Neighboring-Group Participation by Sulfide Sulfur in Solvolytic Interconversion between Penam and Cepham Systems. A Kinetic Study on the Solvolyses of 2′α- and 2′β-Halogeno-substituted-6-phthalimidopenam and 3β-Halogeno-substituted-7-phthalimidocepham Methyl Esters[1]

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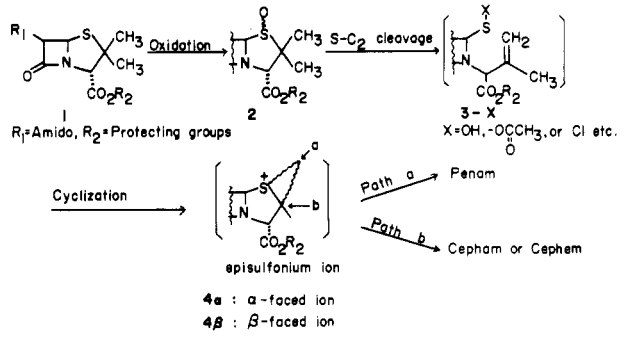
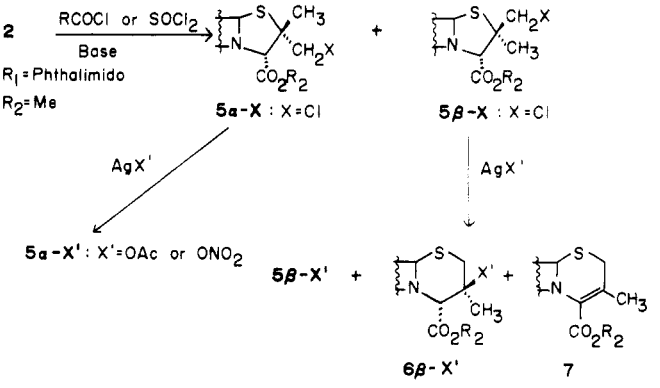
Solvolysis rate constants of 2′α- and 2′β-chloro-6-phthalimidopenam and 3β-chloro-7-phthalimidocepham methyl esters (**5α**-Cl, **5β**-Cl, and **6β**-Cl) in 80% aqueous ethanol were determined under neutral conditions to be 2.93 × 10^{-4}, 4.96 × 10^{-4}, and 9.07 × 10^{-7} s^{-1}, respectively. The relative rates of penam chlorides in comparison with those of neopentyl chloride, which were 9.8 × 10^{7} and 1.65 × 10^{8}, respectively, show a large rate enhancement in the penam system independent of the configuration of the leaving chloro group, while the rate of the cepham chloride when compared with that of 1-methylcyclohexyl chloride was 0.01, showing instead rate retardation in the cepham system. Product analysis revealed that solvolysis of **5α**-Cl afforded ring-retained penam compounds (**5α**-OEt and the lactone **13A**) with complete retention of configuration, while that of **5β**-Cl yielded ring-rearranged cepham products (**6β**-OH, **6β**-Cl, **6β**-OEt, and cephem **7**) with retention of configuration; the same products were found with **6β**-Cl. On the other hand, **5α**-Cl thermally isomerized in Me_2SO gave rise to the same ring-enlarged cepham products obtained from **5β**-Cl, indicating possible existence of a common pathway of isomerization in this solvent. These results were rationalized by invoking neighboring sulfur participation in the penam system but not in the cepham one. A tentative energy diagram is presented for the carbonium ion rearrangement between penam and cepham systems. Finally, as a synthetic extension of this study, a 2′α,2′β-dichloropenam compound was prepared and converted into a 3′-chlorocephalosporin compound.

For the mechanistic interpretations of the penicillin sulfoxide[2-5] rearrangement, the intermediacy of both sulfenic acid **3** and episulfonium ion **4** has been invoked to account for the products and stereochemical consequences of the reaction by Morin et al.[2,3] (see Scheme I). **3** was considered to be formed in a thermal six-electron sigmatropic reaction at an initial stage and **4** in an internal S_N2 displacement by the double bond at a subsequent ring-reclosing step, respectively. In particular, a number of trapping[5] and isolation[6] studies were done under the assumption that the penicillin sulfoxide derived sulfenic acid **3** existed to verify this mechanism. As for the ring-reclosing step, however, mechanistic details are not clear and some ambiguities remain in spite of some related studies.[2,3] This is partly due to the difficulty of producing an episulfonium ion **4** of a known configuration since after the S–C_2 bond cleavage, two regional cases of S_N2 displacement (from the α or β side) which lead to competitive formation of two isomeric episulfonium ions always occur. Thus, stereochemical argument[3] concerning the ring rearrangement becomes more subtle, with the products depending upon various factors such as the side chain, relative thermodynamic stabilities of episulfonium ions, nucleophilicity of a counterion, and the reaction conditions employed.

