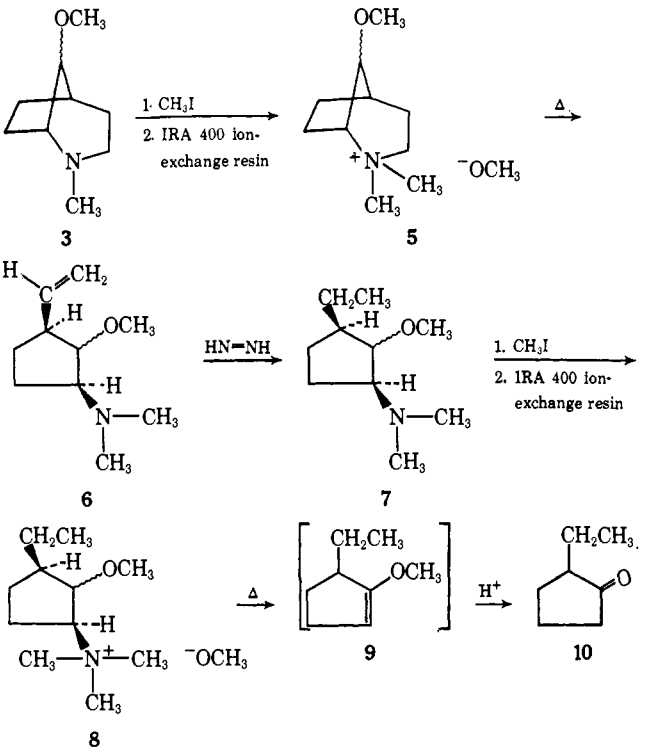
tablishing the presence of an N-methyl and a secondary O-methyl group, nuclear magnetic resonance spectroscopy provided little evidence for the skeletal structure of the intramolecular cyclization product.

Since spectroscopic studies failed to provide sufficient data for distinguishing between **3** and **4**, a classical degradation procedure was utilized as outlined below.[6] This degradation gave the known 2-ethylcyclopentanone (**10**), identical in all respects with an authentic



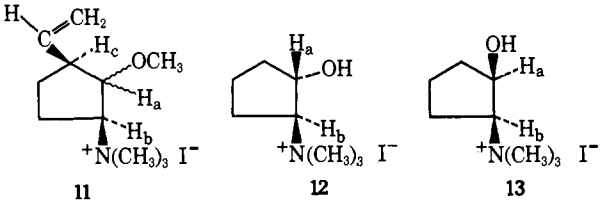
sample.[7] The presence of the ethyl group on the carbon adjacent to the carbonyl function requires that the ethyl group be next to the ether linkage in **7**. This would be the case if the cyclization product was **3**. Hence cyclization must have occurred exclusively at the 1 position of **2**.

The only feature of the cyclization which remains to be established is the stereochemistry at C-8. Mechanistically ionic additions to olefins generally yield *trans* products. In the special case of carbocyclics prepared *via* intramolecular cationic cyclization, only *trans* addition to the double bond was found.[2] Thus, on purely mechanistic analogy it would be predicted that the 8-methoxyl group should be *anti* to the nitrogen (*trans* to the nitrogen-containing bridge). Attempts to unequivocally establish the mechanistic prediction were unsuccessful. Very tentative evidence for the suspected stereochemistry was obtained from a comparison of the nmr spectra[8] of **11**, **12**, and **13**. In **11**, H_a, which appeared as a quartet centered at τ 6.73, showed a coupling constant of 9 cps with H_c and 6 cps with H_b In the model compound **12**, J_{ab} was 6 cps, while in the

(6) Satisfactory elemental analyses were obtained for **6** and for the picrates of **3**, **6**, and 7. The quaternary methoxides, **5** and **8**, were not analyzed because of their extremely hygroscopic nature. The crude vinyl ether **9** was hydrolyzed without purification.

(7) E. Zbiral, F. Wessely, and E. Lahrmann, *Monatsh. Chem.*, **91**, 92 (1960).

(8) Nmr measurements were made using a Varian HA-100 nuclear magnetic resonance spectrometer. Coupling constants were measured utilizing double and triple resonance techniques. We wish to acknowledge the assistance of Mr. Richard Cryberg in obtaining these spectra.



cis isomer **13**, J_{ab} was 4 cps. Unfortunately, even though the H_a–H_b coupling constants of **11** and **12** were identical, the proximity of J_{ab} for **13** does not allow an unequivocal assignment of the stereochemistry of the methoxy function of **3**.

