was found to be homogeneous in paper chromatography in two solvents, $R_{f\ BAW}$ 0.81 and $R_{f\ SBA}$ 0.81.

Anal. Calcd. for $C_{88}H_{138}N_{18}S_2O_{22}$ (1864): C, 56.7; H, 7.46; N, 13.5. Found: C, 56.4; H, 7.62; N, 13.3.

N^{ϵ}-*t*-Butyloxycarbonyl-lysyl-prolyl-valyl-glycyl-N^{ϵ}-*t*-butyloxycarbonyl-lysyl-N^{ϵ}-*t*-butyloxycarbonyl-lysyl-N^{G}-tosyl-arginyl-N^{G}-tosyl-arginyl-proline *t*-Butyl Ester (IV).—Compound III, (1.86 g., 1 mmole) was dissolved in 40 cc. of methanol and submitted to catalytic hydrogenolysis using a Vibro-mixer[25] in the presence of Pd freshly prepared from 1 g. of $PdCl_2$ for 8 hr. The catalyst was filtered off and the filtrate and washings were evaporated to dryness. The residue was purified by countercurrent distribution in the toluene system for 100 transfers. A single peak with $K = 1$ was seen and isolated to yield 1.4 g. (81%) of IV, m.p. 120–130°, $[\alpha]^{25}D$ −42.7° (*c* 1, methanol). Compound IV was found to be homogeneous in paper chromatography, $R_{f\ BAW}$ 0.76 and $R_{f\ SBA}$ 0.81.

Anal. Calcd. for $C_{80}H_{132}N_{18}S_2O_{20}$ (1730): C, 55.6; H, 7.70; N, 14.6. Found: C, 55.9; N, 7.59; N, 14.4.

N^{α}-Carbobenzoxy-N^{ϵ}-tosyl-lysyl-prolyl-valyl-glycyl-N^{ϵ}-tosyl-lysyl-N^{ϵ}-tosyl-lysyl-N^{G}-tosyl-arginyl-N^{G}-tosyl-arginyl-proline *t*-Butyl Ester (VIII).—N^{α}-Carbobenzoxy-N^{ϵ}-tosyl-lysyl-prolyl-valyl-glycine[1] (IX, 0.69 g., 1 mmole) was dissolved in 30 cc. of acetonitrile. The solution was cooled to 0° and 0.14 cc. (1 mmole) of triethylamine and 0.254 g. (1 mmole) of N-ethyl-5-phenylisoxazolium 3'-sulfonate[11] were added. The mixture was stirred at 0° for 1 hr., 1.36 g. (1 mmole) of N^{ϵ}-tosyl-lysyl-N^{ϵ}-tosyl-lysyl-N^{G}-tosyl-arginyl-N^{G}-tosyl-arginyl-proline *t*-butyl ester[9] (X) was added and the stirring continued at room temperature for 36 hr. The solvent was removed *in vacuo* and the residue submitted to countercurrent distribution in the toluene system for 100 transfers. A large peak with $K = 0.22$ corresponding to the desired nonadecapeptide and two small peaks, $K = 1.22$ (unreacted X) and $K = 4.56$ (unreacted IX, were observed and were well separated from one another. The major peak ($K = 0.22$) was pooled, evaporated to dryness, the residue dissolved in methanol, filtered free of traces of insoluble material, and evaporated to dryness to yield 1.45 g. (71.5%) of the protected nonapeptide VIII. The peptide VIII was found to be homogeneous in paper chromatography, $R_{f\ BAW}$ 0.91 and $R_{f\ SBA}$ 0.82, $[\alpha]^{25}D$ −45.9° (*c* 1, methanol), m.p. 115–120°.

Anal. Calcd. for $C_{94}H_{135}N_{18}S_3O_{22}$ (2030): C, 55.7; H, 6.56; N, 12.4. Found: C, 55.5; H, 6.41; N, 12.6.