Scheme I. Proposed Mechanism for Penicillin Sulfoxide Rearrangement



Scheme II. Solvolytic Rearrangement of 2′-Halogenopenicillin Esters



Three groups[7] of investigators, including us, almost coincidently found that penicillin sulfoxides, when thermally treated with an appropriate halogenating reagent,

(1) Presented in part by H. Tanida, an invited lecturer at the 33 Autumn Annual Meeting of Chemical Society Japan, Fukuoka, October 1975; Abstracts Part III, pp 1302–1305.

(2) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, **85**, 1896 (1963); *ibid.*, **91**, 1401 (1969).

(3) E. H. Flynn, Ed., "Cephalosporins and Penicillins", Academic Press, New York and London, 1972. R. D. G. Cooper, L. D. Hatfield, and D. O. Spry, *Acc. Chem. Res.*, **6**, 32 (1973), and references cited therein. For recent reviews, see R. J. Stoodley, *Prog. Org. Chem.*, **8**, 102 (1973); P. G. Sammes, *Chem. Rev.*, **76**, 113 (1976); A. K. Mukerjee and A. K. Singh, *Tetrahedron*, **34**, 1731 (1976).

(4) R. D. G. Cooper and F. L. Jose, *J. Am. Chem. Soc.*, **92**, 2575 (1970); R. D. G. Cooper, *ibid.*, **92**, 5010 (1970).

(5) D. H. R. Barton, F. Comer, D. G. T. Greig, G. Lucente, P. G. Sammes, and W. G. E. Underwood, *J. Chem. Soc. D*, 1059 (1970); D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. W. Taylor, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *ibid.*, 1683 (1970); D. H. R. Barton, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. H. Hewitt, B. E. Looker, and W. G. E. Underwood, *ibid.*, 1137 (1971); D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc. C*, 3540 (1971).

(6) D. O. Spry, *J. Am. Chem. Soc.*, **92**, 5006 (1970).

(7) (a) S. Kukolja and S. R. Lammert, *J. Am. Chem. Soc.*, **94**, 7169 (1972); (b) S. Kukolja, S. R. Lammert, M. R. Gleissner, and A. I. Ellis, *J. Am. Chem. Soc.*, **97**, 3192 (1975); (c) H. Tanida, T. Tsuji, T. Tsushima, H. Ishitobi, T. Irie, T. Yano, H. Matsumura, and K. Tori, *Tetrahedron Lett.*, 3303–3306 (1975); (d) T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, *ibid.*, 3001 (1973).

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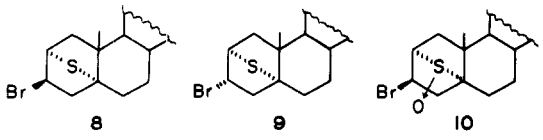
Chart I. Example of Conformational Dependence of Sulfur Participation (k_{rel})



	8	9	10	
90% dioxane		2.3×10^7	1.0	
70% dioxane		1.2×10^8	1.0	
60% dioxane			1.0	0.79

exclusively gave 2-halogeno-substituted penams 5-X which could be successively converted into 3-substituted cephams or cephems under solvolytic conditions. This provided a new procedure for generating episulfonium ions of a known configuration, excluded complications arising from S–C_2 bond breaking, and thus simplified stereochemical explanation of the rearrangement. Along this line, Kukolja[7] et al. were the first to explain the mechanism and stereochemistry of ring rearrangements via the episulfonium ions of known α and β configuration, as shown in Scheme II. They found that the α-chloride 5α-Cl with silver salts affords only one product, i.e., 5α-OAc, and the β isomer 5β-Cl yields three compounds (5β-OAc, 6β-OAc, and 7), which evidently indicates different reactions under the same reaction conditions. Their mechanistic interpretation was that in the case of the β isomer, chlorine is abstracted by a silver ion and the resultant carbonium ion is stabilized by nucleophilic sulfur to form a β-thiiranium ion which gives rise to the three products, while with the α isomer two possible mechanisms are conceivable: (i) participation of the ester group in the stabilization of the carbonium ion or (ii) an "abnormal" type of S_N1 substitution in which the bulky phthalimido group sterically makes difficult the access of sulfur to form a strong bond with the reaction center.

