitrile—100% of the hypochlorite was accounted for as alcohol and acetone produced. In trichloroethylene the material balance was only 89%, presumably because of some addition to the double bond.[8] This side reaction, of course, should have no effect on the alcohol:acetone ratios measured.

Finally, we have compared our results with those obtained with *t*-butoxy radicals generated from other sources Table (I). Good agreement is observed with

TABLE I

t-BUTYL ALCOHOL:ACETONE RATIOS FROM REACTION OF *t*-BUTOXY RADICALS WITH CYCLOHEXANE

	—70°, 0.5 *M* C_6H_{12}—		—40°, 0.1 *M* C_6H_{12}—	
Solvent	*t*-BuOCl	*t*-BuOOCOC$_6$H$_5$ + CuCl	*t*-BuOCl	(*t*-BuO$_2$CO)$_2$
$C_2F_3Cl_3$	5.75	6.2	5.50	7.5
C_6H_6	3.95	3.9	2.62	3.5
C_6H_5Cl	3.20	3.5	2.32	2.9
Pyridine	..	2.7	..	...
CH_3CN	1.70	1.9	1.78	1.6
CH_3COOH	0.90	0.5	0.70	1.1

(1) Taken from the Ph.D. Thesis of P. J. Wagner, 1963. Support of this work by grants from the National Science Foundation is gratefully acknowledged. For a preliminary report, *cf.* C. Walling and P. Wagner, *J. Am. Chem. Soc.*, **85**, 3333 (1963).

(2) NSF Predoctoral Fellow 1961–1963.

(3) C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.*, **82**, 6108 (1960).

(4) J. H. Raley, F. F. Rust, and W. E. Vaughan, *ibid.*, **70**, 1336 (1948).

(5) A. L. Williams, E. A. Oberright, and J. W. Brooks, *ibid.*, **78**, 1190 (1956).

(6) G. A. Russell, *J. Org. Chem.*, **24**, 300 (1959).

(7) F. L. Patmore and R. J. Gritter, *ibid.*, **27**, 4196 (1962).

(8) The preference of *t*-butoxy radicals for hydrogen abstraction over double bond addition has been noted previously; C. Walling and W. Thaler, *J. Am. Chem. Soc.*, **83**, 3877 (1961). With electronegatively substituted olefins, reactivity is still further reduced.

TABLE II

SOLVENT EFFECTS ON 5:1 CYCLOHEXANE–*t*-BUTYL HYPOCHLORITE SYSTEMS

Solvent	k_a/k_d[a] 100°	70°	40°	25°	0°	$E_D - E_A$[b]	log A_a/A_d[c]	s_r[d]
None			202, 346, 584, 982[e]			10.56	−4.61	±0.23
$CFCl_2CF_2Cl$	4.29	12.2	52.8	99	487	9.65	−5.04	.17
CH_3CN	(0.68)[f]	2.33	8.12	19.8	81.9	9.54	−5.73	.17
Benzene	2.82	7.62	24.7	48.6	207	8.66	−4.63	.12
m-$C_6H_4Cl_2$	2.81	7.07	24.3	45.7	178	8.40	−4.49	.10
C_6H_5Br	2.90	7.33	25.4	45.2	162	8.17	−4.34	.11
o-$C_6H_4Cl_2$	2.15	5.82	19.2	35.2	120	8.14	−4.43	.10
C_6H_5CN	1.90	4.87	16.9	33.4	109	8.28	−4.58	.11
C_6H_5F	2.73	6.94	22.4	43.4	127	7.85	−4.15	.17
C_6H_5Cl	2.65	5.62	16.4	28.6	91.7	7.21	−3.82	.11
CH_3COOH[g]	(0.65)[f]	1.34	2.90	4.87	12.6	5.95	−3.66	.06
C_2Cl_4	4.14	11.1	39.0	87.8	293	8.72	−4.49	.16
trans-$C_2H_2Cl_2$[g]	2.26	5.55	14.2	33.0	98.9	7.69	−4.16	.24
C_2HCl_2	2.01	4.87	14.2	24.6	75.7	7.34	−3.99	.08
cis-$C_2H_2Cl_2$	1.57	3.74	9.12	16.9	52.2	7.04	−3.92	.12

[a] Slope of plots of Me_3COH/Me_2CO formed *vs.* initial cyclohexane concentration, corrected for thermal expansion of solvent; *cf.* Fig. 1. [b] Difference in activation energies, in kcal. mole^{-1}. [c] Logarithm of the ratio of *PZ* factors. [d] Probable error (standard deviation) in $E_D - E_A$. [e] Four vapor phase values at 60, 50, 40, and 30°, respectively. [f] Extrapolated value, too low to actually measure accurately. [g] k_a/k_d values represent slopes of plots of $C_6H_{11}Cl/Me_2CO$ formed *vs.* initial cyclohexane concentration, corrected for solvent expansion.

alcohol:acetone ratios obtained from the copper-catalyzed reaction of *t*-butyl perbenzoate, providing further evidence that free *t*-butoxy radicals are indeed produced in this reaction.[9,10] The data also indicate a strong solvent effect with pyridine, in which the hypochlorite reaction could not be studied.[11]

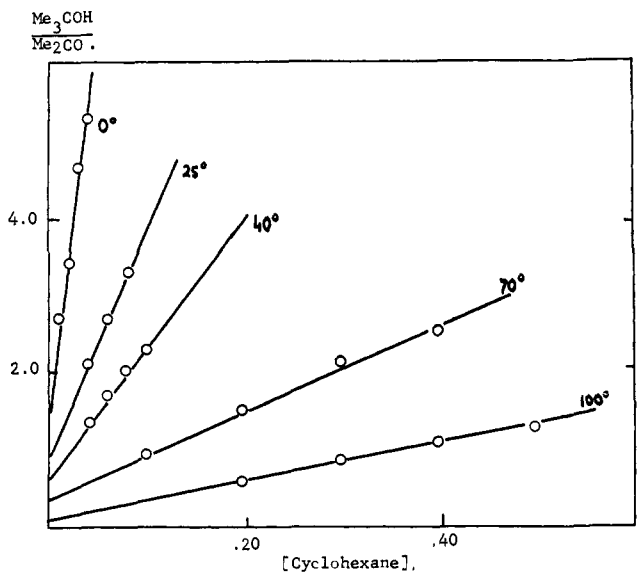


Fig. 1.—Alcohol:acetone ratios in *t*-butyl hypochlorite chlorination of cyclohexane in chlorobenzene solvent.

