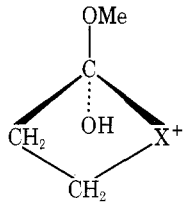
$RO(CH_2)_3$ with $R(CH_2)_4$ suggests no significant difference in υ. The question arises, then, as to how to account for the behavior of groups of the type XCH_2CH_2 where X = RO, Cl, I, RS. Such groups appear to have unexpectedly large υ values. A possible explanation is that the protonated ester is stabilized as shown in I and therefore is less reactive to the water molecule.



I

A comparison of υ values for groups in which CH_2 is replaced by S (Table IV) shows little effect when the group is of the type RSCHR.[1]

Taft[8] has suggested that the E_S values of α,β-unsaturated substituents such as Ph and C_2H_3 include an appreciable resonance effect. If we choose appropriate alkyl groups as models of the steric effect of α,β-unsaturated substituents and compare their respective υ values (Table IV) we can arrive at an estimate of the magnitude of the resonance effect. The cyclopropyl group shows a somewhat smaller but still considerable resonance effect, as might be expected.[9] The propanoyl and butanoyl groups show a small increase in υ which may not be significant. Thus, the resonance contribution to υ for these groups is at best small.

Let us consider the effect of chain length on the υ values for normal alkyl groups. Inspection of the values shown in Table IV shows that once the chain has reached a length of three carbon atoms the value of υ remains essentially constant. Finally, we may examine the behavior of cycloalkyl groups as compared with the corresponding alkyl groups (Table IV). Excluding the cyclopropyl group because for this substituent υ undoubtedly includes a resonance contribution, the cycloalkyl groups all show υ values very much smaller than those of the corresponding alkyl groups.

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Nucleophilicity of Aromatic Sulfenamides and the "α Effect"

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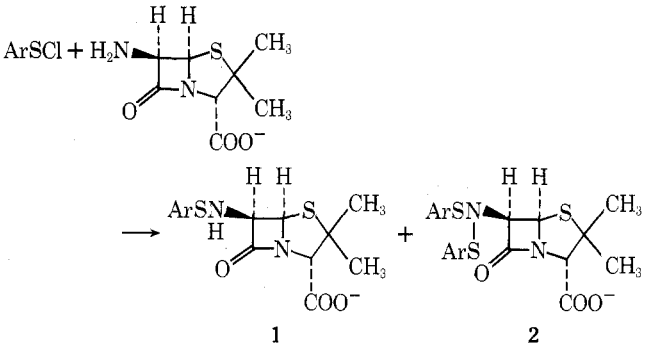
Sulfenamides, the sulfenic acid isosteres of carboxylic acid amides, resemble such amides generally in being water insoluble, crystalline compounds of greatly reduced basicity. The greater nucleophilicity of sulfenamide nitrogen has been noted, however, in that sulfenamides of ammonia or primary amines may be condensed with carbonyl compounds to yield sulfenimines or acylated with activated carboxylic acids under relatively mild conditions to yield *N*-acylsulfenamides. The ready cleavage of the S–N linkage by dilute mineral acid has also been noted.[1-3] The literature concerning mechanistic aspects of the chemistry of the sulfur–nitrogen bond in sulfenamides has been reviewed.[4] In this paper we report further observations on the nature of the nucleophilic character of nitrogen in primary aromatic sulfenamides derived from 6-aminopenicillanic acid (6-APA) which suggest that in certain instances, this nucleophilicity obeys the rules of the "α effect" postulated by Klopman et al.[5] and is sensitive to and regulated by substitution on the aromatic ring.