N^{ϵ}-Tosyl-lysyl-prolyl-valyl-glycyl-N^{ϵ}-tosyl-lysyl-N^{ϵ}-tosyl-lysyl-N^{G}-tosyl-arginyl-N^{G}-tosyl-arginyl-proline *t*-Butyl Ester (XI).—Compound VIII (1.4 g., 0.69 mmole) was dissolved in 30 cc. of methanol and decarbobenzoxylated by catalytic hydrogenolysis in the presence of Pd freshly prepared from 1 g. of $PdCl_2$. After CO_2 evolution had stopped (8 hr.), the catalyst was filtered off, washed with methanol, and the filtrate and washings evaporated to dryness *in vacuo*. The residue was purified by countercurrent distribution in the toluene system for 100 transfers. A single symmetrical peak with $K = 0.76$ was seen. The material in the peak was pooled, evaporated to dryness, redissolved in methanol, and precipitated from anhydrous ether to yield 1.04 g. (80%) of XI, m.p. 120–130° $[\alpha]^{25}D$ −37.1° (*c* 1, methanol). Peptide XI was found to be homogeneous in paper chromatography, $R_{f\ BAW}$ 0.86 and $R_{f\ SBA}$ 0.88.

Anal. Calcd. for $C_{86}H_{129}N_{18}S_3O_{20}$ (1895): C, 54.5; H, 6.86; N, 13.3. Found: C, 54.1; H, 6.51; N, 13.1.

Carbobenzoxy-seryl-tyrosyl-seryl-methionyl-γ-benzyl-glutamyl-histidyl-phenylalanyl-N^{G}-tosyl-arginyl-tryptophyl-glycyl-N^{ϵ}-*t*-butyloxycarbonyl-lysyl-prolyl-valyl-glycyl-N^{ϵ}-*t*-butyloxycarbonyl-lysyl-N^{ϵ}-*t*-butyloxycarbonyl-lysyl-N^{G}-tosyl-arginyl-N^{G}-tosyl-arginyl-proline *t*-Butyl Ester (VI).—The decapeptide[9] V (0.336 g., 0.2 mmole) and IV (0.346 g., 0.2 mmole) were dissolved in 2 cc. of dimethylformamide and cooled to 0°. Dicyclohexylcarbodiimide (0.046 g., 0.22 mmole) was added and the mixture was stirred at 0° for 1 hr. and kept at 4° for 3 days. Glacial acetic acid (0.5 cc.) was added, and after 2 hr. the solution was evaporated to dryness *in vacuo*. The residue was submitted to countercurrent distribution in the carbon tetrachloride system for 80 transfers to remove unreacted V ($K = 1$). The material from tubes 0 to 14 was isolated and washed exhaustively with water followed by methanol to remove unreacted IV. Peptide VI was obtained in 38% yield (0.255 g.).

Seryl-tyrosyl-seryl-methionyl-glutamyl-histidyl-phenylalanyl-arginyl-tryptophyl-glycyl-lysyl-prolyl-valyl-glycyl-lysyl-lysyl-arginyl-arginyl-proline (VII).—Compound VI (0.362 g., 0.107 mmole) was dissolved in 25 cc. of trifluoroacetic acid and stirred at room temperature for 2 hr. The solvent was removed *in vacuo* and the residue purified by countercurrent distribution for 100 transfers in the system 1-butanol–acetic acid–water (4:1:5 by volume). The peak with $K = 3$ (ultraviolet and ninhydrin positive) was isolated to yield 0.205 g. (63%) of the partially protected nonadecapeptide. This material was dissolved in 150 cc. of freshly distilled liquid ammonia and treated with small pieces of sodium until the blue color persisted for 30–40 min. The ammonia was then allowed to evaporate and the residue dried over concentrated H_2SO_4 and P_2O_5. The residue was dissolved in 20 cc. of 0.1 *N* acetic acid and desalted on IRC-50 resin as described earlier.[9] The crude nonadecapeptide was eluted with pyridine–acetic acid–water (30:4:66 by volume) and isolated by lyophilization to yield 0.164 g. of material. This was applied on a carboxymethylcellulose column and chromatographed using continuous gradient elution with ammonium acetate (Fig. 2). The major peak was isolated and rechromatographed on CMC (Fig. 3). Peptide VII was then isolated by lyophilization (3×) in a yield of 43% (0.085 g.; peptide content based on ultraviolet, 82%). Peptide VII was found to be homogeneous by electrophoresis on paper (mobility relative to lysine, 0.81; pH 3.7, 400 volts, 4 hr.) and polyacrylamide gel. The amino acid composition of VII as determined by the chromatographic and microbiological procedures was found to be in excellent agreement with theoretically expected values (Table I); $[\alpha]^{25}D$ −84.9° (*c* 0.5, 0.1 *M* acetic acid).