The solvolytic π route offers an attractive synthetic method for the preparation of a large variety of elusive azabicyclics. We are presently investigating the scope, limitations, and mechanistic details[9] of the addition of divalent electron-deficient nitrogen to olefins.

Acknowledgment. We wish to thank the National Cancer Institute of the Public Health Service for Grant CA-07110 which supported this research.

(9) As with analogous carbocyclic examples,[2] it is probable that π-electron participation is involved in the ionization of the N–Cl bond. It should be noted that such participation requires the intermediacy of a partially electron-deficient nitrogen species along the reaction pathway but forgoes the presence of a divalent nitrogen intermediate with a unit positive charge on nitrogen.

(10) Alfred P. Sloan Research Fellow, 1967–1969.

(11) National Science Foundation Undergraduate Research Participant, 1966–1967.

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Macromolecule–Small Molecule Interactions. A Synthetic Macromolecule with High Esterolytic Activity

Sir:

The pathway of action of an enzyme (E) involves[1] combination with a substrate (S) followed by one or more transfer or cleavage steps to yield products (P) (eq 1). Many efforts have been directed toward re-

$$E + S \rightleftharpoons ES \longrightarrow \longrightarrow E + P \qquad (1)$$

producing this phenomenon with synthetic macromolecules. Interactions, polar or apolar, which increase the concentration of the complex (ES) should increase the reactivity of E. For esterolytic reactions the steps following ES formation are facilitated by nucleophilic acid–base groups, and hence insertion of these in a synthetic macromolecule should favor esterolytic activity.

Many water-soluble synthetic polymers have been found to bind small molecules.[2-6] In our experience these linear polymers do not have an avidity comparable to the protein serum albumin.[7] We have now found, however, that a derivative of highly branched water-soluble poly(ethylenimine) (PEI-6)[8] with a small

(1) L. Michaelis and M. L. Menten, *Biochem. Z.*, **49**, 333 (1913).
(2) U. P. Strauss and E. G. Jackson, *J. Polymer Sci.*, **6**, 649 (1951).
(3) W. Scholtan, *Makrmol. Chem.*, **11**, 131 (1953).
(4) S. Sato, *Kolloid Z.*, **154**, 19 (1957).
(5) I. M. Klotz and V. H. Stryker, *J. Am. Chem. Soc.*, **82**, 5169 (1960).
(6) P. Molyneux and H. P. Frank, *ibid.*, **83**, 3169 (1961).
(7) I. M. Klotz, F. M. Walker, and R. B. Pivan, *ibid.*, **68**, 1486 (1946).
(8) Dow Chemical Co. Bulletin "Montrek® Polyethyleneimine." PEI-6 has an average degree of polymerization of 15.

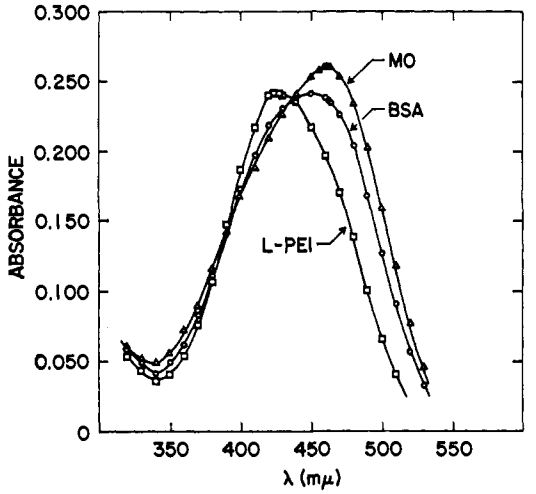

Figure 1. Absorption spectra at 25° of methyl orange in the presence of buffer alone (MO), in the presence of 0.05% bovine serum albumin (BSA), and in the presence of 0.05% lauroylpoly(ethylenimine) (L-PEI) containing 10 residue mole % lauroyl groups. All solutions in 0.01 *M* N-2-hydroxyethylpiperazine-N′-2-ethanesulfonate buffer, pH 7.3.

proportion (10 residue mole %) of apolar side chains has an affinity for small molecules superior to that of serum albumin. For example, Figure 1 shows the shifts in absorption spectra of methyl orange in the presence of serum albumin and of N-lauroylpoly(ethylenimine), which can be correlated with extent of binding.[9] It is obvious that the synthetic polymer binds more strongly.

