Table I. Methanolysis of *p,p'*-Dimethoxybenzhydryl Mesitoate at 26 ± 1°

No.	Ester concn, *M*	Added salts (Concn, *M*)	Method[a]	k, sec^{-1}
1	5×10^{-5}	None	Uv	$6.0 (\pm 0.3) \times 10^{-4}$
2	5×10^{-5}	$NaClO_4$ (5.0×10^{-4})	Uv	$6.1 (\pm 0.3) \times 10^{-4}$
3	5×10^{-5}	NaN_3 (5.0×10^{-4})	Uv[e]	$6.0 (\pm 0.3) \times 10^{-4}$
4	8×10^{-5}	NaN_3 (2.0×10^{-3}) *p*-NO_2PhOK (1.2×10^{-4})	Vis[e]	$6.0 (\pm 0.3) \times 10^{-4}$
5	7.7×10^{-5}	*p*-NO_2PhOK (1.2×10^{-4})	Vis[b]	$6.41 (\pm 0.05) \times 10^{-4}$
6	7.7×10^{-5}	$NaClO_4$ (1.1×10^{-2}) *p*-NO_2PhOK (1.2×10^{-4})	Vis[b]	$6.8 (\pm 0.1) \times 10^{-4}$
7	7.7×10^{-5}	NaMes[c] (1.0×10^{-2}) *p*-NO_2PhOK (1.2×10^{-4})	Vis[b,d]	$5.25 (\pm 0.1) \times 10^{-4}$

[a] Uv, runs followed at 244–255 nm; vis, runs followed at 390 nm. [b] These runs utilized a thermostated cell holder which gave temperature control of better than ±0.1°. [c] Sodium mesitoate. [d] In this run, the conversion of *p*-nitrophenoxide is not quantitative. The rate constant was calculated from the observed concentration of phenoxide and the known pK's of mesitoic acid and of *p*-nitrophenol in methanol. [e] The spectrum of the product solution showed no changes for 24 hr, clearly indicating the stability of the azide product in the solution.

Table II. Selectivities in Azide Trapping in the Methanolysis of *p,p'*-Dimethoxybenzhydryl Mesitoate[a]

Series[b] no.	$[NaN_3]$, *M*	Compd[c] analyzed	Buffer[d] concn, *M*	% RN_3/(% $ROCH_3$·$[NaN_3]$)[e]
1	1.0×10^{-4}	Both	9.0×10^{-3}	1350
1	2.5×10^{-4}	Both	9.0×10^{-3}	1230
1	5.0×10^{-4}	Both	9.0×10^{-3}	1090
2	6.0×10^{-5}	RN_3	9.0×10^{-3}	1350
2	1.2×10^{-4}	RN_3	9.0×10^{-3}	1240
2	1.0×10^{-3}	$ROCH_3$	9.0×10^{-3}	1020
2	5.0×10^{-3}	$ROCH_3$	9.0×10^{-3}	990
3	9.7×10^{-6}	RN_3	9.0×10^{-3}	1850
3	2.4×10^{-5}	RN_3	9.0×10^{-3}	1400
3	4.8×10^{-5}	RN_3	9.0×10^{-3}	1340
3	9.7×10^{-5}	RN_3	9.0×10^{-3}	1330
4	1.0×10^{-3}	$ROCH_3$	9.0×10^{-3}	950
4	1.0×10^{-3}	$ROCH_3$	4.5×10^{-3}	1020
4	1.0×10^{-3}	$ROCH_3$	2.3×10^{-3}	1040
4	1.0×10^{-3}	$ROCH_3$	9.0×10^{-4}	1120

[a] Initial ester concentration, 1.0×10^{-4} *M*; ionic strength = 9.0×10^{-3} *M*. [b] The runs within each series were performed simultaneously. Since solutions were not thermostated and ambient temperature varies wildly in Buffalo summers, slight discrepancies between series may be attributed to temperature variation. [c] In series 1, duplicate runs were made at each azide ion concentration, and both products were determined by isotope dilution. The isolated materials accounted for 95 ± 1% of the total activity added to the solutions. This figure for the purity of the tritiated ester was used for those runs in which only one of the products was actually isolated. [d] The solutions were buffered with triethylamine–triethylammonium mesitoate in a 1:1 ratio. Thus the buffer concentration is equal to the concentration of triethylammonium mesitoate. In the runs of series 4, ionic strength was maintained by addition of sodium perchlorate. [e] Units of M^{-1}.

material was recrystallized from pentane at −20°, using Craig Tube technique, until constant activity was obtained.