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(25) Vibro-mixer, A. G. Fuer Chemie-Apparatebau, Zurich, Model E1.

COMMUNICATIONS TO THE EDITOR

Ion Pairs in Reactions of Trityl Benzoate[1]

Sir:

While R^+X^- ion pairs have been invoked in discussions of solvolysis and exchange reactions of trityl chloride,[2] no actual attempt was made until very recently to estimate for any trityl system the importance of ion pair return under any particular set of conditions. For carbonyl-^{18}O-labeled trityl benzoate (RX) in dry acetone at 60°, Swain and Tsuchihashi[3] recently reported a first-order rate constant of 3.8×10^{-6} sec.$^{-1}$ for ^{18}O equilibration, this equilibration being completely suppressed initially in the presence of LiN_3. First-order rate constants (10^6k) from following disappearance of azide ion were 4.4 ± 0.4 and 6.3 ± 0.6 for 0.006 and 0.010 *M* LiN_3, respectively. A nearly quantitative

(1) Research sponsored by the National Science Foundation.

(2) (a) R. F. Hudson and B. Saville, *Chem. Ind.* (London), 1423 (1954); (b) C. G. Swain and M. M. Kreevoy, *J. Am. Chem. Soc.*, **77**, 1122 (1955); (c) E. D. Hughes, C. K. Ingold, *et al.*, *J. Chem. Soc.*, 1265 (1957); (d) C. G. Swain and E. E. Pegues, *J. Am. Chem. Soc.*, **80**, 812 (1958).

(3) C. G. Swain and G. Tsuchihashi, *ibid.*, **84**, 2021 (1962).

yield of RN_3 was isolated from the reaction with 0.02 M LiN_3. The azide capture rate appeared to be equal to the ionization rate of RX. No data were reported which could have helped decide what kind of species was being captured by azide salt. However, these authors assumed it was probably an ion pair. Since only one assumed ion pair was deemed sufficient to explain their observations, they extrapolated to widely different systems and other solvents and suggested only one ion pair be employed even in situations where we have found it necessary to call on two varieties of ion pair intermediate, one more capturable than the other.[4] It should be obvious that such extrapolations are unwarranted since the number of possible intermediates which have kinetic and chemical significance depends on various ratios of individual rate constants for the intermediates in a reaction scheme and these tend to change as structure and solvent vary.[4]

Our own observations on 0.01–0.04 M trityl benzoate in anhydrous acetone[5] at 75.0° are illustrated in Table I.

TABLE I

^{18}O EQUILIBRATION AND EXCHANGES OF TRITYL BENZOATE IN ACETONE AT 75.0°

Σ(Salt),[a] 10^2M	Salt	10^2M	10^7k (sec.$^{-1}$) k_{eq}	10^7k (sec.$^{-1}$) k_e or k_{N_3}
...	...	...	46	
0.039	Bu_4NOBz	0.039		1.1[b]
.122	Bu_4NOBz	0.122		1.7
.196	Bu_4NOBz	0.196		2.0
.300	Bu_4NOBz	0.300		2.5
1.00	...	...	72[c]	
1.00	Bu_4NOBz	0.198		5.7
1.00	Bu_4NN_3	0.2–0.5		5.3
6.00	Bu_4NOBz	0.1–0.3		10.4
6.00	Bu_4NN_3	0.3–1.1		9.7
0.376	LiN_3	0.376		120
2.04	Bu_4NN_3	1.11	90	420
	$LiClO_4$	1.04		
0.835	$LiClO_4$	0.835	780	

[a] Σ(Salt) brought to listed value with Bu_4NClO_4. [b] Initial value. [c] 72 ± 4; with 0.98 × 10^{-2} M Bu_4NN_3, k_{eq} = 62 ± 10.