Alcohol:acetone ratios obtained from the thermal decomposition of di-*t*-butyl peroxalate at 40° again yield the right order of solvent effects, but for some reason which we have not explored further, ratios are quite consistently somewhat higher in the thermally initiated reactions than in the photoinitiated hypochlorite reaction.

From k_a/k_d ratios obtained from plots such as Fig. 1, Arrhenius parameters may be calculated in the usual manner by plotting log k_a/k_d *vs.* $1/T$. Some examples are shown in Fig. 2, the good straight lines resulting giving further support to a simple competition such as we propose.

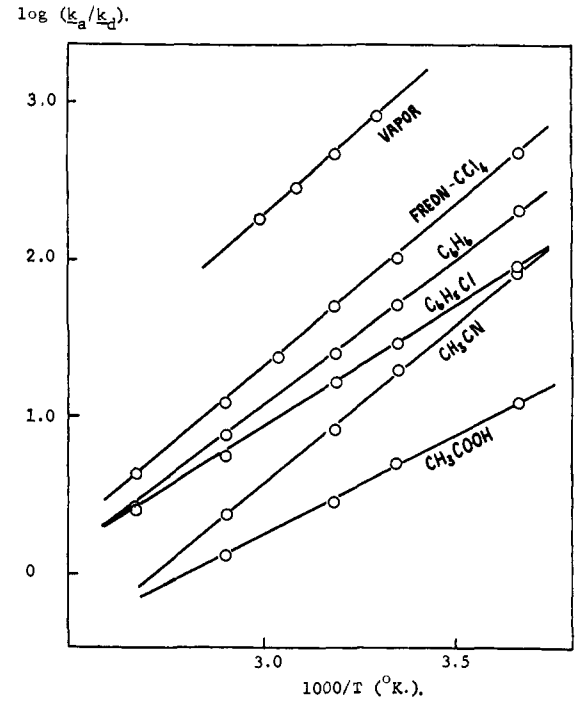


Fig. 2.—Effect of solvents on k_a/k_d in the *t*-butyl hypochlorite chlorination of cyclohexane.

Finally, all of our data in some 14 solvents, plus a series of vapor-phase measurements, are summarized in Table II. While our interpretation of these results are given in more detail below, it is seen that solvent effects on the competition between hydrogen abstraction and β-scission produce changes of over 100-fold at the lower temperatures, activation energy differences range from 10.5 to 5.9 kcal., and ratios of *A* factors change by two powers of 10. Furthermore, quite a variety of solvents is effective in altering reactivity, including aromatic molecules, olefins, and polar materials such as acetonitrile and acetic acid.

(9) J. K. Kochi, *Tetrahedron*, **18**, 483 (1962).

(10) C. Walling and A. Zavitsas, *J. Am. Chem. Soc.*, **85**, 2084 (1963).

(11) A solution of hypochlorite in pyridine turns bright gold, then a deep carmine, concluding its display on a less esthetic note by precipitating a brown sludge.

Some particular systems showed peculiarities which are worth pointing out. In a few cases, as indicated in Table II, k_a/k_d was obtained from plots of cyclohexyl chloride:acetone. This was particularly important in higher temperature runs in acetic acid, where *t*-butyl alcohol was consumed by esterification or dehydration. The possibility that acetyl hypochlorite, perhaps formed by the exchange may be involved in acetic

$$(CH_3)_3COCl + CH_3COOH \rightleftharpoons (CH_3)_3COH + CH_3COOCl$$

acid reactions, was eliminated by showing that no CO_2 could be detected in the reaction products as would be anticipated from decomposition of the acetoxy radical.[12] At 0° different k_a/k_d ratios were obtained in frozen and liquid supercooled acetic acid, and the latter was used since it gave better agreement with higher temperature results. Interestingly, no deviation from extrapolation of liquid phase results was observed in frozen benzene at 0°. In bromobenzene small amounts of chlorobenzene were produced (10% compared with cyclohexyl chloride in a 0.04 *M* cyclohexane reaction at 0°). If this arises from the known displacement by chlorine atoms produced in the photoinitiation,[13] kinetic chains of about 10 are indicated and *t*-butyl peroxide would be a possible detectable termination product. Unfortunately, it is not separated from cyclohexane under our analytical conditions (Carbowax column), but addition of *t*-butyl peroxide was shown to have no effect on measured alcohol:acetone ratios. The possibility of displacement of halogen by *t*-butoxy or methyl radicals was investigated by decomposing *t*-butyl hypochlorite in pure iodobenzene at 40°. Although chlorobenzene was again produced, neither toluene nor phenyl *t*-butyl ether could be detected.

As noted above, the intercepts of plots such as Fig. 1 yield reactivities of solvents toward hydrogen abstraction. In general these decrease with increasing temperature, indicating a lower activation energy than for for the β-scission, although precision was too low to calculate actual values. Nevertheless, these intercepts are, in general, very small, averaging 1.5 for aromatic solvents at 0°; *e.g.*, for benzene k_a/k_d = 0.0074, 1/1700 that for cyclohexane. Corresponding values of k_a/k_d for acetic and acetonitrile are 0.04 and 0.01, 1/250 and 1/800 those of cyclohexane in the same solvents. In the same way if the failure to account for 11% of the products in reaction of 0.30 *M* cyclohexane at 40° in trichloroethylene is ascribed to addition, k_{addn}/k_d = 0.048 l. mole^{-1}. No *cis–trans* isomerization of either dichloroethylene was observed in any reactions in which they were used as solvents, eliminating the possibility of a faster reversible addition to their double bonds.

