COMMUNICATIONS TO THE EDITOR

THE PHOTOLYSIS OF CARBON SUBOXIDE

Sir:

Carbon suboxide, $O=C=C=C=O$, is similar in its chemical reactivity and its ultraviolet absorption spectrum to the ketenes, $R_2C=C=O$. The photolysis of ketenes[1] results in the splitting of the carbon–carbon double bond: *e.g.*, $H_2C=C=O + h\nu \rightarrow CH_2 + CO$. A similar cleavage was expected for the photolysis of carbon suboxide.

Mixtures of carbon suboxide and ethylene were photolyzed at room temperature in a quartz and Pyrex system equipped with an externally driven circulating pump. The partial pressure of carbon suboxide was about 1 mm. Research grade hydrocarbons were added to make up the total pressure to 50 to 750 mm. Samples of the mixture were withdrawn from time to time and analyzed directly on a gas chromatograph or mass spectrometer. A low pressure mercury arc and a f/2 quartz monochromator were used as a light source. Slits 1 mm. wide gave sufficient resolution to isolate the 2537 Å. line which was used for most of the runs.

Two products were formed from the photolysis of a mixture of carbon suboxide and ethylene at a total pressure of 150 mm. One product appeared at the "air" peak on the gas chromatogram and the other had a retention time five times as long. By freezing out the unphotolyzed suboxide and most of the ethylene with liquid nitrogen, the "air" peak was identified as carbon monoxide on the mass spectrometer. The retention time of the second product was found to be identical with allene. This identification was confirmed by analyzing the separated product on the mass spectrometer. After calibrating the gas chromatograph with known mixtures of carbon monoxide and allene, it was observed that the mole ratio of products CO/allene is 2.4 ± 0.3. This ratio remains constant throughout the photolysis. Varying the total pressure from 50 to 750 mm. had no effect on the ratio. A dark run, using no ultraviolet light, showed no allene formation and only a slight increase in the "air" peak (approximately 10% of the increase observed during the photolysis run), probably due to spontaneous decomposition of the unstable suboxide.[2] Thus the over-all photolysis reaction appears to be I.

$$O=C=C=C=O + H_2C=CH_2 + h\nu \rightarrow$$
$$2CO + H_2C=C=CH_2 \quad (I)$$
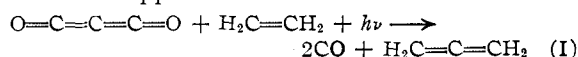
Adding 18% oxygen or 24% nitric oxide did not change the rate of allene formation significantly.

Although special care was taken to assure that no mercury vapor was admitted to the system, the possibility of a mercury sensitized decomposition was tested by using longer wave length radiation. Because the absorption of carbon suboxide is less intense[3] and the emission of the mercury arc is less

at the longer wave lengths, the quartz monochromator was not used. Instead the mercury arc was placed 4 cm. from the reaction cell and a 2 mm. thick Pyrex sheet, having a strong absorption below 3000 Å., was inserted between the two. The run appeared identical in every respect with those using the 2537 Å. radiation. Therefore, the reaction is not being caused by mercury sensitization.

Since both the reactants and the products of I contain the unusual $C=C=C$ chain, it was necessary to consider the possibility that the carbon suboxide was simply exchanging its terminal oxygen atoms for the hydrogen atoms of the ethylene in a chain reaction. To test this possibility, a mixture of carbon suboxide and propylene was photolyzed. If the $C=C=C$ group is remaining intact and simply exchanging terminal groups with the unsymmetrical olefin, then three products would be expected, allene, methylallene, and 1,3-dimethylallene. Only carbon monoxide and methylallene (identical retention time with known sample) were observed in the reaction products; there was no evidence for allene formation. Excluding the rather unlikely possibility that the suboxide might exchange both end groups with the olefin in a single collision (involving the simultaneous migration of at least eight atoms), it is concluded that the $C=C=C$ chain in the product allene is not derived intact from the carbon suboxide.