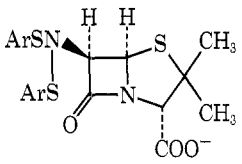
The desirability of readily available, stable, crystalline sulfenamide derivatives of 6-APA which could be subsequently acylated and converted into useful semisynthetic penicillin derivatives provided the impetus for our initial efforts in this area. The ready availability and suitable reactivity of aromatic sulfenyl halides[6] led to the use of phenylsulfenyl chloride in initial experiments. The sulfenylation of 6-APA under aqueous conditions was achieved by means of a modified Schotten–Baumann procedure. From the outset it was readily apparent that the major product from this reaction was not the desired 6-APA phenylsulfenamide (1) but was instead



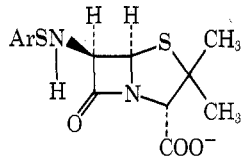
the dibenzenesulfenimide (2). The structure of 2, produced in about 90% yield (based on sulfenyl chloride), was determined through its spectral characteristics and it was separated from approximately 10% of the minor product (1) by conversion of the mixture to their respective methyl esters with diazomethane and column chromatography. Differences thus determined between the NMR shifts of the β-lactam protons were found to be characteristic of the series and were used to assign product ratios in subsequent experiments (see below).

Whereas dibenzenesulfenimides of ammonia,[7] amidines,[8] and other amines[9] have been known for some time, the conditions for their formation have generally been more vigorous and the formation of dibenzenesulfenimides under weak base catalysis has been reported to proceed in poor yield.[10] Since 2 was formed preferentially over a wide range of reaction conditions, other factors affecting the course of this reaction were investigated. To this end, the reaction conditions were held constant while the aromatic substitution pattern of the phenylsulfenyl chloride was varied. As the electron-withdrawing power of the aromatic ring substituents increased, an orderly *decrease* in the proportion of 6-APA diarylsulfenimide formed occurred together with a corresponding increase in the proportion of 6-APA arylsulfenamide, culminating in the isolation of quantitative yields of *o*-nitro- and *p*-nitrophenyl-6-APA sulfenamides (Table I). This observation strongly suggests that the initial product forming step in the sulfenylation of 6-APA is the formation of the desired sulfenamide (1) but, with appropriate aryl substitution present, this sulfenamide may itself react with 6-APA competitively, thus generating a mixture of sulfenamide 1 and

Table I



A



B

Ar	Yield (A + B), %	A/B ratio[a]	Salt[b]
4-CH_3O-C_6H_4	25	100/0	TEA
C_6H_5	52	90/10	NEP, TEA
2-Cl-C_6H_4	36	80/20	NEP, TEA
4-Cl-C_6H_4	68	60/40	NEP
2-$NO_2C_6H_4$	88	0/100	NEP
4-NO_2-C_6H_4	43	0/100	TEA

[a] Derived from NMR integrals; ±5%. [b] NEP = *N*-ethylpiperidine; TEA = triethylamine.

dibenzenesulfenimide (**2**), the proportions of which are dependent upon the aryl substitution. Further evidence in support of the trend outlined above was obtained from the reaction of *p*-methoxybenzenesulfenyl chloride with 6-APA from which none of the sulfenamide could be isolated. These results imply strong control of sulfenamide nitrogen nucleophilicity by aromatic ring substitution acting through the sulfur linkage. The following considerations appear to support this contention.

It has been established in certain cases that heteroatoms directly attached to heteroatoms bearing unshared pairs of electrons are more nucleophilic (although less basic) than the parent hetero compounds. This phenomenon has been explained in terms of the so-called "α effect", such hetero nucleophiles being defined as "supernucleophiles".[5] For a reagent to display supernucleophilicity, it must participate in the rate-determining step, i.e., the new bond must form either simultaneously with the departure of the leaving group (a concerted reaction) or be closely followed by an easy decomposition of the transition state. In addition, the ability of the unshared pair(s) on the adjacent heteroatom to contribute to the nucleophilic character of the reagent is highly important and delocalization of these unshared pairs elsewhere should decrease or eliminate supernucleophilic properties from a given system. The interaction of sulfur–nitrogen unshared pairs in aromatic sulfenamides has been demonstrated by chemical[11] and spectroscopic[12] techniques and shown to be related to substitution on the aromatic rings. From these considerations, and the above observations, it is possible to conclude that aromatic sulfenamides of 6-APA meet the criteria for supernucleophilicity in those cases in which delocalization of sulfur unshared pairs is discouraged, with a progressive decrease in this effect, culminating in derivatives totally lacking such properties, being seen with increased electron-withdrawing substitution.

