the other two-thirds forms ethylene and carbon monoxide in the usual manner.

In a recent communication[14] the formation of *cis*-1,2-dimethylcyclopropane from methylene and *cis*-2-butene in the gas phase is reported. A transition state which is an approximately isosceles triangle is proposed, as we suggest for the reaction with ketene. In the analogous reaction with ethylene, only propylene[2,3] is obtained. The explanation is that the lifetime of the "hot" cyclopropane is much shorter than that of the 1,2-dimethylcyclopropane due to the numerous internal degrees of freedom in the latter. The conclusion of Skell and Woodworth[14] that their results require methylene to be in the singlet electronic state is not binding unless it is shown, as we have done above, that the reaction probability is very high. Even this proves only that the photochemically formed methylene radicals are in the singlet state. Their ground state might still be triplet.

(14) P. S. Skell and R. C. Woodworth, THIS JOURNAL, **78**, 4496 (1956).

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RECEIVED OCTOBER 2, 1956

THE EFFECT OF SOLVENT ON CHARGE-TRANSFER COMPLEX SPECTRA

Sir:

In view of previous indications that pyridinium iodide charge-transfer complex absorption moved to longer wave lengths in solvents of lower solvating ability,[1] the effect of various mixtures of methanol, ethanol, and acetone with water on the charge-transfer (c-t.) band of 1-methyl-4-carbomethoxypyridinium iodide has been investigated. The c-t. band is quite sensitive to the solvent, and when spectral transition energies (E_T) (in kcal./mole) for the band *maximum* are plotted against the Y values[2a] reported by Fainberg and Winstein,[2c] straight lines are obtained over most of the available range (Y = −2.76 to +0.80) (Fig. 1). Although different slopes result from a change in the organic component, these converge when extrapolated, and the value of E_T at the Y for water (+3.49) is the *same for all three* (94.1 ± 0.1 kcal./mole), well within the estimated experimental error (0.25). Interesting deviations occur at very low water concentrations.[3]

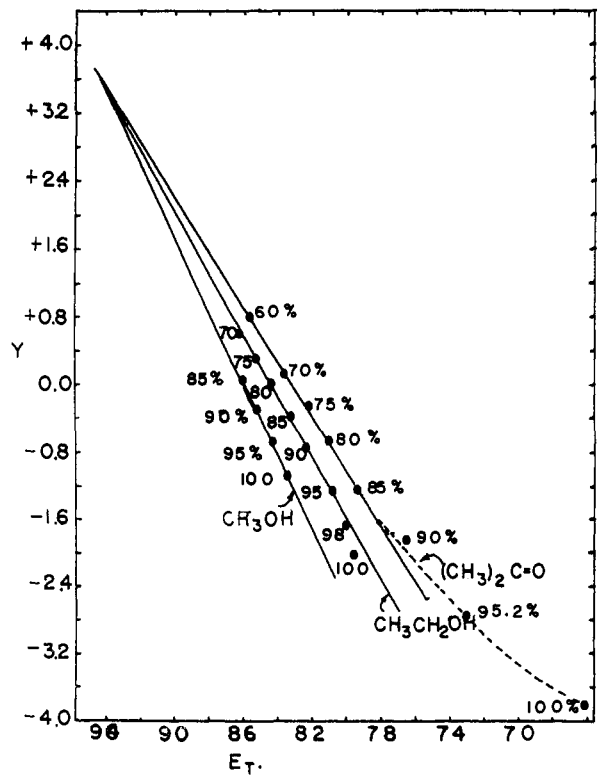
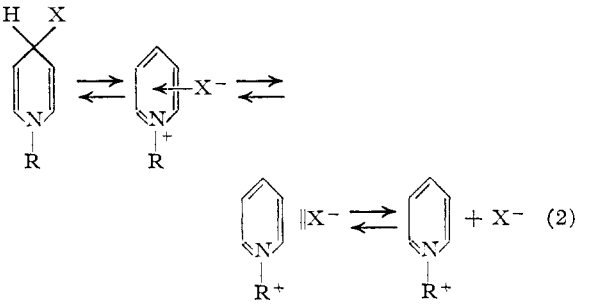


Fig. 1.—Y *vs.* E_T: the numbers represent the volume percentage of the organic component. The Y value for 100% acetone is an extrapolation from the data of Winstein and Fainberg, ref. 2c.

