

Figure 11. Schematic representation of DNA photolesions in complementary sites.

nine bases proceeds *via* the opening of one aromatic system of each base, the second aromatic system of each base may remain unaffected. Due to the presence of an aromatic system within the photoproduct, which is correspondingly characterized by a strong uv absorbance, photoreactions in deoxyadenylic acid chains cannot be detected by uv absorbance measurements as easily as, *e.g.*, the photodimerization of pyrimidine bases. Some types of photoreactions may even be rather difficult to detect by uv absorbance measurements. In such cases measurements of the circular dichroism would be expected to detect photodeflects with much higher sensitivity.

Strong evidence for the proposed mechanism of the photoreaction in deoxyadenylic acid chains is obtained from the chain length dependence of the photoreactivity. A simple model based upon the reaction probability of an excited adenine with an adjacent adenine residue would predict a chain length dependence of photoreactivity according to the following scheme

$$P_1 = 0, P_2 = 1, P_3 = 1.33, P_4 = 1.5, P_\infty = 2$$

where  $P_n$  are photoreactivities in nucleic acid chains of chain lengths  $n$ . Although this scheme is too simple to describe the observed chain length dependence of the quantum yields correctly, it may serve to illustrate a possible major reason for the existence of this dependence. A chain length dependence of the nucleotide conformation may also give rise to some variation of the photoreactivity. Furthermore, transfer of excitation energy between adjacent nucleotide residues may be a process, that has to be considered for a more quantitative understanding of the photoreaction.

Finally the measuring procedure applied in the present investigation may give rise to some simulated chain length dependence in the measured quantum yields. The Cotton effects of single-stranded polynucleotides

such as poly(dA) are due to the secondary structure induced by the stacking interactions between adjacent nucleotide residues. Thus a photoreaction between adjacent nucleotides will not only affect the stacking interaction between the reacting residues but at the same time influence the stacking interaction to their neighbors. Accordingly a single photoreaction in the deoxyadenylic acid chain may lead to the dissociation of three stacks accompanied by a corresponding reduction of the CD amplitude. This neighbor effect may lead to the simulation of a higher quantum yield than the "intrinsic" value. However, quantum yields obtained from CD measurements will accurately reflect the photosensitivity with respect to changes in the secondary structure.

The photoreaction analyzed in the present investigation merits particular attention from different points of view. One interesting aspect of this reaction is its high specificity which has been discussed already in a previous publication. It is very likely that the high specificity of the photoreaction is due to a specific difference of the conformations in single-stranded oligomers and polymers of deoxy- *vs.* riboadenylic acids.<sup>6</sup>

Another probably more important aspect of the photoreactivity in deoxyadenylic acid chains is the now evident possibility of a new type of photolesions in DNA (*cf.* Figure 11). Previous discussions of DNA photolesions have been based on the assumption that purine bases are almost completely photoresistant. Any photolesions induced in pyrimidine bases will damage one of two complementary sites only. This type of photolesions may be repaired by repair enzyme systems.<sup>3,16</sup> If, however, both complementary sites are damaged, the genetic information is lost and thus a repair becomes impossible (*cf.* Figure 11). The probability for this type of photolesion may be rather low, since two photoreactions have to be induced at the same site. On the other hand, the biological effect of this type of photolesion may be considerable, resulting in mutation or even inactivation (*cf.* ref 17).

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(16) J. Berndt, *Angew. Chem.*, **85**, 289 (1973).

(17) E. Freese, *Angew. Chem.*, **81**, 1 (1969).

## Communications to the Editor

### Specific Cation Participation in Alkali-Carbanion Initiated Epoxide Cleavage Reactions

Sir:

In a recent investigation on the cation solvating power of a number of small-ring ethers we found the rate of cleavage of ethylene oxide (EO) and similar epoxides by carbanions to be highly dependent on

alkali cation. This was of particular interest since we were able to determine the extent and structure of ion pairing in the systems investigated making possible a correlation between ion pair structure and reactivity.