This paper presents a kinetic study on solvolyses of the three chlorides 5α-Cl, 5β-Cl, and 6β-Cl to check the validity of the above mechanistic proposals. Our interest is mainly focused on the role of the neighboring sulfur atom at the position β to the reaction center, since we have shown previously[8] that the 3-*endo* bromide of 2α,5-epithio-5α-cholestan (8) solvolyzes in 70% dioxane 1.2×10^8 times faster by sulfur participation than the corresponding 3-*exo* bromide 9 (see Chart I). As seen from this instance, conformational dependence of neighboring sulfur participation is generally remarkable. Thus, with the aid of our previous structural study[9] on 5α-Cl, 5β-Cl, and 6β-Cl, we discuss in this paper the conformational dependence of neighboring sulfur participation in the solvolyses of both penam and cepham systems.

Results

Hydrolysis Rates. A previously reported procedure[7] was used to prepare the three isomeric chlorides 5α-Cl, 5β-Cl, and 6β-Cl and their solvolysis rates in 80% (v/v) aqueous ethanol were determined by using a Metrom pH-stat titrator (pH meter Model E300B, Impulsomat E473) at constant pH (ca. 7.0), which prevented facile β-lactam ring cleavage. As shown in Figure 1, titration curves were obtained by neutralizing the resultant chloride ion by automatically adding 0.2 N sodium hydroxide solution in 80% EtOH as the solvolysis proceeded. Good first-order kinetic plots were obtained for both 5α-Cl and 5β-Cl. The

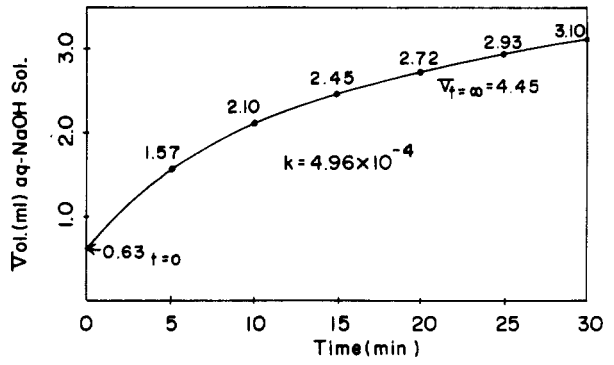


Figure 1. Hydrolysis rate titration curve.

Table I. Rate Constants and Relative Rates of Solvolysis in 80% EtOH

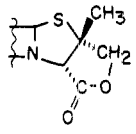
compd	k_1, s^{-1} (60 °C)	k_1, s^{-1} (50 °C)	k_{rel}
5α-Cl	2.93×10^{-4}	1.32×10^{-4}	9.8×10^7
5β-Cl	4.96×10^{-4}	1.88×10^{-4}	1.65×10^8
 17			10^9–$10^{8\,c}$
 11		$3.0 \times 10^{-12\,a}$	1.00
6β-Cl	9.07×10^{-7}		~0.01
 18			620[c]
 19			0.06[c]
 12		4.15×10^{-5} (45 °C)[b]	1.00

[a] The S_N1 rate constant of neopentyl chloride was estimated from that of neophyl chloride, $(CH_3)_3CCHC_6H_5Cl$, $k_1 = 3.36 \times 10^{-7}$ at 50 °C, which was divided by the rate enhancement factor of the substitution of hydrogen by phenyl in hydrolysis in 80% EtOH at 50 °C: $k_{C_6H_5}/k_H = 1.1 \times 10^5$; ref 15 and ref 16. [b] Taken from ref 17. [c] Taken from ref 18.

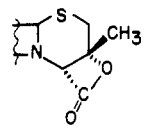
solvolysis of 6β-Cl, however, was so slow that β-lactam ring cleavage occurred even under neutral conditions when the run took a period of 10 half-lives. Therefore, titration values for the first half-life and at theoretical infinity were used in the kinetic plot, which was of first-order like the penam cases. Unfortunately, temperature-variation experiments to obtain activation parameters were aborted because of various experimental difficulties (see Experimental Section). The rate constants thus obtained are listed in Table I. For comparison of relative reactivities, the rate constants of neopentyl chloride (11) for 5α-Cl and 5β-Cl and 1-methylcyclohexyl chloride (12) for 6β-Cl were chosen from the literature as reactivity standards showing no sulfur participation. For product determination, both isomeric penam chlorides (5α-Cl and 5β-Cl) were solvolyzed under the conditions used for kinetic measurement, and the resultant product mixtures of each series were separated over a silica gel precoated PLC plate (Merck Art 5717) for further characterization and identification. Products from 5α-Cl consisted of two crystalline compounds (fractions 1 and 2 in the order of decreasing R_f value on TLC), with isolation yields of 36.7% and 21.8% and melting points of 239 and 113–114 °C, respectively. The IR spectrum of fraction 1 showed a remarkably high carbonyl absorption at 1810 cm^{-1} as well as other β-lactam and phthalimido carbonyl bands at 1780 (two signals

