TABLE I

EXCHANGE REACTIONS CATALYZED BY THE P ENZYME

In experiment A, the complete system contained 1.3 μM. succinyl CoA, 50 μM. TRIS *p*H 7.4, 5 μM. C^{14}-succinate, 0.17 mg. enzyme protein (5.2 units), 5 μM. PO_4 and 5 μM. $MgCl_2$; 2.5 μM. ADP added when indicated; final volume 1.0 ml.; incubated 6 minutes at 20°. After incubation, NH_2OH was added and the succinohydroxamic acid separated from succinate by chromatography on Dowex 1. About 0.90–1.17 μM. of succinohydroxamic acid was isolated from the column. The specific radioactivity of the succinate after incubation varied between 11800 and 12200 c.p.m./μM. In experiment B, the complete system contained 1.5 μM. P^{32}-labeled ADP, 4.5 μM. ATP, 50 μM. TRIS *p*H 7.4, 5 μM. $MgCl_2$, 0.012 mg. enzyme protein (0.34 unit), 10 μM. of succinate and 0.7 μM. of CoA-SH or derivatives; 5 μM. GSH added when indicated; final vol. 1.0 ml.; incubated 10 minutes at 20°. The specific radioactivity of the ADP after incubation varied between 11,000 and 12,000 c.p.m./μM.

A			B		
Components	Succinohydroxamic acid, c.p.m./μM.	Exchange, %	Components	ATP, c.p.m./μM.	Exchange, %
Complete	1663	14.4	Complete	760	22.8
Complete + ADP	1208	10.4	+ Succinate	790	23.8
No phosphate	629	5.4	+ CoA	360	10.9
No Mg^{++}	45	0.4	+ Acetyl CoA	770	23.3
			+ Oxidized CoA	710	21.4
			+ GSH	750	22.6
			+ GSH + Pantethine[a]	780	23.4
			No enzyme	84	

[a] Kindly supplied by Dr. E. E. Snell.

which could lead to labeling of ATP in the presence of P_{32}-ADP.[8] That the exchange is indeed catalyzed by the P enzyme is further supported by the finding that a loss in the ADP–ATP reaction parallels the loss in the over-all activity in aged enzyme preparations.

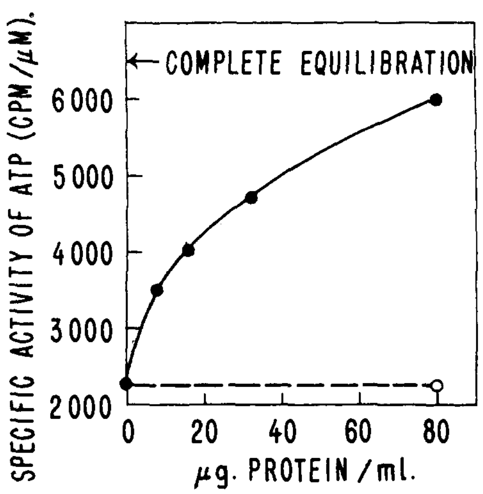

Fig. 1.—Rate of ADP–ATP exchange as a function of P enzyme concentration. The complete system contained 1.0 μM. P^{32}-ADP, 1.0 μM. ATP, 50 μM. TRIS *p*H 7.4, 5.0 μM. $MgCl_2$; final volume 1.0 ml.; incubated 10 minutes at 20° (open circle, system without $MgCl_2$). The enzyme solution had 44 units/ml., and 3.2 mg. protein/ml.; it was dialyzed free of phosphate prior to the experiment. The specific radioactivity of ADP at the end of incubation varied between 6000 and 8400 c.p.m./μM. in the individual experiments.