The fluoradenyl carbanion<sup>1,2</sup> (FD<sup>-</sup>) was used in this

(1) H. Rapoport and G. Smolinski, *J. Amer. Chem. Soc.*, **82**, 934 (1960).

(2) T. E. Hogen-Esch, *ibid.*, **95**, 639 (1973).

**Table I.** Pseudo-First-Order Rate Constants of the Ethylene Oxide Cleavage Reaction by Fluoradenyl-Alkali Salts in Bulk Ethylene Oxide at 23°

[FD-M <sup>+</sup> ] × 10 <sup>3</sup>	Order in [FD-M <sup>+</sup> ]	[NaBPh <sub>4</sub> ] × 10 <sup>3</sup>	k <sup>c</sup> × 10 <sup>3</sup> , sec <sup>-1</sup>	[FD-M <sup>+</sup> ] × 10 <sup>3</sup>	Order in [FD-M <sup>+</sup> ]	[Ether] × 10 <sup>3</sup>	k × 10 <sup>3</sup> , sec <sup>-1</sup>
FD <sup>-</sup> Na <sup>+</sup>				FD <sup>-</sup> Na <sup>+</sup>			
0.55	2		1.49	0.88	1-2	(DBE) <sup>a</sup> 3.0	0.18
0.80	2		1.76	0.77	1-2	(DCHE) <sup>a</sup> 0.9	0.074
1.12	2		2.47	1.00	1-2	(TG) <sup>a</sup> 2700	0.84
2.36	2		3.89	0.71	1-2	(DAPE) <sup>a</sup> 1.2	0.011
5.06	1-2		5.17	FD <sup>-</sup> Li <sup>+</sup>			
9.42	1-2		6.44	5.0			>100 <sup>b</sup>
		[NaBPh <sub>4</sub> ] × 10 <sup>3</sup>		0.42	1-2	(TG) 5300	6.47
0.02	1	1.2	2.72	FD <sup>-</sup> K <sup>+</sup>			
				0.65	1-2		0.26
0.89	1	12.5	4.85	FD <sup>-</sup> Cs <sup>+</sup>			
0.49	1	60.1	7.70	1.58			<0.001

<sup>a</sup> DBE, *tert*-butyldibenzo-18-crown-6; DCHE, dicyclohexyl-18-crown-6; TG, tetraglyme; DAPE, diazohexaaxobicyclic polyether. <sup>b</sup> Due to fast cleavage only a minimum rate constant could be determined. <sup>c</sup> First-order rate constants were calculated from the initial slope of the optical density *vs.* time trace.

work because of its desirable properties as a uv-visible spectroscopic probe for ion pairing similar to the fluorenyl carbanion<sup>3</sup> and because of its relative stability due to the high acidity of its hydrocarbon, fluoradene ( $pK_a \approx 11$ ).

The ethylene oxide ring opening by the fluoradenyl carbanion<sup>4</sup> is, therefore, relatively slow, making spectral measurements as well as convenient spectrophotometric determination of the ether cleavage rate possible.

The reaction product was identified by reacting the recrystallized LiFD salt with EO and adding excess methanol. The resulting product was recrystallized from petroleum ether and was identified as 2-fluoradenylethanol by nmr and mass spectrometry.<sup>5a</sup>

The lithium, sodium, and potassium salts in EO were found to exist as separated ion pairs while the Cs salt was predominantly of the contact ion pair variety,<sup>5b</sup> indicating that in these systems EO is a substantially stronger coordinating solvent than THF and THP, a finding that seems to run counter to the well-documented<sup>6</sup> basicity sequence of cyclic ethers: (CH<sub>2</sub>)<sub>3</sub>O > THF > THP > EO.<sup>7</sup>