(8) T. Tsuji, T. Komeno, H. Itani, and H. Tanida, *J. Org. Chem.*, 36, 1648 (1971), and references cited therein.
(9) K. Tori, T. Tsushima, Y. Tamura, H. Shigemoto, T. Tsuji, H. Ishitobi, and H. Tanida, *Tetrahedron Lett.*, 3307 (1975); and our publication cited in ref 7.

overlapping) and 1728 cm^{-1}. The NMR spectrum showed complete disappearance of the ester methyl signal, and the mass spectrum had the molecular ion peak at m/e 344. All these spectral data suggested that this compound has a lactone moiety. The elemental analysis also supported this. The conceivable structures were **13A** with a penam nucleus



13-A



13-B

and **13B** with a ring-expanded cepham nucleus. However, the methylene NMR signal appearing as an AB-type quartet centered at δ 4.37 and 4.60 seemed to have shifted too low and the coupling constant, J_{gem} = 10.0 Hz, seemed too small for the **13B** structure. The corresponding signals of cepham compounds usually appeared around δ 2.8–3.2 with the magnitude of the coupling constant in the range of 15–18 Hz. On the other hand, structure **13A** satisfactorily accounted for these results since 2′-substituted penam methylene signals usually appeared at a lower field (usually δ 4.50–3.80) and showed distinctively smaller coupling constants ($J \approx 12$ Hz) than those of the cepham ones as described in our previous publication.[7,9] Although this lactone a priori favored a cis ring-fused structure as shown in **13A**, this was confirmed by comparing the observed chemical shift of the methyl group (δ 1.83) with those of 5α-Cl (δ 1.94 for 2β-Me), 5β-Cl (δ 1.60 for 2α-Me), and **1** (R_1 = phthalimido, R_2 = Me; δ 1.52 for 2α-Me and 1.83 for 2β-Me), which showed disappearance of the lower 2α-methyl signal. Thus, structure **13A** was adopted for this compound. In the structural elucidation of the fraction 2 compound, the presence of the ethoxy group in this molecule was revealed by mass and NMR spectroscopy (see Experimental Section) and the NMR data given above indicated that this compound had the penam nucleus with a β-oriented methyl group. It was noteworthy that the methylene NMR signal appeared as a singlet in this case probably because of free rotation around the C_2–C_2' bond axis, making a sharp contrast with the cleanly split AB-type quartet signal of the corresponding cepham methylene. Thus, structure 5α-OEt was assigned to this compound. On the other hand, the solvolysis of 5β-Cl yielded four β-lactam compounds (fractions 3, 4, 5, and 6, in the order of decreasing R_f on TLC) which were obtained in isolated yields of 3.6%, 10.7%, 26.5%, and 36.2% and had mp 166–167 °C, 194–196 °C, no mp (amorphous), and 200 °C, respectively. The structures of the three products fractions 3, 4, and 6 were easily shown to be **7**, 6β-Cl, and 6β-OH, respectively, using authentic samples. The NMR spectrum of the fraction 5 compound also showed a clear AB-type quartet (δ 2.84 and 3.14 with J = 15.0 Hz) which could be undoubtedly assigned to cepham methylene as well as signals due to the ethoxy group. Based on the similarity of the ^{1}H NMR spectra of 6β-Cl, 6β-OH and this compound, the structure of 6β-OEt was assigned to the fraction 5 compound.

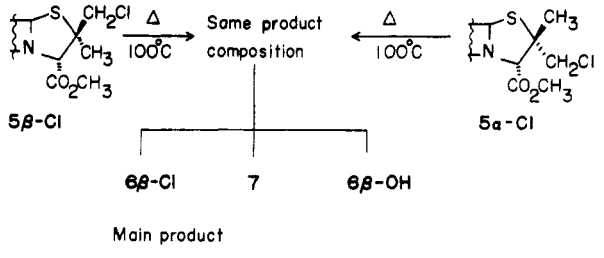
Analysis of the solvolysis products of 6β-Cl was difficult because of accompanying β-lactam ring cleavage. Therefore, structural confirmation of products formed in the first stage of the solvolysis was done by comparing their R_f values on TLC and IR spectra with those of authentic samples. These products were essentially the same as those in the case of 5β-Cl but their ratio was different; they were a mixture of **7**, 6β-OH, and 6β-OEt, besides the starting material. Although the precise product ratio was not sought out in this case, more **7** seemed to have formed than that in the solvolysis of 5β-Cl. Table II summarizes the structures and isolated yields of all solvolysis products.