The rate constant for ^{18}O equilibration, 10^7k_{eq}, is 46 ± 5 sec.$^{-1}$, and it rises slightly as tetrabutylammonium perchlorate (Bu_4NClO_4) is added. First-order rate constants (k_e) for exchange with tetrabutylammonium carboxyl-^{14}C-labeled benzoate (Bu_4NOBz) are much smaller and rise somewhat as salt concentration increases. At a constant total salt concentration, using Bu_4NClO_4 as an "inert" salt, first-order rate constants (k_{N_3}) for consumption of azide ion from added Bu_4NN_3 are equal to the k_e values with Bu_4NOBz and neither k_{N_3} nor k_e depends on nucleophile concentration (Bu_4NN_3 or Bu_4NOBz). While Bu_4NN_3 does not suppress ^{18}O equilibration, it does suppress exchange. For example, in a run containing 1.34 × 10^{-3} M Bu_4NOBz and 6.01 × 10^{-2} M Bu_4NN_3, k_e was depressed to *ca.* 1% of the value in the absence of the azide salt. This gives an azide/benzoate competition factor of *ca.* 2. Competition experiments on trityl perchlorate in dry acetone with the same salts yielded a corresponding competition factor of 2.0 ± 0.2 for initial azide : benzoate salt ratios varying from 0.4 to 1.1.

Taking k_{eq} or (k_{eq} + k_{N_3}) as an estimate of the ionization rate constant,[4e] we see that ionization rates exceed chemical capture rates by factors of 40 down to *ca.* 13 at 0.01 M tetrabutylammonium salt concentration. The situation here is qualitatively similar to the one observed by Darwish and Preston[6] in the isomerization of trityl 2-methylbenzenesulfinate to the sulfone in acetonitrile solvent where Bu_4NN_3 only partially suppresses rearrangement. We visualize that ^{18}O equilibration[4e] proceeds by way of an ion pair intermediate not easily capturable by added salts. However, the latter do compete for and trap very efficiently one or more further intermediates. From the behavior of trityl benzoate in slightly moist acetone[7] and considerations regarding ion pair dissociation rates,[4d] it is clear that a dissociated trityl species is also very important in dry acetone. "Capture" presumably occurs solely at this stage of ionization–dissociation[4] at very low salt concentrations. How much capture may occur at a solvent-separated ion pair stage[4] with higher concentrations of salt is not yet clear. Since the ion pair dissociation rate constant[4d] is not apt to exceed 10^9 sec.$^{-1}$ at 25°, it does seem possible at the higher salt concentrations that diffusion-controlled encounter of a trityl benzoate ion pair with a salt ion or ion pair will begin to compete somewhat with dissociation.

The present results contrast markedly with those reported by Swain and Tsuchihashi.[3] Our k_{eq} in acetone is considerably smaller than the value reported by these authors. As regards the effect of LiN_3, we could not directly check their reported experiments since this salt is only difficultly soluble and we could not achieve their reported LiN_3 concentrations in our acetone solvent. What experiments we have done show that lithium salts produce abnormally high ionization rates. Thus, with 0.00376 M LiN_3 even the chemical capture rate is much higher than the whole ionization rate with a corresponding concentration of tetrabutylammonium salts. Simulating a higher concentration of LiN_3 with a mixture of 0.01 M Bu_4NN_3 and 0.01 M $LiClO_4$, (k_{eq} + k_{N_3}) has the extremely large value of 510 × 10^{-7} sec.$^{-1}$. However, 10^7k_{eq} has the relatively normal value of 90 and represents less than one-fifth of the ionization rate constant. The enormous accelerating effect of lithium salts on ionization rate is illustrated by a 10^7k_{eq} value of 780, a value 17 times that in the absence of salt, when 0.00835 M $LiClO_4$ is added. As in other instances, lithium salts are very effective in introducing specific salt-promoted ionization.[8] The indications here and in slightly moist acetone solvent[7] are that the salt-promoted ionization leads predominantly to trityl azide while the salt-unassisted ionization leads to a relatively normal partition between ion pair return and chemical capture.

As nearly as we can diagnose Swain and Tsuchihashi's experiments, their acetone solvent was not as dry as ours, their k_{eq} in the absence of salt was too high, and LiN_3 appeared to suppress ^{18}O equilibration completely, at least partly because it strongly introduced salt-

(4) S. Winstein, *et al.*: (a) *Chem. Ind.* (London) 664 (1954); (b) *J. Am. Chem. Soc.*, **78**, 328 (1956); (c) *ibid.*, **80**, 169 (1958); (d) *ibid.*, **86**, 2072 (1964); (e) see, also, H. L. Goering and J. F. Levy, *ibid.*, **86**, 120 (1964).