There are several significant implications of this relationship. The recent excellent work of Winstein and his group on "special salt effects" has been explained in terms of the solvolysis scheme[4] Y values are an empirical measure of the effect of solvent upon the transition state for solvolysis.[2]

$$\underset{\text{alkyl halide}}{RX} \rightleftharpoons \underset{\text{transition state}}{R\overset{\delta+}{\cdots}X\overset{\delta-}{}} \rightleftharpoons \underset{\text{"intimate ion-pair"}}{R^+X^-} \rightleftharpoons \underset{\text{solvent separated ion-pair}}{R^+\|X^-} \rightleftharpoons \underset{\text{dissociated ions}}{R^+ + X^-} \quad (1)$$

If one includes the fact that certain nucleophiles add to the pyridinium ring[5] along with the information that both solvent-separated ion pairs[1b] and dissociated ions[6] are in equilibrium with the c-t. complex, one may write



The shift of the c-t. band in less polar media is due to the relative destabilization of the charged ground state as compared with the "neutral" excited state.[1,7,8]

(1) (a) E. M. Kosower and P. E. Klinedinst, Jr., THIS JOURNAL, **78**, 3493 (1956); (b) E. M. Kosower and J. C. Burbach, *ibid.*, **78**, in press (1956).

(2) (a) E. Grunwald and S. Winstein, *ibid.*, **70**, 846 (1948); (b) S. Winstein, E. Grunwald and H. W. Jones, *ibid.*, **73**, 2700 (1951); (c) A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2770 (1956).

(3) Even with the somewhat limited range of solvents used, plots against $(D-1)/(2D+1)$ are unsatisfactory in several respects.

(4) S. Winstein, *Experientia Supplementum*, **II**, 152 (1955).

(5) N. O. Kaplan, *Rec. Chem. Progress*, **16**, 177 (1955).

(6) E. M. Kosower, THIS JOURNAL, **77**, 3883 (1955).

(7) This straightforward explanation is oversimplified and some of the complications are indicated in the next paragraph.

(8) For a discussion of the theory of c-t. complexes, see R. S. Mulliken, *ibid.*, **74**, 811 (1952); *J. Phys. Chem.*, **56**, 801 (1952).

The parallelism between E_T and Y as well as the obvious similarity between equations (1) and (2) suggests that the first intermediate in solvolysis, the "intimate ion-pair" may derive a portion of its binding energy from charge-transfer forces, and that charge-transfer may contribute to the stabilization of the transition state for its formation. Simple electrostatic attraction *cannot account* for the light absorption of the pyridinium iodide complexes; in addition, theory[8] implies that the behavior of E_T with solvent change is, in part, a reflection of a change in the degree of bonding between the pyridinium ion and the iodide ion. The empirical constant, Y, is therefore a measure of the total solvent effect, summing changes in binding as well as changes in solvation for the pyridinium iodide complexes. The expression of the first ion-pair (and of the intermediate of Streitwieser and Doering)[9] as a c-t. complex is a formulation which may permit application of the theory already available to solvolysis problems.[8] The correspondence of the equations (1) and (2) also implies that the complex *is* the intermediate in additions to the pyridinium ring,[10] and therefore, in nucleophilic aromatic substitution as well, especially of the "activated" type.[11] The study of the interaction of ethoxide ion with polynitroaromatics points in the same direction.[12]

The E_T values offer an interesting way of investigating solvent "ionizing power" with respect to structure, salt effects, and temperature, and is of special utility for those solvents which are unsuitable for the usual kinetic measurements.

(9) *Cf.* A. Streitwieser, Jr., *Chem. Rev.*, **56**, 570 (1956).

(10) E. M. Kosower, THIS JOURNAL, **78**, 3497 (1956).

(11) The results of Ross with aniline and 2,4-dinitrochlorobenzene are probably due to a complex which has the incorrect orientation for substitution; S. D. Ross, *et al.*, *ibid.*, **76**, 3000 (1954); **77**, 4916 (1955).

(12) J. B. Ainscough and E. F. Caldin, *J. Chem. Soc.*, 2528, 2540, 2546 (1956).