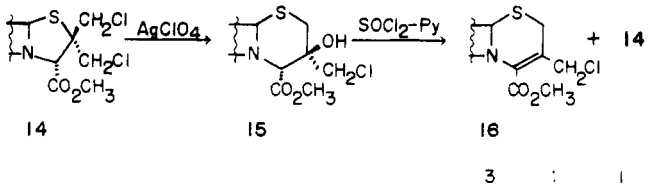
Table II. Solvolysis Products

compd	solvent	temp, °C	products (isolated % yield)
5α-Cl	80% EtOH	60	5α-X, X = OEt (21.8) 13A (lactone) (36.7)
5β-Cl	80% EtOH	60	6β-X, X = OH (36.2) X = OEt (26.5) X = Cl (10.7) 7 (cephem) (3.6)
6β-Cl[a]	80% EtOH	60	6β-X, X = OH X = OEt 7 (cephem)
17[b]	80% acetone		17-OR (2.2)[c] 18-OR (97.8)[c]
18[b]	80% acetone		17-OH (1.4)[c] 18-OH (98.6)[c]
5α-Cl	Me_2SO	100	6β-X, X = Cl (51.6) X = OH (4.4) 7 (4.6)
5β-Cl	Me_2SO	100	6β-X, X = Cl (45.0) 7 (4.6)

[a] Isolated yields were not determined because the reaction was very sluggish. [b] See ref 18. These compounds are *p*-nitrobenzoates. [c] Private communication from Professor S. Ikegami.

Scheme III. Ring Rearrangement in Dimethyl Sulfoxide





Next, since we found in a previous study that heating a mixture of 5α-Cl and 5β-Cl in dimethyl sulfoxide in the presence of weak base, e.g., urea, afforded **7** in a satisfactory yield, thermal rearrangements of 5α-Cl and 5β-Cl to check the solvolytic internal return of chloride anion were carried out in the absence of urea. Both chlorides 5α-Cl and 5β-Cl gave rise to the same product mixture consisting of 6β-Cl as a main component and **7** and 6β-OH as minor ones, suggesting the existence of a common intermediate according to NMR and IR spectroscopic measurements and isolation experiments, as illustrated in Scheme III. Next, as a partial synthetic extension of this reaction, the 2-bis(chloromethyl)penam derivative **14** was prepared and converted by treatment with $AgClO_4$ in aqueous Me_2SO into the 3α-(chloromethyl)-3β-hydroxycepham derivative **15**. Reaction of **15** with thionyl chloride in CH_2Cl_2 yielded 3′-chlorocephalosporin esters **16** and **14** in the approximate ratio of 3:1.

Discussion

A glance at the relative reactivities in Table I clearly discloses the marked solvolytic rate enhancement of the order of ca. 10^8 with both penam chlorides (5α-Cl and

Scheme IV

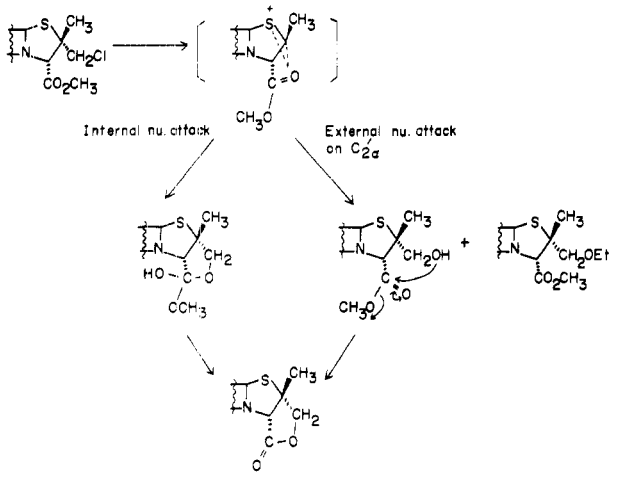
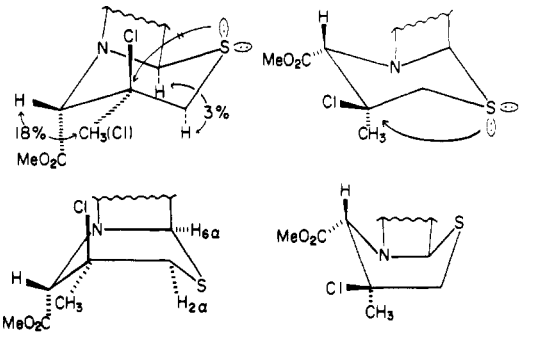