(5) Acetone was dried with and distilled from molecular sieves [S. Smith, A. H. Fainberg, and S. Winstein, *ibid.*, **83**, 618 (1961)]. The solvent batches employed in this work analyzed for *ca.* 0.003% water when fresh and up to 0.01% water when nearly completely consumed.

(6) D. Darwish and E. A. Preston, *Tetrahedron Letters*, No. **1** and **2**, 113 (1964).

(7) S. Winstein and B. Appel, *J. Am. Chem. Soc.*, **86**, 2720 (1964).

(8) (a) S. Winstein, S. Smith, and D. Darwish, *ibid.*, **81**, 5511 (1959); (b) S. Winstein, E. Friedrich, and S. Smith, *ibid.*, **86**, 305 (1964).

promoted ionization. It was not that LiN_3 was such an effective trap for R^+X^- ion pairs, but instead it introduced another ionization path conducive to RN_3 formation. The LiN_3-promoted ionization may be visualized as producing an ion quadruplet[8] which prefers "covalent return" to RN_3 rather than RX.

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Ion Pairs and Dissociated Ions from Trityl Benzoate in Moist Acetone[1]

Sir:

Since trityl systems represent rather a structural extreme among possible RX substrates in solvolysis, trityl benzoate provides an important calibration point for our understanding of ion pairs and dissociated ions[2] in solvolysis and the gap between ionization and chemical capture rates.[3]

The behavior of 0.01–0.04 *M* carbonyl-^{18}O-labeled trityl benzoate in 95% acetone is illustrated in Table I.

TABLE I

^{18}O EQUILIBRIUM, SOLVOLYSIS, AND AZIDE FORMATION FROM TRITYL BENZOATE IN MOIST ACETONE

Σ(Salt),[a] 10^2M	Salt	10^2M	10^5k (sec.$^{-1}$) k_{eq}	k_t
	95% Me_2CO; 50.0°			
...	...	...	0.55	2.8
1.00	...	...	0.57	2.9
6.00	...	...		3.3
0.046	Bu_4NOBz	0.046		0.72
5.67	Bu_4NOBz	5.67		0.26
1.04	Bu_4NN_3	1.04		0
6.00	Bu_4NN_3	1.46		3.3[b]
	99.2% Me_2CO; 75.0°			
...	...	...	1.9[c]	0.32[d,e]
1.01	...	...		0.57[d]
1.02	BuNOBz	1.02		0.070
0.99	Bu_4NN_3	0.99	1.5	0.61[b,d]
0.98	LiN_3	0.98	3.3[c]	6.4[b]
1.03	$LiClO_4$	1.03	*ca.* 10[f]	23.8

[a] Σ(Salt) brought to listed value with Bu_4NClO_4. [b] k_{N_3} value. [c] ±0.3. [d] ±0.03. [e] Mean value; rate constant drifts up from *ca.* 0.24 to 0.36 over first 50% of the reaction, presumably due to benzoic acid catalysis; such catalysis increases with decreasing water content of the solvent. [f] One point rate.

The ^{18}O equilibration[3e-g] rate constant (k_{eq}) is considerably larger than in dry acetone,[4] but now this rate is much less than the rate of chemical capture represented by the titrimetric rate constant (k_t). Solvolysis shows strong common-ion rate depression,[2b] and it is possible to depress k_t to a very small fraction of the undepressed value by inclusion of Bu_4NOBz. Inclusion of Bu_4NN_3 quenches solvolysis essentially quantitatively, the azide-capture rate constant (k_{N_3}) being the same as k_t in the presence of an equivalent concentration of "inert" salt, Bu_4NClO_4. In 97.5% acetone, the solvolysis rate of trityl benzoate is lower, but the common-ion rate depression picture is similar to the one in 95% acetone.