The results of these experiments are shown in Table II and Figure 1.

The variation of the quantity (% RN_3)/([% $ROCH_3$]·$[NaN_3]$) with concentration of NaN_3 shows clearly that at least two intermediates with different selectivities are being trapped by azide ion.

The data are consistent with Winstein's solvolysis scheme[6] involving an ion pair and a free carbonium ion, both of which may react with either methanol or azide ion. The quantitative evaluation of the selectivities of the two intermediates from the present data depends on details of the kinetic scheme assumed, but it is clear that the ion pair is considerably less selective than is the carbonium ion.

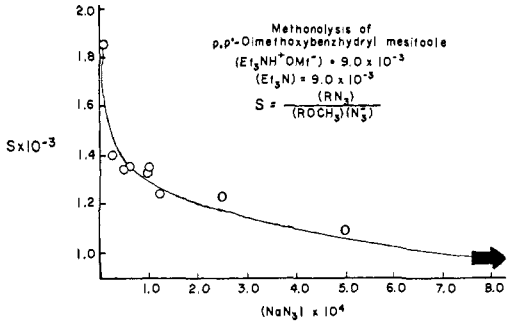

Figure 1. Plot of the quantity S (M^{-1}) = (% RN_3)/(% $ROCH_3$·$[NaN_3]$) *vs.* $[NaN_3]$ (*M*).

It seems quite likely that a major factor influencing the reactivity–selectivity relationship for "SN1" solvolyses is a variation in the proportion of product arising from free ions and ion pairs from various reactants. It is also clear, however, that the interpretation of selectivities determined from runs at only one azide concentration could be misleading.

Our studies of the trapping of SN1 intermediates are continuing.

Acknowledgment. I wish to express my appreciation to Dr. Dupont Durst of this department for many helpful suggestions and discussions concerning the isotope labeling and counting techniques used in the present study.

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(6) S. Winstein, P. E. Klinsdinst, Jr., and G. C. Robinson, *J. Amer. Chem. Soc.*, **83**, 885 (1961), and earlier papers cited therein.

The Directed Mixed Ester Condensation of Two Acids Bound to a Common Polymer Backbone

Sir:

In previous reports from this laboratory, it has been demonstrated that a cross-linked polymer exerts a strong immobilizing effect on molecules covalently bound to it. The effect was illustrated by the directed

Table I. The Condensation of Two Acids Bound to a Common Polymer Backbone

Enolizable acid (**2**)	Concn of **2** in **5**, mmol/g	Nonenolizable acid **4**	Concn of **4** in **5**, mmol/g	Product, mp, °C (lit.)	Yield,[f] %	Yield of analogous reaction in solution, %
$CH_3(CH_2)_6CO_2H$	0.20	*p*-$ClC_6H_4CO_2H$	0.60	*p*-$ClC_6H_4CO(CH_2)_6CH_3$,[a] 58–59 (57.5–58)	35	30
$C_6H_5CH_2CO_2H$	0.11	$C_6H_5CO_2H$	0.52	$C_6H_5COCH_2C_6H_5$,[b] 56 (55–56)	45	
$C_6H_5(CH_2)_2CO_2H$	0.10	$C_6H_5CO_2H$	1.01	$C_6H_5CO(CH_2)_2C_6H_5$,[c] 72 (72–73)	85	42
$CH_3(CH_2)_4CO_2H$	0.07	$C_6H_5CO_2H$	1.71	$C_6H_5CO(CH_2)_4CH_3$[d] 23–24 (24.7°)	95	
$C_6H_5(CH_2)_2CO_2H$	0.04	*p*-$ClC_6H_4CO_2H$	1.70	*p*-$ClC_6H_4CO(CH_2)_2C_6H_5$,[e] 76–77 (78)	85	20