Chart II



5β-Cl) when compared with neopentyl chloride. It is surprising here that 5α-Cl shows the same magnitude of rate enhancement as 5β-Cl, 8, and 17, although it gives exclusively unrearranged penam products (5α-EtO and 13A) with absolute retention of configuration. Two mechanistic rationales by Kukolja et al. for this solvolysis have been quoted in the introduction and seem to eliminate neighboring sulfur participation. Indeed, one of the proposed mechanisms which involves ester participation can account for both observations of large rate enhancement and significant lactone formation in this solvolysis if the rate enhancement observed is a result of a fortuitous coincidence of magnitudes of both neighboring ester and sulfur participation. However, no clear evidence seems to exist for participation by an un-ionized carboxyl group in substitution reactions at a saturated carbon.[10,11] In addition, the question arises here that the formation of 5α-OEt cannot simply be rationalized by the ester participation mechanism which involves a lactone intermediate.[12] Furthermore, as 5α-Cl and 5β-Cl have the same ring conformation, according to a previous study,[9] it seems to be peculiar that neighboring sulfur participation occurs only in the solvolysis of 5β-Cl (as seen later) and not in that of 5α-Cl. Therefore, the new mechanism shown in Scheme IV is proposed. Namely, sulfur participation takes place in the initial stage leading to the transition state and forms the α-faced episulfonium ion intermediate, e.g., 4α. This intermediate is supposed to be trapped partially by the intramolecular ester group acting as an internal nucleophile or totally by an external nucleophile from the α face of the C_2 position. At present, no evidence exists to establish which of the two possible paths to lactone formation is actually used. This scheme assumes that the more favorable γ-lactone 13A is selectively formed in comparison with the β-lactone 13B and the neighboring ester group sterically suppresses nucleophilic attack by an external anion at the C_3 position.

Next, the solvolysis of 5β-Cl in 80% ethanol was considered and found to be undoubtedly controlled by neighboring sulfur participation which causes a large rate enhancement of 10^8 and formation of ring-rearranged products with retention of configuration similar to the case of 17. This mechanistic conclusion agrees with that previously proposed by Kukolja et al.[7b] It is then deduced that crossover between the two solvolytic processes of 5α-Cl and 5β-Cl is strictly prohibited under these reaction conditions, since no common product was obtained in both solvolyses. Heating in Me_2SO, however, gave the same products (6β-Cl, 6β-OH and 7) from 5α-Cl and 5β-Cl in approximately the same yields. This result suggests that crossover may be possible under the special conditions used. If so, crossover from the α-faced intermediate, e.g., 4α, to the β-faced one, 4β, would take place probably via a classical carbenium ion intermediate to give the more thermodynamically stable cepham products 6β-Cl and 6β-OH, rather than penam ones, in addition to 7.

The results from the solvolysis of 6β-Cl in 80% ethanol provide information on the conformational dependence of sulfur participation in the cepham nucleus as shown in Table I. The very low relative rate of 0.01 with 6β-Cl indicates the absence of neighboring sulfur participation in this system. Indeed, comparison of this value with two other typical cases of 3-chlorothiane 18 and 4-chlorothiane 19, the former demonstrating neighboring sulfur participation by the 620-fold rate enhancement and the latter its absence by a rate factor of 0.06, rules out the participation in the solvolysis of 6β-Cl. Products mainly consisting of β-substituted cephams, except olefin 7, also support this. This can be accounted for by the previously determined ring conformation[9] of 6β-Cl. A nuclear Overhauser effect (NOE) of 18% between the α-methyl group at C_3 and the β-proton at C-4 and of others unambiguously pointed to the left configuration in Chart II for 6β-Cl. Furthermore, observation of an NOE of 3% between $H_{6\alpha}$ and $H_{2\alpha}$ suggested that these two protons have a 1,3-diaxial configuration and thus excluded the boat conformations. Therefore, the upper-left chair structure was elucidated as being the most suitable for 6β-Cl. Inspection of this conformation shows that the C_3–Cl bond and one lone pair of electrons on sulfur are in syn parallel alignment and consequently unsuitable for sulfur participation in the ionization step. Therefore, the solvolysis of 6β-Cl proceeds without neighboring sulfur participation to form sequentially a classical type of carbenium ion at first and a β-episulfonium ion from which the observed products result by external nucleophilic attack.

Next, as Kukolja et al. and we observed, both 3β-hydroxy-substituted cephams (6β-OH and 15), when treated with thionyl chloride in the presence of pyridine, give rise to ring-rearranged penam products (5α-Cl and 5β-Cl from 6β-OH and 14 from 15). This reverse rearrangement from the cepham to the penam nucleus probably involves episulfonium ion intermediate(s) formed by sulfur participation at some stage of the reaction. If the formation of a classical cepham carbenium ion were to precede that of the episulfonium ion(s), it might produce both α- and β-episulfonium ions nonselectively. As another possibility, if labile 6α-Cl were to be formed by chlorination

(10) B. Capon, *Q. Rev., Chem. Soc.*, 18, 45 (1964); G. Kohnstam and D. L. H. Williams, "The Chemistry of Carboxylic Acids and Esters", S. Patai, Ed., Interscience-Publishers, London, New York, 1969, Chapter 16, p 765.