The results of the isotope experiments and the failure to obtain indications for the formation of a free intermediate are consistent with the scheme

$$\text{Enz} + \text{ATP} \underset{}{\overset{(\text{Mg}^{++})}{\rightleftarrows}} \text{enz-P} + \text{ADP} \qquad (2)$$

$$\text{Enz-P} + \text{CoA} \rightleftarrows \text{enz (P-CoA)} \qquad (3)$$

$$\text{Enz (P-CoA)} + \text{succinate} \overset{(\text{Mg}^{++})}{\rightleftarrows} \text{enz} + \text{succinyl-S-CoA} + \text{P} \qquad (4)$$

The occurrence of succinyl P as a bound intermediate (as represented by the reaction sequence 2, 3a, 4a) cannot be ruled out even though the enzyme fails to catalyze an exchange of C^{14}-succinate with synthetic succinyl P.[4,9]

$$\text{Enz-P} + \text{succinate} \rightleftarrows \text{enz (succinyl P)} \qquad (3a)$$

$$\text{Enz (succinyl P)} + \text{CoA} \rightleftarrows \text{enz} + \text{succinyl-S-CoA} + \text{P} \qquad (4a)$$

In a further attempt to decide between the two alternate schemes, the effect of added substrates on the ADP-ATP exchange was investigated. As shown in Table I, succinate has no significant effect on the rate of exchange. In contrast, CoA markedly inhibits the reaction. That the CoA effect is specific, is shown by the absence of inhibition by equivalent amounts of oxidized CoA, acetyl CoA or pantetheine. The results would seem to favor the reaction sequence 2 to 4. The mechanism of reaction 1 is basically different from that of the ATP-CoA-acetate reaction which involves an enzyme-AMP intermediate.[10]

We are indebted to Mrs. Suzanne Loebl for technical assistance.

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[8] The best preparations of the spinach enzyme contain traces of ATPase. It has been shown that myosin ATPase does not catalyze this exchange at a significant rate.

(9) S. Kaufman, synthesis of succinyl monophosphate, to be published.

(10) M. E. Jones, F. Lipmann, H. Hilz and F. Lynen, THIS JOURNAL, **75**, 3285 (1953).

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RELATIVE IMPORTANCE OF STERIC AND INDUCTIVE EFFECTS IN S_N2 DISPLACEMENT REACTIONS

Sir:

It is well known that the reactivity of saturated isomeric alkyl halides in typical S_N2 type reactions varies in the order primary > secondary > tertiary. The decrease in reactivity as alkyl groups are added to the carbon atom containing the halogen atom has been explained as being due to (a) the inductive effect of the alkyl groups and/or (b) a steric effect whereby the extra alkyl groups hinder the entering group from attacking from the rear. There has been no way of determining the relative importance of inductive and steric effects in this type of reaction.[1]

We have now obtained evidence which shows the inductive effects to be of little, if any, importance

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(1) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 409–410.

and the steric effect to be the major factor. Phenacyl chloride reacts with iodide ion in acetone 9,000 times more rapidly than does *n*-butyl chloride. If methyl groups are successively substituted into the phenacyl side chain, the resulting secondary and tertiary halides should still be extremely reactive if inductive effects are the deciding factor, but the reactivity should decrease many fold for each methyl group substituted if steric effects are of major importance. The argument for the first statement, assuming inductive effects to be of major importance, is that the increase in electron density at the reacting carbon atom due to the electron releasing ability of the methyl groups must be insignificant compared to the decrease in electron density due to the adjacent carbonyl group. Otherwise a carbonyl group adjacent to a $-CH_2Cl$ group would not increase the SN2 reactivity nine thousand-fold whereas a methyl group in the same position decreases the reactivity ten to twenty-fold at most (methyl *versus* ethyl halides in various S_N2 reactions).[2] Accordingly, the substitution of methyl groups into the phenacyl side chain should not change the electron density at the reacting carbon atom appreciably, and the reactivity should show little change as one progresses from the primary to the secondary to the tertiary keto halides. On the other hand, if steric effects are deciding, the secondary halide should react much more slowly than the primary halide (as happens when one goes from *n*-butyl chloride to *sec*-butyl chloride in typical SN2 reactions) and the tertiary halide should be even less reactive. This is the way the reactivities of phenacyl chloride, α-chloropropiophenone and α-chloroisobutyrophenone were, in fact, found to be. All of our data have been obtained at 0°, and are summarized in Table I.