Synthetic polymers containing nucleophilic groups, such as poly(vinylimidazole) or poly(vinylpyridine), might be expected to show accentuated esterolytic activity.[10,11] When the polymer also contains charged residues which increase electrostatic attraction of a charged substrate increases in catalytic activity have been observed.[10,11] Attempts to facilitate hydrolysis of an uncharged substrate by incorporating apolar residues in polymers[12,13] have not been particularly successful although some increases have been observed in special instances. Some apolar interactions have also been found in ester cleavage in the presence of micelle-forming detergents.[14,15]

Since N-lauroylpoly(ethylenimine) contains a high local concentration of nucleophilic acid–base groups and some pendant apolar groups providing sites for binding small molecules, it should provide in one macromolecule circumstances favorable for high esterolytic activity. Exploratory experiments have been carried out, therefore, with uncharged nitrophenyl esters.

The hydrolyses of *p*-nitrophenyl acetate and of *p*-nitrophenyl laurate were followed spectrophotometrically by the increase in absorbance at 400 mμ due to release of nitrophenolate ion. Some results at pH 7.3 are shown in Figure 2.

In this buffer, spontaneous hydrolysis of nitrophenyl

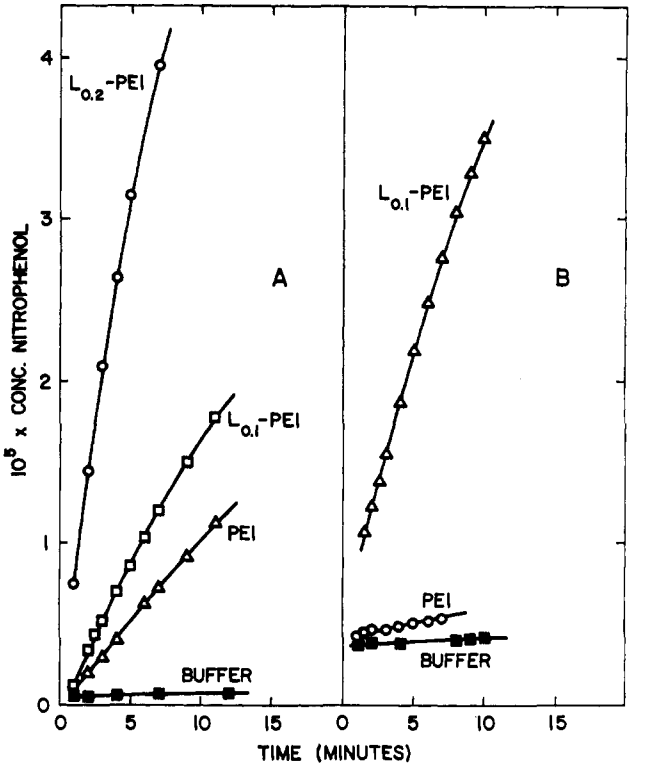

Figure 2. Rate of release of *p*-nitrophenol in 0.01 *M* N-2-hydroxyethylpiperazine-N′-2-ethanesulfonate buffer, pH 7.3, at 25°. (A) *p*-Nitrophenyl acetate (5×10^{-5} *M*) in the presence of buffer alone (buffer); in the presence of 0.05% polyethylenimine (PEI); in the presence of 0.05% N-lauroylpoly(ethylenimine) containing 10 residue mole % lauroyl groups ($L_{0.1}$-PEI); in the presence of 0.05% lauroylpoly(ethylenimine) containing 20 residue mole % lauroyl groups ($L_{0.2}$-PEI). (B) *p*-Nitrophenyl laurate ester (5×10^{-5} *M*) under corresponding conditions.

acetate is very slow. A pseudo-first-order rate constant, k_1, calculated from relation 2 where $(S)_0$ is the

$$\frac{1}{(S)_0}\left(\frac{d(S)}{dt}\right)_0 = k_1 \qquad (2)$$

initial concentration of nitrophenyl acetate and t is the time, gives $k_1 \simeq 2 \times 10^{-5}$ sec^{-1}.