Solvent Effects on Competitive Hydrogen Abstraction.—The large effects of solvents on k_a/k_d ratios described in the previous section encouraged us to reexamine the effect of solvents on the selectivity of *t*-butoxy radicals in hydrogen abstraction, *i.e.*, of k_{a1}/k_{a2} ratios in reactions 2 and 3. The most extensive study was made on the relative reactivities of aliphatic primary and tertiary hydrogens. For this purpose 0.2 *M* *t*-butyl hypochlorite was photolyzed in the presence of 0.8 *M* 2,3-dimethylbutane and the products analyzed for 1-chloro-2,3-dimethylbutane and 2-chloro-2,3-dimethylbutane by g.l.c. Results in 16 solvents expressed as selectivities per hydrogen are listed in Table III. Arrhenius plots gave good straight lines and differences in Arrhenius parameters are given for each solvent. Runs in acetic acid and 80% acetone were not carried out above 40° and stored cold until analysis to minimize solvolysis, so Arrhenius parameters are of lower precision. From the table we see that the relatively polar solvents acetone, acetonitrile, and acetic acid are particularly effective in perturbing the selectivity observed in aliphatic solvents. Activation energy differences increase from 2 to 4.5 kcal./mole., while ratios of *A* factors change by 100-fold. Since these variations largely compensate each other, the actual selectivities change by no more than a factor of 5.

TABLE III

EFFECT OF SOLVENT ON 2,3-DIMETHYLBUTANE–*t*-BUTYL HYPOCHLORITE SYSTEMS k_t/k_p[a]

Solvent	k_t/k_p[a] 100°	70°	40°	25°	0°	$E_p - E_t$[b]	log A_t/A_p[c]	s_r[d]
$C_6H_5OCH_3$	..	45	65	72	106	2250	+0.22	±150
C_6H_5Br	..	47	64	78	104	2130	+ .32	90
$C_6H_5C(CH_3)_3$	..	44	63	75	96	2050	+ .35	160
Benzene[e]	..	..	55	70	89	1990	+ .35	60
None[e]	..	..	44	54	68	1850	+ .35	120
trans-$C_2H_2Cl_2$	..	40	50	61	75	1740	+ .49	120
cis-$C_2H_2Cl_2$	..	29	40	47	60	1890	+ .27	100
C_6H_5Cl	(26)[f]	35	54	66	94	2580	− .08	150
o-$C_6H_4Cl_2$	..	34	50	66	91	2630	− .14	170
C_6H_5CN	..	25	40	48	67	2570	− .22	100
$(CH_3)_3COH$	13	20	30	38	...	3060	− .66	80
CH_3COCH_3	20	30	51	76	128	3770	− .92	100
80% acetone[g]	..	..	27	36	69	4020	−1.38	150
CH_3CN	10	17	33	47	...	4570	−1.67	140
CH_3COOH	..	..	20	28	53	4210(?)	−1.64(?)	?
CH_3COOCH_3	..	10	14	17	25	2350	−0.49	130

[a] Ratio of tertiary abstraction to primary abstraction, per C–H bond. [b] Difference in activation energies, in cal. mole^{-1}. [c] Logarithm of the ratios of *PZ* factors. [d] Probable error (standard deviation) in $E_p - E_t$. [e] Values at 40, 20, and 0°, taken from ref. 3. [f] Extrapolated value. [g] 80% acetone, 20% water, by volume.

Table IV lists similar measurements on secondary:primary hydrogen selectivity obtained with *n*-butane in four solvents. We see that the order of solvent effects is quite similar, and $E_p - E_s$ values are approximately one half of $E_p - E_t$ values in the same solvent.

TABLE IV

EFFECT OF SOLVENT ON *n*-BUTANE–*t*-BUTYL HYPOCHLORITE SYSTEMS

Solvent	k_s/k_p[a] 70°	40°	25°	0°	$E_p - E_s$[b]	log A_s/A_p[c]	s_r[d]
CCl_4	..	10.2	10.9	12.8	930	+0.36	±90
C_6H_5Cl	8.85	10.8	11.5	14.6	1320	+0.11	80
CH_3COOH	3.99	5.88	7.23	10.6	2590	−1.04	50
CH_3CN	4.83	6.52	8.30	10.9	2190	−0.71	140

[a] Ratio of secondary abstraction to primary abstraction per C–H bond. [b] Difference in activation energies, in cal. mole^{-1}. [c] Logarithm of the ratio of *PZ* factors. [d] Probable error (standard deviation) in $E_p - E_s$.

Nature and Energetics of Solvation Effects.—As has been pointed out elsewhere,[14] measurements of the

(12) CO_2 is, of course, a major product in the decomposition of acetyl peroxide in essentially all solvent systems. For a recent discussion *cf.* H. J. Shine, J. A. Waters, and D. M. Hoffman, *J. Am. Chem. Soc.*, **85**, 3613 (1963).

(13) B. Miller and C. Walling, *ibid.*, **79**, 4187 (1957).

(14) J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955); J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, Chapter 9.

effect of solvents on competing reactions of the sort we have just described measure *directly* only the effects of solvents on the transition states involved. Our problem is thus to see what can be deduced concerning the nature of the solvation involved and what in turn may be inferred about the interactions with solvent of *t*-butoxy radicals themselves.

A convenient starting point is the concept of isokinetic temperature, introduced by Leffler[14] and based upon Hammett's earlier discussions[15] of linear free energy relationships. In a large number of examples scattered through chemistry, changes in a single variable lead to proportional changes in activation entropies and enthalpies. Such changes may be in a substituent (as in the familiar Hammett ρ–σ treatment) or, as here, in reaction media. In such a situation

$$\Delta H_1^* - \Delta H_2^* = \beta(\Delta S_1^* - \Delta S_2^*) \qquad (5)$$

where subscripts refer to any two values of the variable. If (5) is obeyed, an isokinetic temperature $T_k = \beta$ exists at which the variable has no effect on the reaction rate. Below T_k changes in rate with the variable reflect changes in ΔH^*; above T_k the changes in ΔS^* dominate. If an isokinetic temperature exists, plotting ΔH^* *vs.* ΔS^* (or *vs.* log A in the Arrhenius form of the rate expression) yields a straight line.