TABLE I

SECOND-ORDER RATE CONSTANTS FOR ORGANIC HALIDE REACTING WITH SODIUM OR POTASSIUM IODIDES IN DRY ACETONE AT 0°[a]

Compound	Time for 50% reaction if solution 0.1 *M* in each reactant	*k* in liters moles^{-1} hours^{-1}
n-Butyl chloride	111 days	0.00375[b]
sec-Butyl chloride	5 years	<0.0026[b]
tert-Butyl chloride	6 years	<0.0002[b]
Phenacyl chloride	18 min.	33.6[b]
α-Chloropropiophenone	50 hours	0.200
α-Chloroisobutyrophenone	11 years	<0.0001
Chloromethyl *p*-tolyl sulfone	No measurable reaction[c]	

[a] The reaction rates were determined by the electrometric titration with silver nitrate of the unreacted iodide ion isolated from solutions originally 0.1 *M* in each reactant. That the reactions were second order was also established by paired runs 0.2 *M* in one reactant and 0.1 *M* in the other in the case of phenacyl chloride and α-chloropropiophenone. [b] Previous values reported[3] for the butyl chlorides and phenacyl chloride with sodium iodide or potassium iodide in acetone are: *n*-C_4H_9Cl, 0.040 at 50°, 0.10 at 60°; *sec*-C_4H_9Cl, 0.0022 at 60°; *t*-C_4H_9Cl, 0.0018 at 60°; phenacyl chloride, 22 at 0°. [c] Several workers have previously reported α-halo sulfones to be inert, but no quantitative data are available.

The above data show that the relative reactivities of primary, secondary and tertiary chlorides in the phenacyl series are 1:0.006:0.000003. This is a more pronounced change than is encountered in the butyl chloride series, and, in view of the previous argument, appears to provide conclusive evidence that the decrease in reactivity as one goes from primary to secondary to tertiary halides is almost entirely due to a steric effect. The two thousand-fold decrease in reactivity as one goes from the secondary to the tertiary chloride is outstanding, and suggests that the keto chloride rate values illustrate the relative reactivities of primary, secondary and tertiary halides in a reaction going entirely by the SN2 mechanism better than the usually given butyl chloride rate values. We are now studying more carefully the reaction of *t*-butyl chloride with sodium iodide to determine if an SN1 mechanism contributes appreciably to its relatively high reactivity.

If inductive effects are of little importance, one wonders why phenacyl chloride is as reactive as it is. Several investigators[4] have suggested that an approaching nucleophilic group can form a loose bond with the carbon atom of the polarized carbonyl group in the transitional state and thus be in a sterically favorable position for the ensuing nucleophilic attack on the alpha carbon. In chloromethyl *p*-tolyl sulfone, this cannot happen unless the valence shell of the sulfur is expanded, and an unreactive halide is the result. The unreactivity of this compound provides additional evidence of the minor role played by inductive effects.

Studies are underway on solvent and temperature effects and the more accurate determination of the *k* values of the slow reactions.

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[2] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 154.

[3] J. B. Conant and W. R. Kirner, THIS JOURNAL, **46**, 232 (1924); J. B. Conant and R. E. Hussey, *ibid.*, **47**, 476 (1925).

[4] Priority for this suggestion apparently belongs to J. W. Baker. *J. Chem. Soc.*, 445 (1938).

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SOME MAGNETIC CONSEQUENCES OF CHEMISORPTION ON SUPPORTED NICKEL CATALYSTS

Sir:

Michel[1] has shown that nickel–silica catalysts give thermomagnetic curves as in Fig. 1(3).

We may consider such curves as being made up of a large number of steps, each step representing a nickel particle in which the Curie temperature, T_c, is related, as a first approximation, to the *average* number of nearest nickel neighbors, *z*, by the expression $T_c/631° = z/12$, where 631° and 12 are, respectively, the Curie temperature (°K.) and the coördination number in massive nickel.

The average quantity *z* is related to particle size. Thus any point σ_{T_c} on the thermomagnetic curve represents that fraction of total reduced nickel present in particles in excess of a determinable size.

With this information we may construct dis-

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[1] A. Michel, R. Bernier and G. LeClerc, *J. chim. phys.*, **47**, 269 (1950).