Poly(ethylenimine) itself, without attached apolar groups, accentuates the rate of hydrolysis of nitrophenyl acetate. This is not surprising since ethylenediamine, which corresponds to monomeric residues of the polymer, also shows reactivity in esterolytic reactions.[16] If one assumes that, in the presence of polymeric acid–base groups, k_1 should be replaced by eq 3,

$$k_1 = k_2(P) \qquad (3)$$

where (P) is the concentration of polymeric additive, then a second-order rate constant, k_2, can be calculated. If one uses the residue molar concentration for (P), $k_2 \times 10^2$ (M^{-1} sec^{-1}) is 3.3, 9.0, and 48 for poly(ethylenimine), polymer with 10% lauroyl groups, and polymer with 20% lauroyl groups, respectively. Since the apolar groups provide the site for binding, and only 1–3 of these are present per macromolecule, one might also have used the macromolecule concentration for (P). In this case $k_2 \times 10^2$ (M^{-1} sec^{-1}) is 40, 112, and 550, respectively.

It is obvious from these calculations, as well as from

(9) I. M. Klotz, *J. Am. Chem. Soc.*, **68**, 2299 (1946).
(10) R. L. Letsinger and T. J. Savereide, *ibid.*, **84**, 3122 (1962).
(11) H. Morawetz, C. G. Overberger, J. C. Salamone, and S. Yaroslavsky, *ibid.*, **90**, 651 (1968).
(12) I. Sakurada, Y. Sakaguchi, T. Ono, and T. Ueda, *Makromol. Chem.*, **91**, 243 (1966).
(13) K. Kopple, private communication.
(14) M. T. A. Behme, J. H. Fullington, R. Noel, and E. H. Cordes, *J. Am. Chem. Soc.*, **87**, 266 (1965).
(15) T. E. Wagner, C. J. Hsu, and C. S. Pratt, *ibid.*, **89**, 6366 (1967).
(16) W. P. Jencks and J. Carrioulo, *ibid.*, **82**, 1778 (1960).

Figure 2A, that the attachment of apolar groups to poly(ethylenimine), which increases the binding affinity of the polymer for small molecules, produces marked increases in esterolytic activity.

Apolar interactions also manifest themselves in a comparison of two substrates with differing lengths of acyl group in the nitrophenyl ester. Lauroylpoly(ethylenimine) hydrolyzes *p*-nitrophenyl laurate ester more rapidly than it does *p*-nitrophenyl acetate ester, as is evident in Figure 2. For *p*-nitrophenyl laurate[17] the comparative increase over that produced by PEI without acyl side chains is even more striking.

It is thus apparent that N-acylpoly(ethylenimines) of different molecular weights and containing a variety of attached side chains should provide polymers with interesting effects in a number of biochemically important reactions.

(17) Althougn 5×10^{-5} *M* aqueous solutions of nitrophenyl laurate appear clear, we are not absolutely certain that the substrate is completely in solution.

(18) This investigation was supported in part by a grant from the National Science Foundation.

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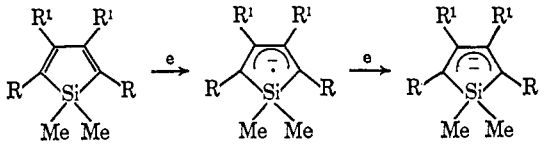
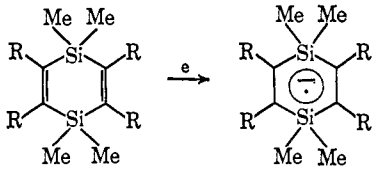
1,4-Disilacyclohexadiene Anion Radicals[1,2]

Sir:

In a previous communication the alkali metal reduction of phenyl-substituted silacyclopentadienes to the corresponding radical anions and dianions was described.[1c]



We wish to report on another monocyclic organosilane system, the 1,4-disilacyclohexadiene anion radicals.



These systems are of interest because with silicon providing an unfilled 3d orbital the ions have the same number of π centers and π electrons as well-known carbon analogs with "aromatic" character.

The potassium reduction of Ia in dimethoxyethane (DME) at Dry Ice–acetone temperatures ($\sim -70°$) gives a five-line esr spectrum which at lower temperatures resolves into the spectrum shown in Figure 1. The reconstructed spectrum assumes 4 equivalent hydrogens with hyperfine splitting (hfs) equal to 3.04 G and 12 equivalent hydrogens with a hfs of 0.24 G. These couplings are assigned to the vinyl and methyl hydrogens of IIa.