(11) E. F. Caldin and J. H. Wolfenden, *J. Chem. Soc.*, 1239 (1936).

(12) If 5α-OEt is formed from the intermediate lactone 13A, it should not bear the ester group but the free carboxylic acid.

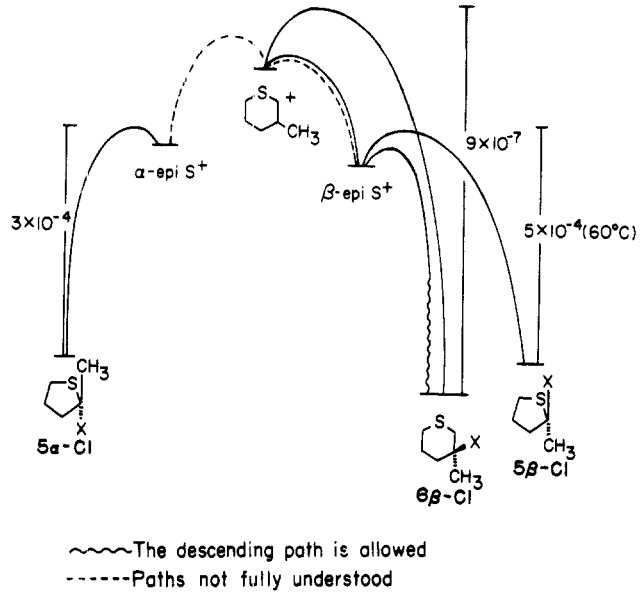


Figure 2. Free-energy diagram of solvolytic interconversions between penams and cephams.

in the first stage, this compound could be ionized quickly due to sulfur participation (see Chart II) to preferably form the α-episulfonium ion from which 5α-Cl and olefin could be derived. In this case, formation of 5β-Cl might be due to a partial interconversion of episulfonium ions. Unfortunately, however, at present no clear evidence has been obtained for these arguments.

As a summary of the discussion thus far, Figure 2 presents a tentative free-energy diagram. We assumed structure 4α for the α-faced intermediate in Figure 2 without any direct evidence against the alternative ester participation mechanism. The neighboring sulfur participation causes stereospecific formation of α- and β-faced episulfonium ions with retention of the configuration in the solvolyses of 5α-Cl and 5β-Cl, respectively. These two solvolytic processes are not interconvertible under normal conditions but possibly become convertible via an intermediately formed classical cepham carbenium ion under special conditions like those in Me_2SO. The α-faced episulfonium ion 4α, accessible from the α-substituted penam 5α-Cl, appears to be thermodynamically less stable than the β-faced one, 4β, which can be directly formed from 5β-Cl but only indirectly from 6β-Cl through an intermediate classical cation because of conformational restraints. Thus, formation of 3β-cepham products is preferable to that of 2β-substituted penam ones under kinetically controlled reaction conditions as well as thermodynamically controlled ones, as shown with the solvolyses of 5β-Cl and 6β-Cl in 80% ethanol. Although the origin of the olefinic cephem product 7 has not been clarified, it may have resulted from 3α-substituted cepham compounds by favorable trans β-elimination or directly from intermediate cations as thermodynamically the most favored process in the above scheme. In conclusion, we have clarified in this study that solvolyses of three penam and cepham chlorides proceeded in different ways from each other under complex steric environments comprised of multiple functional groups in a molecule. Our hope is that this information may be useful for elucidating the mechanisms of chemical and biological transformation reactions between penam and cepham nuclei.

Experimental Section

General. Unless otherwise stated, the uncorrected melting points were determined by using a Yanagimoto hot-stage apparatus. NMR spectra were taken on a Varian T60 spectrometer for solutions in $CDCl_3$ containing 1% Me_4Si as an internal standard, and IR spectra were recorded on a Hitachi 215 grating spectrometer for solutions in $CHCl_3$. $[\alpha]_D$ values were determined by using a Perkin-Elmer 141 polarimeter for solutions in CH_3CN. Mass spectra were obtained with a Hitachi RMU-6 spectrometer. Thin-layer chromatography was performed over Merck precoated Kieselgel GF_{254} plates (Art 5715 and 5717), using a solvent mixture of benzene (3 parts) and ethyl acetate (1 part). The fractions separated are cited in the increasing order of polarity. Table III summarizes some of the experimental data.