The positions of points on the line indicate the magnitude of the effect of the variables on the reaction, and the slope of the line yields T_k. The analogous operation involving differences in ΔH^*'s and ΔS^*'s for two competing reactions involves plotting these differences, and such plots for the competitive hydrogen abstractions of Tables III and IV are shown in Fig. 3. Considering first the t/p ratios observed with 2,3-dimethylbutane and recognizing that the actual experimental uncertainties would be represented by circles 2–3 times the diameters of those shown, the evidence for an isokinetic temperature is excellent, and the s/p ratio data for *n*-butane, while more limited, further lie on another line of experimentally indistinguishable slope. Interestingly, the slopes of the lines correspond to $T_k = 278°$K., a value actually within our experimental temperature range. Although we have thus inadvertently picked experimental conditions which produce the *smallest possible* effect of solvents on our numerical values of relative reactivities, determination of activation parameters serves to show up these effects very clearly. The clump of encircled (unlabeled) points include reactions in 2,3-dimethylbutane, benzene, *t*-butylbenzene, anisole, and the chloroethylenes. Since transition-state solvation would be expected to be minimal in the saturated hydrocarbon, we consider that there is little solvation in the other cases as well. Pursuing this argument, the importance of solvation increases as we go to the more polar aromatics, *t*-butyl alcohol, acetone, acetonitrile, and acetic acid. The limited temperature range available in acetic acid makes its position relative to acetonitrile highly uncertain so that the apparent reversal from the set of butane experiments (where the results are more reliable) is probably not significant.

In attempting to describe the nature of the solvent effect which we observe, it is interesting to compare

(15) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter 7.

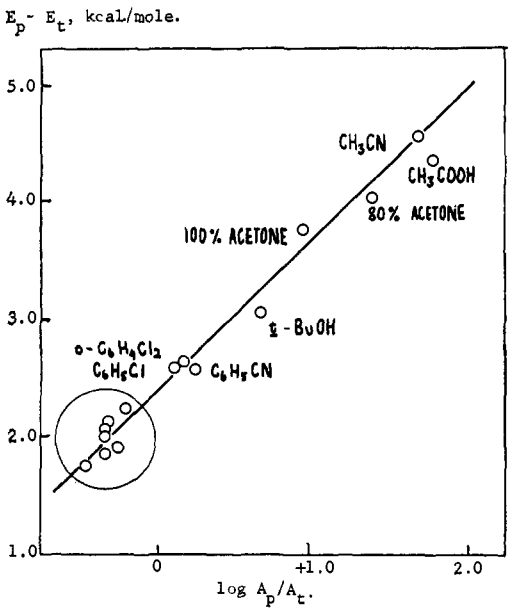


Fig. 3.—Isokinetic relationship in the effect of solvents on t/p ratios in the *t*-butyl hypochlorite chlorination of 2,3-dimethylbutane.

our results with the solvent effects on chlorine atom selectivity reported by Russell.[16] Most of Russell's results were obtained at a single temperature (55°), and with substituted benzenes he noted a regular increase in t/p selectivity with electron-donating ability of the π-electron system as judged by several criteria. This has led him to propose that the predominant factor in solvation effects on chlorine atom reactions is some sort of charge-transfer phenomenon,[16] a plausible suggestion which has been generally accepted.[17] If, for the moment, we accept this interpretation of chlorine atom reactions, charge transfer seems to play little part in the transition states for hydrogen abstraction by alkoxy radicals, since the largest changes in selectivity are observed in polar media, and aromatic solvents have little effect. Further there is no parallel between the ability of aromatic substituents to increase π-electron availability and their effect on selectivity, both benzonitrile and the chlorobenzenes producing larger changes than benzene itself. The alternative would seem to be an explanation in terms of solvent polarity and polarizability. Even here the relation is only qualitative, since in Table V we compare our data with three usual criteria of these properties—dielectric constant, dipole moment, and Kosower Z-value[18]—with little quantitative agreement.

Actually, re-examination of the data on chlorine atom reactions suggests that here too all may not be well with a simple charge-transfer interpretation. Measurements over a temperature range are available in in four solvents[16] and are listed in Table VI. $E_p - E_t$ is increased in the selective solvents as would be expected; but among the aromatic solvents, A_p/A_t increases along with $E_p - E_t$, and neither parallel the observed t/p ratios at 55°. The changes resemble those in Table III and it may be noted that chlorobenzene, the least selective solvent at 55°, shows the largest value of $E_p - E_t$, and would become more selective

(16) G. A. Russell, *J. Am. Chem. Soc.*, **80**, 4987 (1958).
(17) *Cf.*, for example, C. Walling and M. Mayahi, *ibid.*, **81**, 1485 (1959).
(18) E. M. Kosower, *ibid.*, **80**, 3253, 3261 (1958).

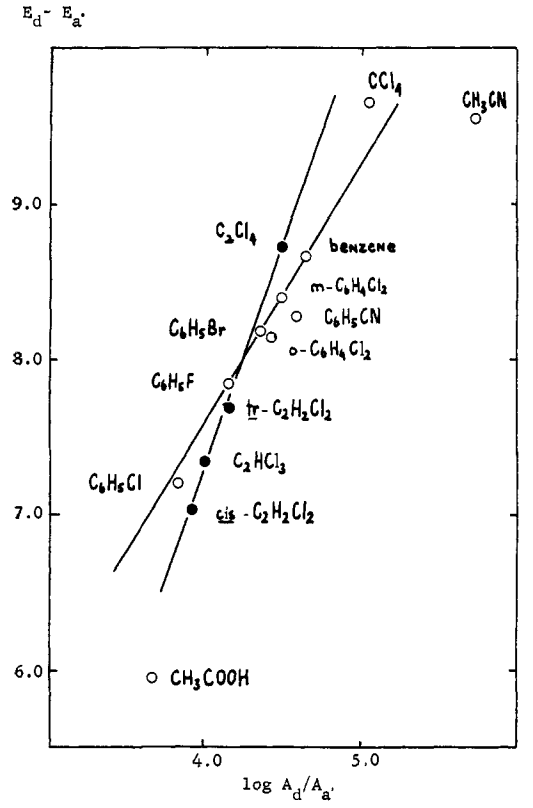


Fig. 4.—Isokinetic relationships in the effect of solvents on k_a/k_d ratios.

than benzene at about 0°. A more careful study of chlorine atom systems over as wide a temperature range as possible would help to resolve the question of possible modes of chlorine atom solvation.