The rate of epoxide cleavage in all cases except for the lithium salt could be conveniently determined by monitoring the decrease of the longest wavelength vis-

ible absorption of the carbanion (560–570 nm). The reactions were in all cases carried out by mixing the dry carbanion salt with EO *in vacuo*.<sup>8</sup> Reproducibility is quite satisfactory ( $\pm 10\%$ ). The pseudo-first-order rate constants for the four salts (Table I) clearly show the dramatic increases in rate of at least 10<sup>5</sup> in going from Cs to Li salt. This result seems to indicate that free anions are relatively unimportant in this reaction because otherwise the reaction rates should be more nearly on the same order of magnitude especially for the Li, Na, and K salts that exist as separated ion pairs and are expected to be dissociated to roughly the same extent.<sup>3</sup>

In addition, no decrease in rate due to common ion effect is observed when the corresponding tetraphenyl borates are added. On the contrary, a marked increase is seen when sodium tetraphenylborate (NaBPh<sub>4</sub>) is added in 1–60 times excess to FDNa in EO (Table I).

Furthermore, in systems where strongly cation solvating molecules such as glymes, crown ethers of various types, etc., are present, significant decreases in rate are observed for Li and Na salts indicating specific cation participation in the reaction (see below).

All of these observations support the contention that free anion by itself is unimportant in these reactions and that very likely ion pairs are the kinetically active species.

The very large differences in rate are most conveniently rationalized by ether oxygen/Lewis acid-cation coordination inductively catalyzing the reaction through stabilization of the transition state by minimizing (alkoxide)<sup>-</sup>M<sup>+</sup> coulombic energy.

The role of the cation in the ether cleavage reaction in addition to the dramatic cation dependence of rate is also illustrated by the decreases in rate observed in the presence of strongly cation coordinating molecules. Thus the first-order rate constants for the Li and Na salt catalyzed cleavage in the presence of tetraglyme are reduced by a factor of about 14 and 3, respectively. Stronger decreases for the Na salt were observed in the presence of equimolar amounts of dibenzo-18-crown-6 ( $\approx 10\times$ ) and dicyclohexyl-18-crown-6 ( $20\times$ ) (Table I). The difference between the dicyclohexyl and the

(3) T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **87**, 669 (1965); **88**, 307, 318 (1966).

(4) This "base catalyzed" S<sub>N</sub>2 type ring opening is well documented; see, for instance, (a) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959); (b) S. Patai, Ed., "The Chemistry of the Ether Linkage," Interscience, New York, N. Y., 1967; (c) S. J. Cristol, J. R. Douglass, and J. S. Meek, *J. Amer. Chem. Soc.*, **73**, 816 (1951).

(5) (a) The mass spectrum shows the expected molecular ion at 284 with C<sub>13</sub> satellite at 285, base peak of the C<sub>12</sub>H<sub>11</sub> fluoradenyl cation at 239, and the fluoradene radical cation at 240. High-resolution mass spectrometry yields 284.1208 as molecular ion mass. Calculated for 2-fluoradenylethanol 284.1200. Nmr spectrum  $\delta$  aromatic protons 7.08–7.80, methylene triplets at 3.29 and 2.23, hydroxyl at 0.87. Position of OH proton was confirmed by deuterium exchange with CH<sub>3</sub>OD. Integration consistent with assigned structure. The heavily deshielded fluoradene bridgehead proton ( $\delta$  5.10) is not observed in the alcohol spectrum. Moreover the aromatic regions of fluoradene and 2-fluoradenylethanol are essentially identical confirming the attachment of -CH<sub>2</sub>CH<sub>2</sub>OH to bridgehead carbon. (b) The presence of substantial concentration of ion pairs was confirmed by conductometry. The structure of the ion pairs was determined by the absorption spectra of the carbanion salts:  $\lambda_{\text{loose ion pair}}$  388 nm,  $\lambda_{\text{contact ion pair}}$  360–380 nm.<sup>2,3</sup>

(6) S. Searles, Jr., and M. Tamres, *Chem. Rev.*, **59**, 296 (1959).