By analogy with ketene, the initial step in the photolysis of carbon suboxide would be a cleavage of one of the carbon–carbon double bonds, II.

$$C_3O_2 + h\nu \rightarrow CCO + CO \quad (II)$$
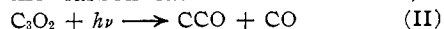
The CCO radical might then decompose to give a free carbon atom and another carbon monoxide molecule, III. A free carbon atom would probably attack the pi electrons of the carbon–carbon

$$CCO \rightarrow C + CO \quad (III)$$
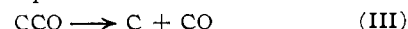
double bond to form a cyclopropylcarbene intermediate,[4] IV, which is known to rearrange ex-

$$(IV)$$

clusively to the allene.[5] However, the possibility that the CCO radical is stable and attacks the olefin directly to give an intermediate which decomposes to carbon monoxide and IV cannot be excluded at this time. In either case, the attack on the double bond must be faster than a reaction with oxygen or nitric oxide.

It seems unlikely that the CCO radical and ethylene react to form a stable cyclopropyl ketene, which then undergoes further photolysis. The ketenes do not absorb strongly at these wave lengths,[6] and therefore the ketene concentration

(1) G. B. Kistiakowsky and N. W. Rosenberg. *J. Am. Chem. Soc.*, **72**, 321 (1950).

(2) L. H. Reyerson and K. Kobe, *Chem. Revs.*, **7**, 479 (1930).

(3) H. W. Thompson and N. Healey, *Proc. Roy. Soc.*, **A157**, 331 (1936).

(4) W. M. Jones, *J. Am. Chem. Soc.*, **82**, 6200 (1960).

(5) W. M. Jones, private communication.

(6) K. Knox, R. G. W. Norrish and G. Porter, *J. Chem. Soc.*, 1477 (1952).

would grow to a significant steady state value. This would be evident by an initial lag in the production of allene. The earliest possible measurements, made when less than 1% of the suboxide had been decomposed, showed no significant increase in the ratio CO/allene.

Preliminary results indicate that a carbon atom can also be inserted into carbon–hydrogen bonds. The photolysis of carbon suboxide in the presence of methane yields ethylene, while in the presence of cyclopropane both ethylene and acetylene are formed. Further experiments are in progress.

Carbon atoms produced by nuclear transformations react with hydrocarbons to give products different from those observed here.[7] This discrepancy could be due to the high energies of the nucleogenic carbon atoms, or to the fact that the CCO radical, and not a carbon atom, is the reactive species in the photolysis of carbon suboxide.

I wish to thank Professor F. E. Blacet for the use of his equipment and for several stimulating discussions.

(7) C. MacKay and R. Wolfgang, Abst. of Papers, 138th Meeting, Am. Chem. Soc., 1960, p. 83-P; C. MacKay and R. Wolfgang, J. Am. Chem. Soc., 83, 2399 (1961).

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POTENTIAL ANTICANCER AGENTS.[1] LXVI. NON-CLASSICAL ANTIMETABOLITES. III.[2] 4-(IODOACETAMIDO)-SALICYLIC ACID, AN EXO-ALKYLATING IRREVERSIBLE INHIBITOR OF GLUTAMIC DEHYDROGENASE

Sir:

Strong evidence for the proposition[2-4] that inhibitors can be constructed which fit the active site of an enzyme reversibly, then become irreversibly bound by alkylation of the enzyme adjacent to the active site (exo-alkylation) has now been observed experimentally.

Since salicylate reversibly inhibits GDH[5] and LDH with I_{50} values[6] of 19 and 20, respectively, 4-(iodoacetamido)-salicylic acid (I)[7] was investigated as a possible irreversible inhibitor of these two enzymes.
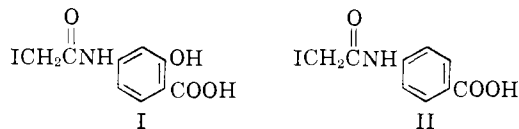
When a solution of GDH·DPNH in tris buffer at pH 7.4 was incubated at 37° with 2 mM. concen-

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, Contract No. SA-43-ph-1892.

(2) For paper II see B. R. Baker, W. W. Lee, W. S. Skinner, A. P. Martinez and E. Tong, J. Med. Pharm. Chem., 2, 633 (1960).