TABLE V

COMPARISON OF SOLVENT EFFECTS WITH VARIOUS MEASURES OF POLARITY

Solvent	ϵ[c]	μ[c]	Z	$E_p - E_t$	$\Delta\Delta H^*_d$[a]
CCl_4	2.24	0	..	1850	0
C_2Cl_4	2.30	0	..	..	1.0
C_6H_6	2.28	0	..	1990	1.3
m-$C_6H_4Cl_2$	5.04	1.48	..	..	1.6
C_6H_5Br	5.40	1.73	59.2	2130	1.8
trans-$C_2H_2Cl_2$	2.14	0	..	1740	1.9
C_6H_5CN	25.20	3.37	65.0	2570	2.0
C_6H_5F	5.42	1.47	60.2	..	2.1
o-$C_6H_4Cl_2$	9.93	2.26	60.0	2630	2.2
C_2HCl_3	3.42	0.9	..	..	2.3
cis-$C_2H_2Cl_2$	9.20	1.89	63.9	1890	2.6
C_6H_5Cl	5.62	1.56	58.0	2580	3.1
$(CH_3)_3COH$	10.9	1.66	71.3[b]	3060	...
CH_3COCH_3	20.7	2.72	65.7[b]	3770	...
CH_3CN	37.5	4.05	71.3[b]	4570	3.5
CH_3COOH	6.15	0.83	79.2[b]	~5000	7.5

[a] Estimated change in enthalpy of transition state for β-scission due to solvation (*cf.* Fig. 5). [b] Kosower Z-values from ref. 18; other values determined in this paper. [c] Dielectric constants and dipole moments from J. A. Riddick and E. Toops, Jr., "Organic Solvents," Vol. VII of "Techniques of Organic Chemistry," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1955.

We may extend our discussion to the competition between hydrogen abstraction and β-scission by constructing an isokinetic temperature plot from the data of Table II as shown in Fig. 4. Here the results are rather more complicated. First, we see that points corresponding to the clumped solvents showing little

TABLE VI

SOLVENT EFFECTS ON PHOTOCHLORINATION OF 2,3-DIMETHYLBUTANE

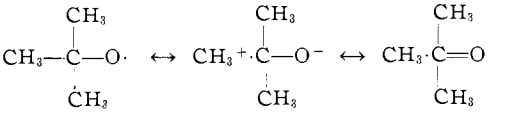
Solvent	k_t/k_p[a] 55°	40°	25°	$E_p - E_t$	log A_t/A_p
4 M $C_6H_5C(CH_3)_3$	24	..	35	2440	−0.25
4 M benzene	14.6	17	20	2040	− .20
None	3.7	3.9	4.2	820	.02
4 M C_6H_5Cl	10.2	13.5	17.1	3340	−1.21

[a] Per C–H bond; all k_t/k_p values from ref. 16.

solvation effects on hydrogen abstraction must solvate β-scission since they are now quite spread out. Second, two groups of structurally different solvents appear to demonstrate different types of solvation, since they lie on lines defining different T_k's. Thus the chloroethylenes all lie on a line corresponding to T_k = 627°K. Since trichloroethylene lies between *cis*- and *trans*-dichloroethylene, the order is not that expected for electron availability, although there is some correlation with dipole moment (*cf.* Table V). Most of the aromatics lie on another line, T_k = 365°K., with the most polar molecules, *o*-dichlorobenzene and benzonitrile, deviating significantly. When we recognize that these molecules also showed evidence for considerable solvation in hydrogen abstraction, we see that their actual position on the plot must be the consequence of two types of solvation of the two quite different transition states involved. Finally, we see that the points identifying the polar solvents acetonitrile and acetic acid are now widely separated, indicating quite different interactions with the transition state for β-scission.

Figures 3 and 4 point up the relations which are implicit in the earlier tables. Solvation effects on hydrogen abstraction are rather small and seem to be of a single type, most plausibly due to dipole interaction between the transition state and polar and polarizable solvent molecules. In hydroxylic solvents, of course, this interaction may also involve some hydrogen bonding. Since we are dealing with an exothermic, low activation energy process, relatively little bond breaking and bond making has occurred in the transition state. Accordingly, we assume that it resembles the reactants in structure, and any interaction with solvent is similar in nature to the solvation of the ground-state solvation of the *t*-butoxy radical, but less in quantity since approach of a *t*-butoxy radical to hydrocarbon must require squeezing out of surrounding solvent. The more difficult the hydrogen abstraction, the greater the need for a bare unsolvated *t*-butoxy radical, and the more complete the resulting solvent release. This release of solvent, in turn, increases the entropy of the transition state, leading to the observed result than in highly polar solvents, $E_p - E_t$ increases but is actually overcome by an increase in A_p/A_t.

The transition state for β-scission, on the other hand, does not require the close approach of another reactant molecule and, accordingly, suffers no steric inhibition of solvation. Further, we are now dealing with an endothermic, higher activation energy process in which bond breaking to give a relatively polar product is well underway.



Accordingly, we ascribe the large solvent effects on k_a/k_d ratios chiefly to solvation of the transition state for the β-scission process. Again there is little evidence for any important role of charge-transfer structures, but some parallel with polarity. In addition, hydrogen bonding (which has already been proposed as stabilizing peroxy radicals[19]) may be important in the acetic acid system.

If certain plausible assumptions are introduced, we may extend our qualitative discussion to the construction of a semiquantitative picture of the effect of solvents on the energy levels involved in t-butoxy radical reactions (Fig. 5). Hershenson and Benson[20] have taken

$$k_d = 10^{10.5}\, e^{-13,000/RT}$$

as an average value for the β-scission reaction in the gas phase. The pre-exponential factor is abnormally low for a unimolecular reaction, and they suggest that, in the pressure range studied, the process may require a third body and be pressure dependent. Combined with our data, their value would give, for reaction with cyclohexane