As an amine, 6-APA is somewhat sterically hindered and is less basic[13] than more typical primary amines, factors which can not be ruled out of participation in the observed results. Further studies of sulfenamide formation in more typical series are required in order to conclusively establish the generality of these observations. Within the present series, however, our results indicate that 6-APA sulfenamide nitrogen possesses supernucleophilic character which is controllable through remote manipulation of electron density on the adjacent heteroatom.

The dependence of aromatic substitution upon the nucleophilicities of the sulfenamides obtained was further demonstrated by subsequent attempts to acylate these products. It was found that although 6-APA phenylsulfenamide could be readily acylated by activated carboxylic acids as expected, this reaction became progressively more difficult as electron-withdrawing groups were added to the aromatic ring until, in the case of the two nitro-substituted derivatives, no acylation conditions permitting the survival of the β-lactam ring could be found. Thus, the nucleophilic character of these sulfenamides toward derivatizing agents other than sulfenyl halides can be readily demonstrated to parallel that outlined above.

Experimental Section[14]

General Procedure for Reaction of Arylsulfenyl Chlorides with 6-Aminopenicillanic Acid (6-APA). A solution of 30 mmol of 6-APA (minimum 99.5% pure) and 30 mmol of sodium bicarbonate in 100 ml of deionized water was stirred mechanically and cooled to 5–10 °C. To this solution was added 30 mmol of the appropriate arylsulfenyl chloride[6] dissolved in 80 ml of CH_2Cl_2 over a period of 30 min. The mixture was then stirred for an additional 10 min at 0–5 °C. The layers were then separated, and the organic layer extracted once with water. The combined aqueous layers were layered with ether and acidified to pH 3.0 with 10% H_2SO_4. The organic layer was separated and combined with one ether extraction of the aqueous phase. The ethereal solution was then dried with Na_2SO_4 and evaporated to yield the free acid derivative or converted to the triethylamine or *N*-ethylpiperidine salt.

Preparation of Methyl 6-(Dibenzenesulfenimido)penicillanoate and Methyl 6-(Benzenesulfenamido)penicillanoate. To an ethereal solution of 6-(dibenzenesulfenimido)penicillanic acid and 6-(benzenesulfenamido)penicillanic acid prepared by the above general procedure was added an excess of ethereal diazomethane. After 15 min, excess acetic acid was added to destroy residual diazomethane and the resulting solution was then washed with 50 ml of 5% Na_2CO_3 solution and dried with $MgSO_4$ and the solvent was removed in vacuo to give the mixture of products in essentially quantitative yield. The products, in a ratio of approximately 90:10, were separated by chromatography on silica gel using 10% ethyl acetate-benzene as eluent.

Methyl 6-(Dibenzenesulfenimido)penicillanoate: NMR ($CDCl_3$) δ 1.42 (3 H, s), 1.65 (3 H, s), 3.55 (3 H, s), 4.44 (1 H, s), 5.28 (1 H, d, J = 4.0 Hz), 5.40 (1 H, d, J = 4.0 Hz), 7.22–7.70 (10 H, m); mass spectrum m/e 446 (parent ion); ir ($CHCl_3$) 5.62, 5.72 μ.

Methyl 6-(Benzenesulfenamido)penicillanoate: NMR ($CDCl_3$ δ 1.48 (3 H, s), 1.61 (3 H, s), 3.72 (1 H, d, J = 10.5 Hz, exchangeable in D_2O/NaOD), 3.75 (3 H, s), 4.40 (1 H, s), 4.65 (1 H, d of d, J = 4.0, 10.5 Hz), 5.38 (H, d, J = 4.0 Hz), 7.15–7.60 (5 H, m); mass spectrum m/e 338 (parent ion); ir ($CHCl_3$) 2.90, 5.62, 5.72 μ.