(3) B. R. Baker, Cancer Chemotherapy Reports, No. 4, 1 (1959), paper I on Non-classical Antimetabolites.

(4) H. F. Gram, C. W. Mosher and B. R. Baker, J. Am. Chem. Soc., 81, 3103 (1959).

(5) Crystalline lactic dehydrogenase (LDH) from rabbit muscle, crystalline L-glutamic dehydrogenase (GDH) from mammalian liver, and reduced diphosphopyridine nucleotide (DPNH) were purchased.

(6) See reference 2 for definition.

(7) C. van der Stelt, A. J. Z. Vourspuij and W. Th. Nauta, Artzneimittel-Forsch., 4, 544 (1954).

tration of I, the amount of inhibition—compared to a control solution without inhibitor run simultaneously—increased with time[8] (Fig. 1).
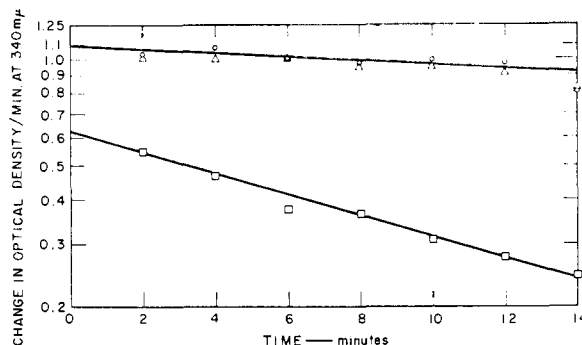

Fig. 1.—Rate of inactivation of GDH at 37° in 0.05 M tris buffer (pH 7.4) containing 0.23 mM. DPHN: O, no other addition; △, 4.48 mM. iodoacetamide; □, 2.00 mM. 4-(iodoacetamido)-salicylic acid.

In order to take advantage of the specificity of the enzyme site,[2,3,9] there is inherent in the design of exo-alkylating irreversible inhibitors the requirement that a reversible complex (V) between inhibitor (IV) and enzyme (III) must form prior to the internal formation of a covalent bond as in VI. It can be argued that I irreversibily alkylated
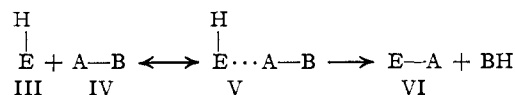
GDH to give VI without prior formation of a reversible complex (V), in the same manner that iodoacetamide alkylates enzymes[10] (tail alkylation); if such were the case, then the N-substituent on the iodoacetamide should not affect the rate of inactivation, providing the activity of the halogen remains the same and there is no added steric hindrance. In contrast, if a reversible complex (V) must be formed first, then the rate of inactivation is dependent upon the amount of reversible complex (V).

Iodoacetamide showed a negligible reversible inhibition of GDH, having an I_{50} of 230 with respect to α-ketoglutarate. When 4.48 mM.[11] iodoacetamide was incubated with GDH·DPNH at 37°, there was no detectable irreversible inhibition; two controls of GDH·DPNH, one with and one without 2 mM. 4-(iodoacetamido)-salicylic acid (I), were run simultaneously, all three solutions being made from a master solution of the enzyme (Fig.

(8) The amount of remaining enzyme was determined by adding 1 mM. α-ketoglutarate and 75 mM. (NH4)2SO4 to an aliquot and observing the rate of disappearance of DPNH at 340 mμ.

(9) H. Fraenkel-Conrat in P. D. Boyer, H. Lardy and K. Myrbäck, "The Enzymes," Academic Press, Inc., New York, N. Y., 1959, Vol. I, pp. 611-613.

(10) M. Dixon and E. C. Webb, "Enzymes," Academic Press, Inc., New York, N. Y., 1958, pp. 376-378.

(11) This concentration of iodoacetamide was employed since the rate of reaction[12] of I with thiosulfate was 2.24 times as rapid as that of iodoacetamide.

(12) Measured by suitable modification of the thiosulfate method of V. K. LaMer and M. E. Kammer, J. Am. Chem. Soc., 53, 2832 (1931).