$$k_a = 10^{5.9}\, e^{-2440R/T}$$

In going from the gas phase to "inert" solvents such as CCl_4 or $C_2F_3Cl_3$, $E_d - E_a$ decreases from 10.56 to 9.63 kcal. and A_d/A_a increases slightly. For lack of any better choice, we will allocate this change to some solvation of the β-scission transition state and a more normal frequency factor. Combining our result with the known activation activation energy differences for primary, secondary, and tertiary hydrogen abstraction in nonpolar solvents gives the energy levels for "inert" solvents shown. In order to place the levels in other solvents we must introduce further assumptions and proceed as follows. In nonpolar aromatics the quantities $E_p - E_s$ and $E_s - E_t$ are expanded from 0.9 to 1.1 kcal. From our model, this represents solvation of the transition states in the order $p < s < t$ and even larger solvation of the reactant t-butoxy radicals. To obtain numerical values, we assume that the actual E's are increased in the same proportion (by 1.1/0.9), so E_t increases from 1.6 to 1.9 kcal. In order to locate the levels on the vertical scale, we make a second assumption: that the fraction of solvation stabilization remaining in the transition state for primary hydrogen abstraction is constant, and take it as one-quarter of the solvation energy of the ground-state t-butoxy radical. This locates the t-butoxy radical at a level $-4/3 \times [E_p$ (aromatic) $- E_p$ $(CCl_4)]$, or -0.9 kcal., and places the rest of the levels as well. Similar calculations were used to locate energy levels in other solvents as shown. Other choices of the amount of solvation left in the transition states would not change the order of energy levels in different solvents, but would make moderate changes in our estimate of t-butoxy radical solvation. Thus in the most extreme case, acetic acid, we obtain -8.1 kcal., a reasonable value for a hydrogen-bonding process and one reason for our choice. Assumptions of zero and one half residual solvation for the primary hydrogen transition state yield stabilizations of 5.7 and 12.2 kcal., respectively, and it seems plausible that the actual value lies within that range.

(19) F. F. Rust and E. A. Youngman, *J. Org. Chem.*, **27**, 3778 (1962).
(20) H. Hershenson and S. W. Benson, *J. Chem. Phys.*, **37**, 1889 (1962).

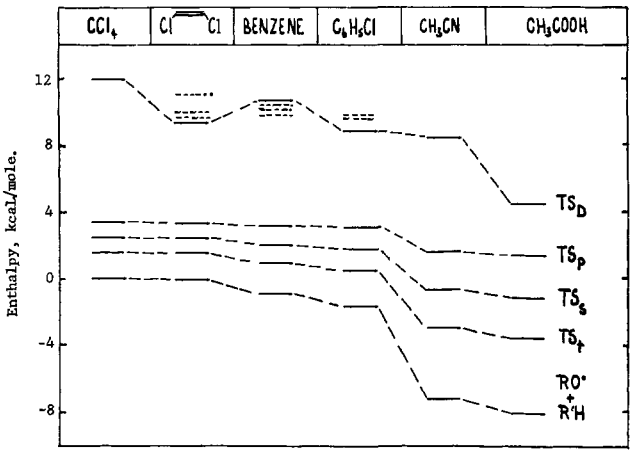


Fig. 5.—Schematic diagram of solvation energies of transition states for β-scission (TS_d), primary (TS_p), secondary (TS_s), and tertiary (TS_t) hydrogen abstraction and of ground-state t-butoxy radicals (RO·).

In the discussion given above we have concentrated our attention on solvation of the t-butoxy radical and have ignored any effect of medium on the properties of the hydrocarbon molecules which are also reactants in the hydrogen abstraction process, even though rigorous treatment should involve consideration of activity coefficients of hydrocarbon and transition states involving hydrocarbon in changing media.[21] We see no quantitative way of taking this into account, but the following argument suggests that any correction would simply magnify the solvent effects which we deduce. If an aliphatic hydrocarbon is transferred from a nonpolar solvent with which it forms an approximately ideal solution to a solvent such as acetonitrile or acetic acid, a large increase in activity occurs,[22] although, in the dilute solutions we have used, Henry's law is probably still obeyed and the activity coefficient is concentration independent. This will have no effect on k_d, but could alter k_a, calculated on the basis of hydrocarbon concentration. If hydrocarbon activity rather than concentration is used in plots such as Fig. 1, points at any one temperature would be shifted to the right by a constant proportional amount (equal to the activity coefficient), and the calculated value of k_a/k_d would be reduced. Since the activity coefficients should decrease with increasing temperature (the solubility of hydrocarbons in these solvents increases with temperature) the result on transferring the new values to Arrhenius plots would be to *decrease* $E_d - E_a$. In short, solvent effects would appear larger. This treatment, however, amounts to assuming that the presence of hydrocarbon in the transition states for hydrogen abstraction contributes nothing to their activity coefficients in changing media. If the contribution is comparable to the changes in ground-state hydrocarbon activity coefficients, the effects cancel completely, and our use of concentrations rather than activities isolates the effect of solvent on the t-butoxy radical as intended. The actual situation probably lies somewhere between these two extremes, so that our estimates

(21) E. M. Arnett, P. M. Duggleby, and J. J. Burke, *J. Am. Chem. Soc.*, **85**, 1350 (1963), have shown, for example, that changes in rates of solvolysis of t-butyl chloride are determined primarily by changes in ground-state enthalpy.
(22) C. Black, *Ind. Eng. Chem.*, **51**, 211 (1959), has reported activity data on a number of our solvent pairs.

TABLE VII
SOLVENT EFFECTS ON $RC(CH_3)_2OCl$ SYSTEMS IN PRESENCE OF 1.0 M CYCLOHEXANE[a]

R	Solvent	k_a/k_d 100°	70°	40°	25°	0°	$E_d - E_a$	log A_d/A_a	s_r
CH_3	$C_2F_3Cl_3$	4.29	12.2	52.8	99.0	487	9.65	5.04	±0.23
	C_6H_5Cl	2.65	5.62	16.4	28.6	91.7	7.21	3.82	0.11
CH_3CH_2	CCl_4	0.21	0.30	0.56	0.75	1.43	3.96	3.03	.14
	C_6H_5Cl	..	.51	.59	.76	0.98	1.80	1.45	.21
$(CH_3)_2CH$	CCl_4	..	.031	.035	.043	.049	1.29	2.33	.19
	C_6H_5Cl	0.121	.114	.098	.088	.080	−0.89	0.39	.07
$C_6H_5CH_2$	CCl_4	..	.72	.83	.92	...	1.10	0.85	.07
	C_6H_5Cl	..	.235	.185	.157	0.122	−1.76	−0.49	.04
C_6H_5	CCl_4	0.92	1.74	4.30	6.42	16.9	5.91	3.51	.10
	C_6H_5Cl	..	1.28	2.83	4.22	9.42	5.28	3.25	.09
	CH_3CN	..	0.90	1.83	2.78	7.36	5.58	3.62	.24
	CH_3COOH	0.86	0.97	1.16	1.47	2.87	....	....	....