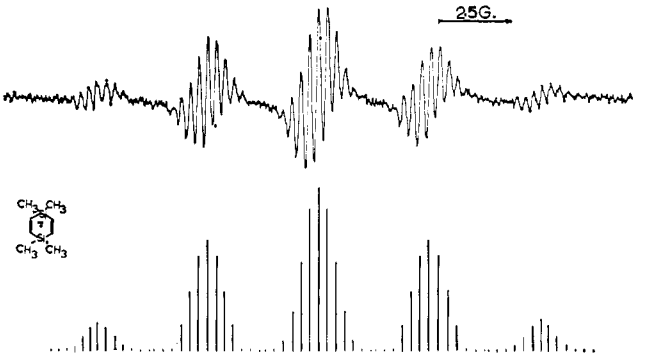


Figure 1.

Support for this structure is obtained from a number of sources. Recently West and coworkers[3] have obtained esr spectra of 1,2-bis(trimethylsilyl)ethylene radical anions by the alkali metal reduction of the corresponding ethylenes. IIa would be expected to be at least as stable. The 0.24-G coupling in IIa is consistent with silyl–methyl hydrogen coupling since this type of coupling varies in the range of 0.14–0.40 G for a variety of organosilane anion radicals.[4,5] A calculated total spin density for the radical is also in agreement with structure IIa. Since a Q value of 28 is found to correlate proton coupling with the spin density on the contiguous carbon for a large number of organosilanes,[4,5] the spin density on each carbon atom is 3.04/28 = 0.11.[6] For at least five organosilanes the Q value relating the spin density on silicon with the (attached) methyl hydrogen coupling is approximately 1.[4,5] The spin density on each silicon atom is thus $\sim$0.24, yielding a total calculated spin density of 0.92. This value is in good agreement with structure IIa considering the approximate nature of the Q values used.[7]

It is of interest to compare Ia and IIa to benzene and benzene anion radical. The vinyl protons in pmr spectra of Ia appear at exceptionally low fields (τ 3.16). Since the SiMe resonance remains a singlet at $-65°$, Ia is probably planar.[8] IIa is also probably planar or the conformers are interconverting more rapidly than 10^8 sec^{-1}. The hfs of 3.04 G for IIa compares with 3.75 G for the benzene radical anion.[11] Like benzene radi-

(1) (a) Organometallic Radicals. III; (b) part I: E. G. Janzen and J. B. Pickett, *J. Am. Chem. Soc.*, **89**, 3649 (1967); (c) part II: E. G. Janzen, J. B. Pickett, and W. H. Atwell, *J. Organometal. Chem.* (Amsterdam), **10**, P6 (1967).

(2) This work is supported by a grant from Dow Corning Corp. Grateful acknowledgment is hereby made.

(3) R. West, Abstracts of the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 9–14, 1967, Paper L64.

(4) M. D. Curtis and A. L. Allred, *J. Am. Chem. Soc.*, **87**, 2554 (1965).

(5) Unpublished results in our laboratory.

(6) The McConnell equation, $A^H = Q\rho$, relates the hfs to the spin density: H. M. McConnell, *J. Chem. Phys.*, **24**, 632, 764 (1956).

(7) Preliminary Hückel–McLachlan MO calculations using $h = -1.2$ and $k = 0.3$ (see ref 4) give the following spin densities: $\rho_{Si} = 0.194$ and $\rho_C = 0.153$.

(8) Several 1,4-digermacyclohexadienes have been shown to be planar.[9,10] However, steric hindrance between substituents in Ib leads to a loss in coplanarity.[9,10]

(9) M. E. Volpin, V. G. Dulova, Yu. T. Struchkov, N. K. Bokiy, and D. N. Kursanov, *J. Organometal. Chem.* (Amsterdam), **8**, 87 (1967).

(10) N. G. Bokiy and Yu. T. Struchkov, *Zh. Strukt. Khim.*, **6**, 571 (1965).

(11) R. W. Fessenden and S. Ogawa, *J. Am. Chem. Soc.*, **86**, 3591 (1964); M. T. Jones, *ibid.*, **88**, 174 (1966). The spectrum of the radical