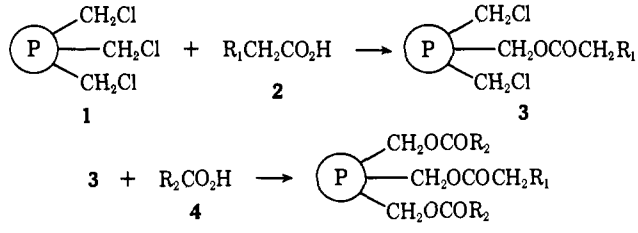
[a] L. N. Nikolenko and K. K. Babievskii, *Zh. Obshch. Khim.*, **25**, 2231 (1955). [b] C. F. H. Allen and W. E. Barker in "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1959, p 156. [c] D. Bar and Mme. Erb-Debruyne, *Ann. Pharm. Fr.*, **16**, 235 (1958). [d] F. L. Breusch and M. Oguzer, *Chem. Ber.*, **87**, 1225 (1954). [e] H. Burton and C. K. Ingold, *J. Chem. Soc.*, 904 (1928). [f] Based on the amount of the pure ketone relative to that of moieties of **2** in **5**.

monoacylation[1] and monoalkylation[2] of polymer esters. It was shown that at sufficiently low concentration and temperature, polymer-bound molecules behave virtually as in an infinitely dilute solution.

In this communication we wish to report on the interaction of *two* compounds bound to the same polymer bead occurring at the other extreme of *high* concentrations of bound species. Apparently under these conditions a close mutual proximity is imposed on some of the bound molecules by the rigid polymeric lattice. The selectivity of such "intrapolymeric" reactions and the high yields obtainable will be illustrated by the mixed ester condensation of two carboxylic acids bound to a common polymer backbone.[3]

A polymer, **3**, containing a low concentration of moieties of an enolizable acid[4] was obtained by treating chloromethylated polystyrene–2% divinylbenzene (**1**)[5] with a limited amount of acid **2**[6] (see Scheme I). After thorough

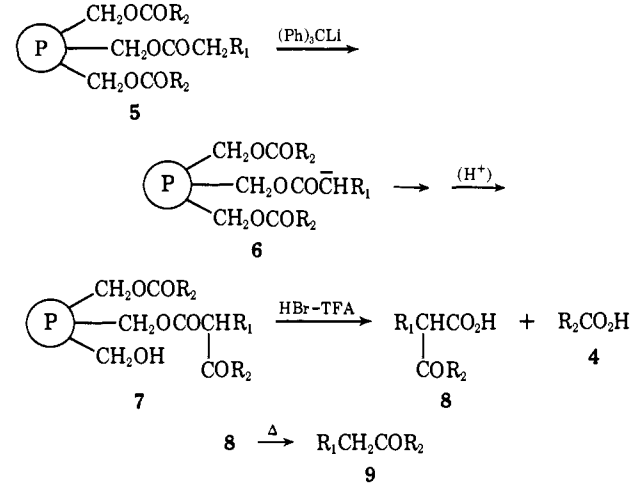
Scheme I



washing and drying, polymer **3** was treated with an excess of a second, nonenolizable acid, **4**, to yield a polymer, **5**, which contained a relatively high concentration of ester moieties of **4**[4] (see Table I).

The ester condensation (Scheme II) was carried out by suspending polymer **5** in dry toluene–20% 1,2-dimethoxyethane under argon, and adding a solution of tritylllithium (1 equiv, corresponding to moieties of **2**) in tetrahydrofuran[7] at room temperature. The red color of the base disappeared within 2 min. After a further 5-min stirring the reaction mixture was neutralized and the polymer filtered and washed thoroughly. Cleavage of the benzyl ester groups in polymer **7** was effected by HBr in trifluoroacetic acid (TFA) (2 hr at room temperature). The polymer was filtered and washed and the filtrate evaporated. The residue was dissolved in toluene and refluxed for 30 min to effect decarboxylation of the β-keto acid, **8**. In every case a single ketone, **9**, and unreacted starting acids were the only products obtained (thin layer chromatography [tlc]).