[a] Symbols have same significance as in Table II.

about the magnitude of *t*-butoxy radical solvation may be a little low.

Recognizing these limitations, we may return to Fig. 5 and summarize our general conclusions. Saturated solvents and the chloroolefins produce little solvation of *t*-butoxy radicals, but the latter do stabilize the transition state for β-scission. Aromatics solvate both *t*-butoxy radicals and the transitions states for β-scission (dashed lines in the figure indicate different levels for particular solvents) and the effects increase with solvent polarity but not with electron availability. Acetonitrile and acetic acid both solvate *t*-butoxy radicals very strongly, but the latter is much more effective in stabilizing the transition state for β-scission, perhaps through a specific hydrogen-bonding process.

At this point it seems unlikely that the details of solvation on these systems can be unscrambled much further by competitive kinetics. Rather, information is required on the actual solvent dependence of individual rate constants, accessible only by nonsteady-state kinetics or direct observation of radical decay by electron spin resonance or other techniques. Our results, however, suggest that effects may be quite large, and suitable solvation may stabilize radicals to the point where they become much more susceptible to direct observation.

In terms of our original objectives, these results show that relative reactivities measured *indirectly* by using aromatic or olefinic hydrocarbons as *solvent* may be subject to considerable error due to the increase in k_d caused by these types of solvent. We are currently investigating how indirect relative reactivities obtained from *dilute* solutions of substrate hydrocarbons, wherein any extraneous effects on k_d should be eliminated, compare with directly measured values.

Solvent Effects on k_a/k_d Ratios with Other Hypochlorites.—In a recent paper[23] we have shown that k_a/k_d ratios for a series of hypochlorites $RC(CH_3)_2OCl$ depend markedly on the structure of the leaving group R and in general decrease in the expected manner with increasing stability of the radical R·. We have now looked briefly at solvent effects on the k_a/k_d ratios in some of these other systems by decomposing the appropriate hypochlorites in the presence of 1.0 M cyclohexane in CCl_4 and chlorobenzene. Since alkoxy radical attack on either solvent should be negligible in the presence of this much cyclohexane, calculations of k_a/k_d ratios from single points rather than plots of alcohol:acetone ratios *vs.* cyclohexane seemed justified and results appear in Table VII. Results in CCl_4 check quite well with those reported previously[23] at different cyclohexane concentrations, and the median deviation of $E_d - E_a$'s from our previous values is only about 0.4 kcal. From the table we see that, in every case except R = phenyl, going from CCl_4 to chlorobenzene decreases $E_d - E_a$ by 2.4 ± 0.3 kcal. On the other hand, going down the series R = methyl, ethyl, and isopropyl, there is an increase in A_a/A_d giving isokinetic temperatures of 164, 25, and −27°. Thus in our experimental range of 0–100° chlorobenzene appears to *increase* rather than decrease k_a/k_d for R = isopropyl, and with R = ethyl the effects of the two solvents cross at room temperature. Looking at A_a/A_d ratios going down the same series in any one solvent, they are seen to increase. Since it is hard to see what major effect R has on the hydrogen abstraction process (different alkoxy radicals are known to show very similar selectivities[23]), these probably reflect increasing conformational restrictions in the transition states for the β-scission of large radicals. This effect is largest with R = benzyl, and here also we note a particularly large dependence of $E_d - E_a$ upon solvent. This, in turn, leads to a high value of T_k and, experimentally, an increased sensitivity of k_a/k_d to transition-state energies, which may provide a partial explanation of the very large solvent effect on β-scission of benzyldimethylcarbinyl hypochlorite observed in olefinic solvents.[23]

In the case of R = phenyl, β-scission takes a different course to yield acetophenone and a methyl radical.[23,24] Solvent effects on k_a/k_d are here quite small (although in the same order), and results in acetic acid do not yield a good Arrhenius plot. We see no obvious explanation of the difference and include the data because of the interest in cumyloxy and cumylperoxy radicals as intermediates in autoxidation reactions.

Experimental

Reagents.—Solvents were in general commercial materials distilled before use and their purity checked by g.l.c. Hypochlorites were prepared as described previously.[23] Di-*t*-butyl peroxylate was prepared by the method of Bartlett, Benzing, and Pincock.[25]

(23) C. Walling and A. Padwa, *J. Am. Chem. Soc.*, **85**, 1593 (1963). References to other studies of the dependence of the ease of β-scission upon alkoxy radical structure also appear in this paper.

(24) M. S. Kharasch, A. Fono, and W. Nudenberg, *J. Org. Chem.*, **15**, 748 (1950).

(25) P. D. Bartlett, H. P. Benzing, and R. H. Pincock, *J. Am. Chem. Soc.*, **82**, 1762 (1960).

Reactions were carried out in sealed degassed tubes placed in thermostats and irradiated to complete reaction as previously. Very dilute solutions at 0° were irradiated for 6 hr. by a 140-watt ultraviolet lamp at a distance of 6 in. Shorter times and weaker light were used in other systems. Reaction times were somewhat arbitrary since the disappearance of hypochlorite color could not be seen in dilute solutions. However, all tubes were checked for complete reaction by reaction with iodide on opening. Gas phase reactions were carried out by attaching a small tube containing a 9:1 mole ratio of cyclohexane and *t*-butyl hypochlorite and a 265-ml. bulb equipped with a side-arm to a vacuum manifold, degassing the system, and allowing it to equilibrate at room temperature. The bulb was then isolated by closing an intervening stopcock and sealed off after freezing out the contents in the side-arm. After irradiation in a thermostat, the contents were again frozen out, sealed off, and held for analysis.

Experiments with CuCl-*t*-butyl perbenzoate and di-*t*-butyl peroxylate were carried out in the same manner as the hypochlorite runs except that no irradiation was required.

Analyses were carried out by g.l.c. using an Aerograph Model 600 Hy-Fi equipped with a flame ionization detector. Columns were 10-ft. lengths of $^1/_8$ in. tubing packed with 60/80 firebrick containing 15% Carbowax 20M, 20% diethylene glycol succinate (DEGS), 20% neopentyl glycol succinate (NPGS), or 20% Ucon polar, depending on the system to be analyzed. Peak areas were determined from the product of heights and width at half-height, and were related to compositions by calibration against known mixtures of acetone–alcohol (or cyclohexyl chloride) in the same solvents.