Preparation of 6-(Phenylacetamido)penicillanic Acid (Penicillin G). A solution of 1.30 mmol of 6-(benzenesulfenamido)penicillanic acid *N*-ethylpiperidine salt in 10 ml of CH_2Cl_2 was treated at room temperature with 3.25 mmol of pyridine followed by 2.86 mmol of phenylacetyl chloride in 5 ml of CH_2Cl_2. After stirring for 90 min, the reaction mixture was extracted three times with 2.5% $NaHCO_3$. The combined extracts were backwashed once with ether, layered with ether, and adjusted to pH 2.5 with 6 N HCl. The aqueous phase was extracted three times with ether and the combined ethereal extracts were dried with Na_2SO_4. After evaporation of the solvent, the residues were dissolved in ethyl acetate and converted to the sodium salt with sodium 2-ethylhexanoate/hexane, yielding 446 mg (77%) of penicillin G sodium salt identical in all respects with a standard sample and which was shown to retain >90% activity vs. *Staph. aureus* by bioautographic techniques.

Acknowledgment. Thanks are due to Dr. W. E. Barth and Dr. I. M. Goldman for helpful discussions and to Mr. L. C. Contillo and Mr. J. W. Homiski for valuable technical assistance.

Registry No.—**1** (R = Ph) NEP, 58816-36-7; **1** (R = Ph) TEA, 58816-37-8; **1** (R = 2-Cl-C_6H_4) NEP, 58816-39-0; **1** (R = 2-Cl-C_6H_4) TEA, 58816-40-3; **1** (R = 4-Cl-C_6H_4) NEP, 58816-42-5; **1** (R = 2-NO_2-C_6H_4) NEP, 58816-44-7; **1** (R = 4-NO_2-C_6H_4) TEA, 58846-85-8; **2** (R = 4-CH_3O-C_6H_4) TEA, 58816-46-9; **2** (R = Ph) NEP, 58816-47-0; **2** (R = Ph) TEA, 58816-48-1; **2** (R = 2-Cl-C_6H_4) NEP, 58816-50-5; **2** (R = 2-Cl-C_6H_4) TEA, 58816-51-6; **2** (R = 4-Cl-C_6H_4) NEP, 58816-53-8; *p*-methoxybenzenesulfenyl chloride, 1950-65-8; benzenesulfenyl chloride, 931-59-9; *o*-chlorobenzenesulfenyl chloride, 14575-10-1; *p*-chlorobenzenesulfenyl chloride, 933-01-7; *o*-nitrobenzenesulfenyl

chloride, 7669-54-7; *p*-nitrobenzenesulfenyl chloride, 937-32-6; 6-aminopenicillanic acid, 551-16-6; 6-(dibenzenesulfenimido)penicillanic acid, 58816-32-3; 6-(benzenesulfenamido)penicillanic acid, 58816-33-4; diazomethane, 334-88-3; methyl 6-(dibenzenesulfenimido)penicillanoate, 58816-34-5; methyl 6-(benzenesulfenamido)-penicillanoate, 58816-35-6; penicillin G, 61-33-6.

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(13) H. D. C. Rapson and A. E. Bird, *J. Pharm. Pharmacol., Suppl.*, **15**, 222 (1963).
(14) Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian A-60 and T-60 spectrometers with DSS or Me_4Si as an internal standard. Ir spectra were determined with a Perkin-Elmer Model 21 spectrometer. All evaporations were conducted in vacuo using a water aspirator.

An Anomeric Effect in Photochemical Hydrogen Abstraction Reactions of Tetrahydropyranyl Ethers[1]

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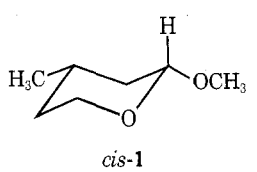
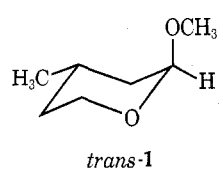
In our previous paper[3] on excited-state ketone initiated hydrogen abstraction reactions of 2-methoxytetrahydropyran, there was some indication that conformational effects might be important. *cis*- and *trans*-2-methoxy-4-methyltetrahydropyran (1) exist primarily in single conformations,[4] and therefore provide an ideal system for studying these effects. The cis isomer exists almost completely in the conformation having the methoxy group equatorial since, in the alternative conformation, a severe 1,3-diaxial interaction between the methyl and methoxy groups is unfavorable. On the other hand, the trans isomer exists almost completely in the conformation with the methyl group in the more favorable equatorial position and the methoxy group axial, which is favored owing to the anomeric effect. A mixture of *cis*- and *trans*-1 was prepared according to literature procedures[5] and a portion was separated by gas chromatography. Assignment of the isomers, based on NMR of the "anomeric" hydrogen, was in agreement with the literature.[5]