Scheme II



The ketones were purified by preparative tlc and identified by their melting points and by nmr, ir, and mass spectra. Results are summarized in Table I.

Similar reactions in solution were carried out in which mixtures of an enolizable and a nonenolizable benzyl ester were treated with tritylllithium. Concentrations, mole ratios, temperatures, and reaction times were identical with those used on the polymer. As a rule yields of reactions in solution were lower (see Table I). Moreover, the mixtures obtained upon ester cleavage (HBr in TFA) and decarboxylation were of much greater complexity, consisting of at least six major components (tlc). It will be noted that in reactions on the polymer the yield of ketone **9** increases with increasing ratio of nonenolizable to enolizable ester. A similar increase

(1) A. Patchornik and M. A. Kraus, *J. Amer. Chem. Soc.*, **92**, 7587 (1970).
(2) M. A. Kraus and A. Patchornik, *Israel J. Chem.*, **9**, 269 (1971).
(3) The *self*-condensation of a polymer ester was mentioned previously.[1]
(4) Determined as described before.[1]
(5) Bio-Rad, SX-2; chlorine content, 5–10%.
(6) R. B. Merrifield, *J. Amer. Chem. Soc.*, **85**, 2149 (1963). The yield of this step is only about 30% but unreacted acid is easily recovered.
(7) P. Tomboulian and K. Stehower, *J. Org. Chem.*, **33**, 1509 (1968).

in ratio in solution did not improve the yield beyond 42%.[8]

Apparently in reactions on the polymer, at sufficiently high ratios the majority of enolizable ester groups (separated from each other by the polymer lattice) have some nonenolizable ester moieties in their close vicinity.

In order to confirm the mechanism proposed in Scheme II, namely the interaction of ester groups within the same polymer bead, equal amounts of two different batches of polymer, each containing a different ester, were mixed and treated with tritylllithium for 10 min. One batch contained *p*-chlorobenzoate groups (1 mmol/g), the other 3-phenylpropionate (0.1 mmol/g). Upon cleavage and work-up as described above, no ketones whatsoever could be detected (tlc), the only products being unreacted starting acids. This result indicates that the condensations described are truly intrapolymeric and that no mechanism such as cleavage followed by condensation is involved.[11]

Acknowledgment. Stimulating discussions with C. Yaroslavsky and B. Amit are gratefully acknowledged.

(8) The mixed condensation of aliphatic with aromatic esters is well documented in the literature.[9] Though in some cases good yields of the condensation product are reported, they do not usually exceed 60%.[10] Self-condensation of the aliphatic ester is often difficult to avoid.

(9) C. R. Hauser and B. E. Hudson, Jr., *Org. React.*, 1, 266 (1942).

(10) E. E. Royals, J. C. Hoppe, A. D. Jordan, Jr., and A. G. Robinson III, *J. Amer. Chem. Soc.*, 73, 5857 (1951); E. E. Royals and D. G. Turpin, *ibid.*, 76, 5452 (1954).

(11) Preliminary attempts to react polymer-bound acid **2** with an excess of a *soluble* ester of **4** have as yet been unsuccessful.

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Preequilibrium Complex Formation and Nucleophilic Addition (and Its Position) As Factors in Flavin-Catalyzed Oxidations

Sir:

Two-electron hydrogen transfer in flavin-catalyzed biological oxidation reactions can be envisaged as involving a hydride ion plus a proton or, alternatively, two protons plus two electrons.[1a] Recent reviews[1a,b] have centered attention on the possible universality of the latter process in which flavin–substrate adduct formation is involved (*e.g.*, eq 1). Although alkaline hydrolysis opens some isoalloxazines at the 10a position,[2] covalent adducts at the 4a position are known from photochemical oxidative decarboxylation[3] and the latter position has been proposed[1a,b,4] as the reactive electrophilic center in nonphotochemical (dark) reactions (*e.g.*, eq 1).