(7) Conceivably this is due to the less steric requirements of the small ethylene oxide molecule in forming the cation solvent shell in the separated ion pair and its higher dielectric constant ( $\epsilon$  13.9 at 0°).

(8) Polymerization was shown not to occur in these cases except for the Cs salt, where polymerization was observed after several days.

dibenzo crown ether is probably caused by a more effective shielding of the cation by the nonplanar dicyclohexyl crown ether.<sup>9</sup>

That the decrease in rate on addition of crown ether is due to a 1:1 complex with carbanion salt is demonstrated when larger than equimolar quantities were added. No further change in rate was observed. Particularly effective (150 times) in reducing the cleavage rate was the diazhexaoxobicyclic polyether,  $N[CH_2-CH_2(OCH_2CH_2)_2]_3N$  (Table I).<sup>10</sup> This is not unreasonable since in this case the metal ion is effectively shielded by the bicyclic cavity.

The cleavage reaction is most likely due to nucleophilic attack of carbanion or carbanion alkali pair on cation complexed ethylene oxide. Both ions, however, may exist in a variety of ionic forms such as ion pairs, triple ions, free ions, etc. Consequently, the reaction may proceed corresponding to a variety of kinetic orders having first- or second-order kinetics or a mixture thereof.<sup>11</sup> Not unexpectedly, therefore, the reaction in some cases was found to be between first and second order in carbanion concentration. A comparison between the pseudo-first-order rate constants of Table I is consequently not strictly correct, and the data have, therefore, only qualitative or semiquantitative significance. In the presence of sodium tetraphenylborate, however,  $FD^-Na^+$  reacts according to first-order kinetics through 90% conversion, indicating a reaction between  $FD^-Na^+$  and  $Na^+BPh_4^-$  complexed EO. This is also suggested by the kinetic order of two observed in the absence of  $BPh_4^-Na^+$ . At higher  $FD^-Na^+$  concentration the order decreases somewhat, possibly because of the formation of triple ions.<sup>11</sup>

It is anticipated that cation participation in these cleavage reactions is quite general. We observed similar phenomena in the cleavage of propylene oxide by alkali carbanions. Other obvious indications of cation participation in small ring cyclic ether cleavage reactions are the trimethylene oxide cleavage by fluorenyl salts. In this case the Li salt cleaves the ether rapidly and the Ba salt less so, while salts containing lower electrostatic field strength cations such as Na and K are essentially stable in this solvent.<sup>12</sup>

In conclusion it was shown that the differences in epoxide cleavage rate initiated by fluoradenyl alkali salts are due to specific cation effects<sup>13</sup> and not as was shown in other reactions<sup>14</sup> to the presence or absence of certain ion pair types or free ions.

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(9) H. K. Frensdorff, *J. Amer. Chem. Soc.*, **93**, 600 (1971).

(10) B. Dietrich, J. M. Lehn, and J. P. Sauvage, *Tetrahedron Lett.*, 2885 (1969). We thank Dr. Lehn for a sample of the ether.

(11) Kinetic orders expected in the cases below, for example, are:  $FD^- + [M(EO)]^+ \rightarrow FDCH_2CH_2O^-M^+$ , order 1;  $M^+FD^- + M^+EOFD^- \rightarrow FDCH_2CH_2O^-M^+ + FD^-M^+$ , order 2;  $M^+FD^- + [M(EO)]^+ \rightleftharpoons [(M^+)_2EOFD^-]^+ \rightarrow FDCH_2CH_2O^-M^+ - M^+$ , order 1.5, assuming that ion pair dissociation and triple ion formation constants are  $\ll 1$ . Kinetic orders between 1 and 2 are also expected if the proportion of the unreactive free anions is substantial.

(12) J. Smid and T. Hogen-Esch, unpublished results.

(13) Specific cation effects have recently been reported for alkyl-acyl migratory insertions: J. P. Collman, J. N. Cawse, and J. I. Braumann, *J. Amer. Chem. Soc.*, **94**, 5905 (1972); for proton transfer reactions: S. Bank and B. Bockrath, *ibid.*, **94**, 6076 (1972); T. E. Hogen-Esch and J. Smid, *ibid.*, **89**, 2764 (1967).