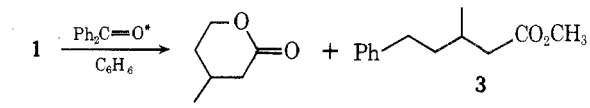


cis-1



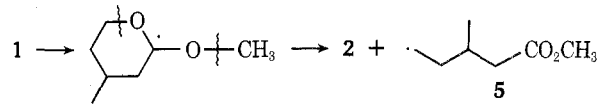
trans-1

Irradiation of mixtures of benzophenone and either the individual isomers of 1 or an isomeric mixture in benzene gave 3-methyl-δ-valerolactone (2) and methyl 3-methyl-5-phenylvalerate (3). The ratio of these products varied somewhat with conditions, but in a typical run, the yields, based on unrecovered starting material, were 29 and 5% for 2 and 3, respectively. Interestingly, no methyl 3-methylvalerate was detected for irradiations in benzene, even though the analogous product was found previously in the 2-methoxytetrahydropyran system.[3]



2

The products are analogous to those observed previously[3] in the 2-methoxytetrahydropyran system, and can be rationalized by initial hydrogen abstraction by excited benzophenone to give free radical **4**, which can then undergo carbon–oxygen bond cleavage in either of two modes to give lactone **2** or open-chain radical **5** which reacts with benzene solvent to give **3**.



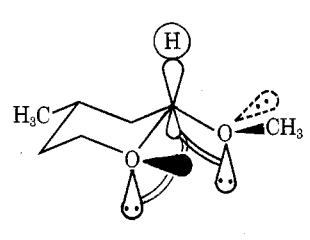
4

The most interesting aspect of the observed chemistry is that the cis isomer of 1 was consumed much more rapidly than the trans isomer. This was obvious when either the individual isomers or isomeric mixtures were irradiated. Relative quantum yields are not a good measure of relative rates of excited state processes. In the present system, the lifetime of benzophenone triplet might be different in the presence of the two individual isomers. Therefore, irradiations of mixtures of the isomers in the presence of benzophenone were carried out and the ratio of rate constants for the disappearance of the individual isomers was calculated by the following formula:[6]

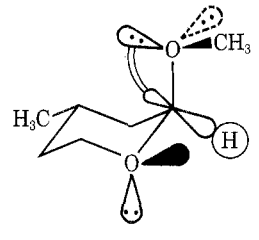
$$k_{cis}/k_{trans} = \ln([cis]/[cis]_0)/\ln([trans]/[trans]_0)$$

The ratio was found to be 8.0 ± 1.4 for several samples irradiated for consumptions of total starting material ranging from 40 to 54%. It was necessary to go to these high conversions to get a large enough change in the trans isomer concentration to determine an accurate ratio. The apparently large variations in the ratio were due to the fact that the function is very sensitive to small changes in the value for the amount of *trans*-1 remaining. The preferential abstraction of an axial hydrogen in this system is even more impressive when comparison is made with 4-*tert*-butylcyclohexanol, which does not contain a ring oxygen. In the latter system, *equatorial* hydrogen abstraction was preferred.[7]

The greater reactivity of *cis*-1, which undergoes abstraction of an axial hydrogen atom, can be rationalized nicely in terms of overlap of nonbonding orbitals on both oxygens with the C–H bond being broken. Thus, the cis isomer has a nonbonding orbital on each of the two oxygens which is antiperiplanar to the bond being broken. The trans isomer, on the other hand, has only one such nonbonding orbital antiperiplanar to the bond being broken and, therefore, the transition state leading to the common free radial 4 is stabilized to a lesser degree by orbital overlap. A similar rationale has been



cis-1



trans-1