Since an alternative mechanism involving a charge-transfer complex[5,6] has been suggested for oxidation of NADH by flavins, we have set about to determine the importance of preequilibrium complex formation as well as the steric availability of the 4a and 10a positions to the dark reactions of flavins. To this end,

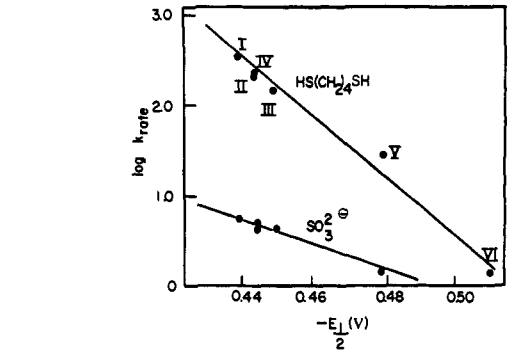
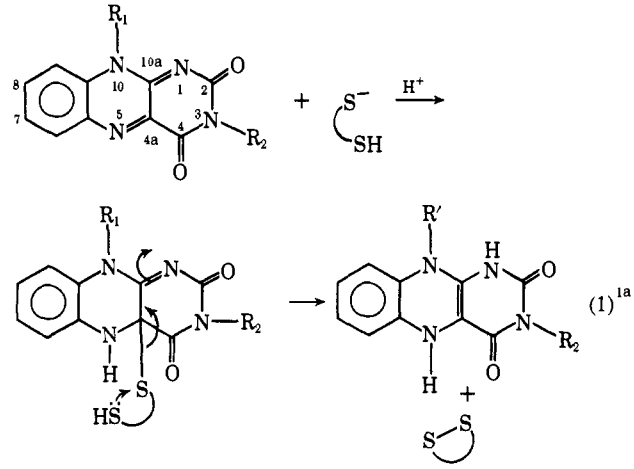


Figure 1. Linear free-energy correlations with polarographic half-wave potentials of rates of reaction of isoalloxazines I–VI with 1,4-butanedithiol and sulfite ion.



reactions of isoalloxazines I–VI (see Table I) have been investigated.[7] Molecular models of I show that (i) approach to the 10a position is hindered above and below the plane of the isoalloxazine ring by the *o*-methyl substituents, and (ii) formation of a face-to-face complex involving that portion of the isoalloxazine ring adjacent to the 10 position is hindered. Both of these steric effects decrease in the order I > II > III > IV = V = VI. In order to assess the effectiveness of the blocking of the 10a position in I, its hydrolysis was investigated (pH 10.5–13.75; eq 2). The first step of the reaction is reversible and I can be regenerated (anaerobic) in 100% yield on acidification of the kinetic

Table I

	R_1	R_2
I	2,6-$(CH_3)_2C_6H_3$	CH_3
II	2-$CH_3C_6H_4$	CH_3
III	C_6H_5	CH_3
IV	CH_3	CH_3, 7-Cl
V	CH_3	CH_3
VI	CH_3	H, 7,8-$(CH_3)_2$

(1) (a) G. A. Hamilton, *Progr. Bioorg. Chem.*, 1, 83 (1971); (b) P. Hemmerich, *Vitam. Horm.*, 28, 467 (1970).

(2) D. E. Guttman and T. E. Platek, *J. Pharm. Sci.*, 56, 1423 (1967).

(3) W. H. Walker, P. Hemmerich, and V. Massey, *Eur. J. Biochem.*, 13, 258 (1970).

(4) L. E. Brown and G. A. Hamilton, *J. Amer. Chem. Soc.*, 92, 7225 (1970).

(5) I. Isenberg, S. L. Baird, and A. Szent-Györgyi, *Proc. Nat. Acad. Sci. U. S.*, 47, 245 (1961).

(6) E. M. Kosower (in "Flavins and Flavoproteins," E. C. Slater, Ed., Elsevier, New York, N. Y., 1965, p 1) has pointed out that the evidence offered in support of such a complex is questionable.

(7) Compounds I–V were synthesized by standard methods, starting with *o*-fluoronitrobenzenes; see J. P. Lambooy, *Heterocycl. Compounds*, 9, 136, 148 (1967). VI was a gift from Dr. H. A. Harbury.