(14) See, for example, M. Shinohara, J. Smid, and M. Szwarc, *ibid.*, **90**, 2175 (1968).

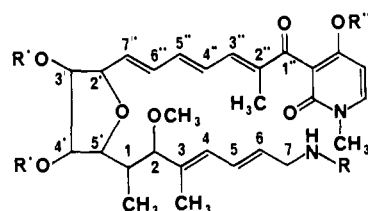
and by the University of Florida through a stipend to one of us (C. J. C.).

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#### Antibiotic X-5108. IV. Structure of Goldinamine<sup>1</sup>

Sir:

Goldinamine 4-bromobenzyl ether (**1**) is a degradation product of antibiotic X-5108 4-bromobenzyl ether<sup>1</sup> with an empirical formula of  $C_{35}H_{43}BrN_2O_7$  derived from elemental analyses of **1** and derivatives thereof. The composition of goldinamine (**1e**),  $C_{28}H_{38}N_2O_7$ , was further confirmed by low- and high-resolution mass spectra of derivatives of **1d**.



**1**, R = R' = H; R'' = 4-BrBzl (goldinamine 4-bromobenzyl ether)

**1a**, R = 2,4-DNP; R' = H; R'' = 4-BrBzl

**b**, R = 2,4-DNP; 2R' =  $(CH_3)_2C$ ; R'' = 4-BrBzl

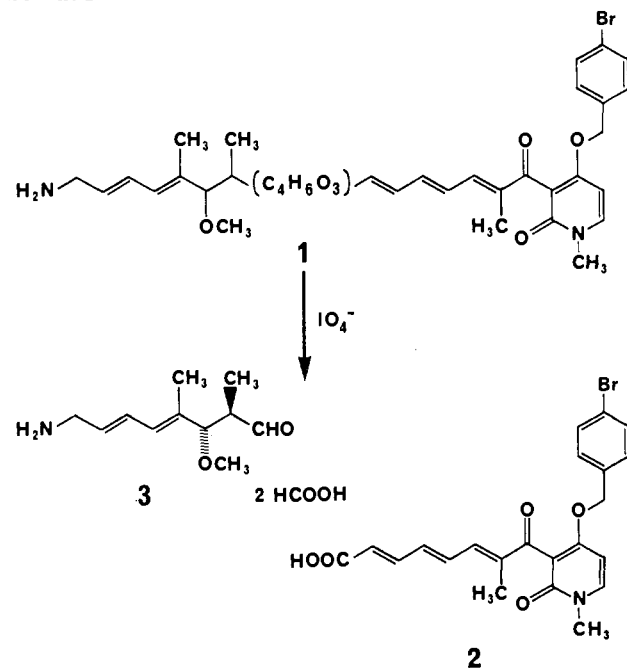
**c**, R = 2,4-DNP; R' =  $CH_3CO$ ; R'' = 4-BrBzl

**d**, R = R' = H; R'' = (goldinamine methyl ether)

**e**, R = R' = R'' = H (goldinamine)

Periodate oxidation of **1** (Scheme I) afforded **2**<sup>1</sup> and

Scheme I



an unstable aldehyde, **3**, or its enantiomer, which was characterized as the *N*-2,4-dinitrophenyl derivative and converted to methyl acetal **4**: mp 124°;  $[\alpha]_D +34.7^\circ$  (*c* 0.5, dioxane);  $C_{19}H_{27}N_3O_7$ , calcd mol wt 409, found  $m/e$  ( $\%$ ) 409 ( $<0.1$ ), 377 (0.3),  $[M - MeOH]$ , 75 (100).

(1) Paper III in this series: H. Maehr, J. F. Blount, M. Leach, A. Stempel, and G. Büchi, *Helv. Chim. Acta*, **55**, 3054 (1972).