Acetone containing 0.450 *M* water (99.2% acetone) is a solvent which still provides the simple common ion rate depression criterion for dissociated intermediates.[2b] However, it is not so far removed from dry acetone in ionizing and dissociating power but that it can furnish some insight into the behavior of substrates in the dry solvent. In the 99.2% acetone, k_{eq} is intermediate between the values in 95% and anhydrous acetone[4] solvents. Contrasting with the 95% solvent, k_{eq} is now greater than k_t by a factor of 6. The solvolysis in the 99.2% solvent still shows very strong common-ion rate depression. The inclusion of Bu_4NN_3 does not suppress ^{18}O equilibration seriously, but it quenches solvolysis essentially completely. The azide capture rate constant (k_{N_3}) is again equal to the appropriate solvolysis rate constant (k_t).

In the aqueous acetone solvents, as in anhydrous acetone,[4] we visualize that ^{18}O equilibration[3e-g] of trityl benzoate proceeds by way of an ion pair intermediate not easily capturable by added salts or water. Chemical capture (solvolysis or azide formation) proceeds very predominantly by way of trityl species which have become dissociated and no longer contain the OBz portion of the original ROBz molecule. If we take ($k_{eq} + k_t$) in the aqueous acetones and k_{eq} in anhydrous acetone as measures of the ionization rate constant[3] at zero or small tetrabutylammonium salt concentrations, we see that rate of chemical capture represents 3%, 14%, and 84% of the ionization rate constant in anhydrous, 99.2%, and 95% acetone solvents, respectively. We see that ion pair return can render an exchange or solvolysis rate of a trityl derivative much smaller than the ionization rate, just as in the case of various benzhydryl derivatives.[3] However, the indications are that ion pair return drops off in importance as water is added to acetone solvent sooner with trityl derivatives than with comparable benzhydryl analogs.

The gap between solvolysis and ionization rates of trityl benzoate is of interest in connection with correlations of solvolysis rates such as the *mY* correlation. In an earlier discussion[5] we inferred that ion pair return, rendering k_t values smaller than ionization rate constants, was one of the disturbances contributing to dispersion of log k_t *vs.* *Y* plots for systems such as α-phenylethyl and benzhydryl. The present observations on trityl benzoate and the earlier gaps between polarimetric k_α or ($k_{eq} + k_t$) values and the corresponding solvolysis rate constants for α-phenylethyl and benzhydryl derivatives[3] confirm the importance of this disturbance.

The effects of LiN_3 and $LiClO_4$ on the behavior of trityl benzoate in the 99.2% acetone solvent are of interest in connection with the report of Swain and Tsuchihashi[6] that LiN_3 suppresses ^{18}O equilibration of trityl benzoate in dry acetone with only small rate enhancement. In 99.2% acetone inclusion of 0.01 *M* LiN_3 increases greatly the ionization rate constant, ($k_{eq} + k_{N_3}$) being more than four times as large as the

(1) Research sponsored by the National Science Foundation.

(2) S. Winstein, *et al.*: (a) *Chem. Ind.* (London), 664 (1954); (b) *J. Am. Chem. Soc.*, **78**, 328 (1956); (c) *ibid.*, **80**, 169 (1958); (d) *ibid.*, **86**, 2072 (1964).

(3) (a) S. Winstein, J. S. Gall, M. Hojo, and S. Smith, *ibid.*, **82**, 1010 (1960); (b) S. Winstein, M. Hojo, and S. Smith, *Tetrahedron Letters*, **No. 22** 12 (1960); (c) Y. Pocker, *Proc. Chem. Soc.*, 140 (1961); (d) S. Winstein, A. Ledwith, and M. Hojo, *Tetrahedron Letters*, **No. 10**, 341 (1961); (e) H. L. Goering and J. F. Levy, *ibid.*, **No. 18**, 644 (1961); (f) H. L. Goering, R. G. Boidy, and J. F. Levy, *J. Am. Chem. Soc.*, **85**, 3059 (1963); (g) H. L. Goering and J. F. Levy, *ibid.*, **86**, 120 (1964).

(4) S. Winstein and B. R. Appel, *ibid.*, **86**, 2718 (1964).

(5) S. Winstein, A. H. Fainberg, and E. Grunwald, *ibid.*, **79**, 4146 (1957).

(6) C. G. Swain and G. Tsuchihashi, *ibid.*, **84**, 2021 (1962).