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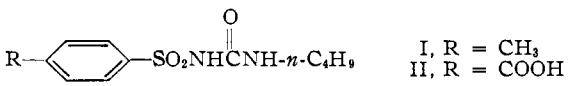
RECEIVED SEPTEMBER 7, 1956

THE STRUCTURE OF A URINARY EXCRETION PRODUCT OF 1-BUTYL-3-*p*-TOLYLSULFONYLUREA (ORINASE)

Sir:

Recent investigations by Franke and Fuchs,[1] Achelis and Hardebeck,[2] Bertram, *et al.*,[3] Mirsky, *et al.*,[4] Kinsell, *et al.*,[5] Miller and Dulin,[6] Ridolfo and Kirtley,[7] and Fajans, *et al.*,[8] have shown that certain arylsulfonylureas reduce the concentration of sugar in the blood of experimental animals and in man after oral administration. An excretion product from one of these drugs, Orinase (I),[9] has been isolated from the urine of normal and diabetic humans. This metabolite does not produce hypoglycemia in dogs, rats[10] or humans.[8] It has been identified as 1-butyl-3-*p*-carboxyphenylsulfonylurea (II).



I, R = CH_3
II, R = COOH

The metabolite crystallized in crude form from urine which had been adjusted to *p*H 1 with hydrochloric acid and allowed to stand at room temperature for 1 to 2 hours. Purification was accomplished by repeated washes with water and three recrystallizations from 70% ethanol, using a Norite decolorization in the first stage.

The amount of this material isolated when 6 g. per day (1.5 g. every six hours) was given to normal men was approximately 75% of the amount of Orinase administered. When 3 to 4 g. was given orally to diabetic subjects, excretion of this metabolite ranged from 24 to 67% of the largest amount possible. These recoveries indicate that this material is very likely the principal metabolic product of Orinase.

The colorless crystalline product melted at 215–217°, and elemental analyses indicated an empirical formula of $C_{12}H_{16}N_2O_5S$. Potentiomeicti tration in water–ethanol showed an equivalent weight of 149.1 and two acidic groups of pK_a' 5.2 in 45% ethanol and 6.2 in 43% ethanol. The pK_a' of 6.2 parallels that of Orinase (pK_a' 6.5 in 44% ethanol) sufficiently so that it can be assigned to the acidic hydrogen of the sulfonyl-urea grouping. The pK_a' of 5.2 is characteristic of a carboxylic acid or a readily enolizable carbonyl.

The infrared spectrum of the excretion product showed that many of the structural characteristics of Orinase had been retained. In addition, the presence of a carboxyl group was indicated by the increased intensity of the carbonyl absorption at 1685 cm.$^{-1}$ relative to that of Orinase; carboxyl OH bands at 2670 and 2550 cm.$^{-1}$; and a band at 931 cm.$^{-1}$ which is characteristic of dimeric carboxylic acids.

This evidence indicated that the excretion product differed from Orinase ($C_{12}H_{18}N_2O_3S$) in having a carboxyl group in place of a methyl group. The ultraviolet absorption maxima (alkaline and acidic ethanol solutions) of the excretion product occurred at longer wave lengths than those of Orinase, indicating that the carboxylic function was on the aromatic ring. That the carboxylic group was indeed on the aromatic ring in the *para* position was proved by hydrolytic cleavage. A quantity of the excretion product was heated under reflux with 50% sulfuric acid for thirty minutes. On cooling, a solid separated which, after recrystallization from water, melted at 275–278°. This material was identified as *p*-carboxybenzenesulfonamide by comparison with authentic material. The comparison included infrared and ultraviolet spectra, elemental

(1) H. Franke and J. Fuchs, *Deut. med. Wochschr.*, **80**, 1449 (1955).

(2) J. D. Achelis and K. Hardebeck, *ibid.*, **80**, 1452 (1955).

(3) F. Bertram, E. Bendfelt and H. Otto, *ibid.*, **80**, 1455 (1955).

(4) I. A. Mirsky, D. Diengott and H. Dolger, *Science*, **123**, 583 (1956).

(5) L. W. Kinsell, F. R. Brown, R. W. Friskey and G. D. Michaels, *ibid.*, **123**, 585 (1956).

(6) W. Miller and W. Dulin, *ibid.*, **123**, 584 (1956).

(7) A. S. Ridolfo and W. R. Kirtley, *J. Am. Med. Assn.*, **160**, 1285 (1956).

(8) S. S. Fajans, J. W. Conn, L. H. Louis, H. S. Seltzer, R. D. Johnson, R. D. Gittler, A. R. Hennes, B. L. Wajchenberg, I. P. Ackerman, to be published.

(9) Orinase is the Upjohn trademark for its brand of 1-butyl-3-*p*-tolylsulfonyl-urea.

(10) W. Miller and W. Dulin, private communication.