In the isomer distribution experiments, peak areas were taken as proportional to concentration. Material balances were determined in some systems by using a small amount of benzene as internal standard and again calibrating against known mixtures. Analyses were in duplicate or triplicate and agreement was within 3%, usually within 2%. Ratios of rate constants and Arrhenius parameters were calculated in the usual manner and standard deviations are indicated in the tables. No correction was made in calculations for the small change in cyclohexane concentration during reaction since measured k_a/k_d ratios were shown to be independent of cyclohexane:hypochlorite ratios from 2:1 to 20:1.

Kosower *Z*-values were not available for a number of our solvents, and were determined from the visible absorption spectra of N-ethyl-4-carbomethoxypyridinium iodide solutions in them.[20] In solvents for which no value is given, the salt was too insoluble for measurement.

Thermal expansion of solvents was determined in a sealed 1-ml. pipet graduated in hundredths, the volume of each solvent being measured two or three times at each experimental temperature. Actual volume changes over the 100° range amounted to 8–15%. Since k_a/k_d ratios obtained from plots such as Fig. 1 have the dimensions of l. mole^{-1} they were corrected accordingly in Table II and Fig. 2.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND LAWRENCE RADIATION LABORATORY, UNIVERSITY OF CALIFORNIA, BERKELEY, CALIF.]

The Biosynthesis of Nicotine in *Nicotiana glutinosa* from Carbon-14 Dioxide. Formation of the Pyrrolidine Ring[1]

BY WILLIAM L. ALWORTH,[2] ARNOLD A. LIEBMAN,[3] AND HENRY RAPOPORT

RECEIVED MARCH 28, 1964

Radioactive nicotine, isolated from the root and aerial portions of *Nicotiana glutinosa* after a 6 hr. exposure to $^{14}CO_2$, was degraded and the activity determined in the pyridine ring, the N-methyl group, and C-2′ and C-5′ of the pyrrolidine ring. The results support previous conclusions reached from $^{14}CO_2$ feedings. In addition, equal activity has been found at C-2′ and C-5′, consistent with the glutamate-symmetrical intermediate hypothesis. However, the labeling pattern required is not derivable from any of the known glutamate biosyntheses. An attempt has been made to reconcile the various data by suggesting a new glutamate biosynthesis.

Introduction

In a previous paper,[4] we presented our initial data on the biosynthesis of nicotine obtained by short-term growth of *N. glutinosa* in the presence of $^{14}CO_2$. Among a number of interesting results was the observation that C-2′ consistently contained a very low fraction of the total nicotine activity, a fact difficult to reconcile with the current hypothesis for biosynthesis of the pyrrolidine ring. In this paper, we present further data on the labeling pattern in the pyrrolidine ring and suggestions as to how these data and those obtained by other precursor feedings might be made compatible.

The current concept for formation of the pyrrolidine ring of nicotine is based on feeding experiments with ornithine-2-^{14}C,[5,6] putrescine-1,4-^{14}C,[7] and glutamic acid-2-^{14}C.[8] Activity at C-2′ in the resulting nicotine was established by oxidation to, and decarboxylation of, nicotinic acid. To determine the activity at C-5′, use was made[7,9] of the small yield of 3-nitro-5-(3′-pyridyl)pyrazole[10] isolated as a by-product from the nitric acid oxidation of nicotine or, more directly,[8,11] by oxidation of the nicotine to cotinine[12] and hydrolysis of the latter to 4-methylamino-4-(3′-pyridyl)-butyric acid, whose N-benzoyl derivative was decarboxylated by the Hofmann amide degradation. In each case, it was established that half of the incorporated activity was at C-2′ and the remainder at C-5′.

On the basis of these expeerimnts, Leete[7,13] proposed the glutamate-symmetrical intermediate hypothesis (Scheme I) for the biosynthesis of the pyrrolidine ring of nicotine. Cyclization of the δ-semialdehyde I, obtainable from glutamic acid and ornithine, gives Δ^1-pyrroline-5-carboxylic acid (II)[14] which, on decarboxyla-

(1) Sponsored in part by the United States Atomic Energy Commission.

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(3) Public Health Service Postdoctoral Research Fellow of the National Institute of General Medical Sciences.

(4) W. L. Alworth, R. C. De Selms, and H. Rapoport, *J. Am. Chem. Soc.*, **86**, 1608 (1964).

(5) E. Leete, *Chem. Ind.* (London), 537 (1955).

(6) L. J. Dewey, R. U. Byerrum, and C. D. Ball, *Biochim. Biophys. Acta*, **18**, 141 (1955).

(7) E. Leete, *J. Am. Chem. Soc.*, **80**, 2162 (1958).

(8) B. L. Lamberts and R. U. Byerrum, *J. Biol. Chem.*, **233**, 939 (1958).

(9) E. Leete and K. J. Siegfried, *J. Am. Chem. Soc.*, **79**, 4529 (1957).

(10) The formation of this compound was first reported by G. A. C. Gough and H. King [*J. Chem. Soc.*, 2968 (1931)] who assigned to it the structure 4-nitro-5-(3′-pyridyl)pyrazole. The correct structure was suggested by H. Lund [*ibid.*, 686 (1933)] and established by synthesis [G. R. Clemo and T. Holmes, *ibid.*, 1739 (1934)].

(11) B. L. Lamberts, L. J. Dewey, and R. U. Byerrum, *Biochim. Biophys. Acta*, **33**, 22 (1959).

(12) A. Pinner, *Ber.*, **26**, 292 (1893).

(13) E. Leete, *J. Am. Chem. Soc.*, **78**, 3520 (1956); recently modified by E. Leete, E. G. Gros, and T. J. Gilbertson, *Tetrahedron Letters*, 587(1964).

(14) Evidence from feeding experiments with Δ^1-pyrroline-5-carboxylic acid-5-^{14}C also has been sighted as support for this hypothesis [V. Krampl and C. A. Hoppert, *Federation Proc.*, **20**, 375 (1961)]; however, 29% of the activity was found in the N-CH_3. This, plus the highly unstable nature of II [H. J. Strecker, *J. Biol. Chem.*, **235**, 2045 (1960)], weaken this evidence.