Starting Materials for Solvolysis (5α-Cl, 5β-Cl, and 6β-Cl). Penam chlorides (5α-Cl and 5β-Cl) were prepared as reported previously[7] and the cepham chloride (6β-Cl) by thermal isomerization of penam chlorides in Me_2SO at 100 °C, as described later. The physical data for these chlorides were as follows. 5α-Cl: mp 163–166 °C; $[\alpha]^{23.5}_D$ +205.8 ± 2.5° (*c* 0.996, CH_3CN). 5β-Cl: mp 107–108 °C; $[\alpha]^{23.5}_D$ +253.7 ± 3.1° (*c* 0.966, CH_3CN). 6β-Cl: mp 194–196 °C; $[\alpha]^{24.0}_D$ +125.3 ± 5.5° (*c* 0.304, CH_3CN). We previously reported the structural elucidation of these compounds.[7,9]

Kinetic Procedures. Aqueous ethanol (80% v/v) used for the kinetic study was prepared by mixing absolute ethanol purified by a known method[13] with distilled water and kept in a double-stoppered storage bottle for use over a long period. The 0.2 N sodium hydroxide solution in 80% aqueous ethanol was freshly prepared for each run. Titration was performed by using a Metrohm pH-Stat Combi-titrator (a titrator combining a E300B pH meter and a E473 Impulsomat). The reaction vessel was a specially made double-bottom 10-mL three-necked flask equipped with a microelectrode (EA 125-X), thermometer, titrant inlet tube with a thin nozzle head, and a magnetic stirrer. The desired temperature was effectively maintained by circulating water of a constant temperature in the outer sphere from the connected Haake-thermostated water bath. A thin nozzle head was used to obtain clean titration curves. Aqueous ethanol (5 mL) was placed in this reaction vessel and preheated to a constant temperature and then 0.1 mmol (39 mg) of each chloride (5α-Cl, 5β-Cl, and 6β-Cl) was quickly added with vigorous stirring. Titration (automatic addition of base) was immediately started to maintain the pH value of the solution at 7.0, but the reading for the calculation of rate constants was taken 5 min thereafter. The reaction was automatically monitored by recording the amount of base added to neutralize the liberated hydrochloric acid. As usual,[14] first-order rate constants were determined graphically by plotting $\log (A_\infty - A_0)/(A_\infty - A_t)$ vs. time, where A and A_0 denote the amounts of the base consumed at infinity and at initiation time, respectively. With penam cases, very good first-order plots were obtained. Rate measurement over a sufficiently wide temperature range to obtain activation parameters was aborted due to significant solvent evaporation which changed solvent polarity at a temperature over 60 °C. Reproducibility of the rate constants determined was confirmed by repeated experiments. A typical example of the run with 5β-Cl was as follows:

time, min	0	5	10	15	20	25	30
A_t	0.63	1.57	2.10	2.45	2.72	2.93	3.10

$A_\infty = 4.45$, $k = 4.96 \times 10^{-4}$ s^{-1}

The solvolysis of 6β-Cl was so sluggish that β-lactam ring cleavage accompanied it during a long period. Fortunately, however, products at an early stage were confirmed to be solely β-lactam compounds by their TLC and IR spectra. The kinetic plot using the theoretical infinity value increasingly curved downward after the half-life time, also suggesting β-lactam ring

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Table III. Experimental Data

compd	mp, °C	IR ($CHCl_3$), cm^{-1}	NMR ($CDCl_3$, Me_4Si), δ	mass spectrum, m/e
13A (fraction 1)[a]	239	1813, 1795, 1780, 1728	1.83 (s, 3 H, $C_{2\beta}$-CH_3), 4.37, 4.60 (AB q, 2 H, CH_2, J = 10.0 Hz), 5.36 (s, 1 H, C_3-H), 5.47, 5.95 (2 d, 2 H, β-lactam), 7.97 (m, 4 H, aromatic)	344 (M^+), 316, 231, 218, 205, 204, 203, 187, 170, 132, 104
5α-OEt (fraction 2)[a]	113-114	1795, 1780, 1740, 1725	1.77 (s, 3 H, $C_{2\beta}$-CH_3), 1.17 (t, 3 H, OEt, J = 7.0 Hz), 3.34, 3.56 (q, 2, OEt, J = 7.0 Hz), 3.60 (s, 2 H, $C_{2\alpha}$-CH_2), 3.80 (s, 3 H, $COOCH_3$), 4.66 (s, 1 H, C_4-H), 5.61 (m 2 H, β-lactam), 7.83 (m, 4 H, aromatic)	404 (M^+), 376, 358, 345, 317, 290, 285, 271, 257, 258, 244, 218, 187, 172, 132, 104
7 (fraction 3)	166-167 167-168[b]			
6β-Cl (fraction 4)	194-196 194-196[b]			
6β-OEt (fraction 5)	no	175, 1780, ~1730 (two peaks)	1.40 (t, 3 H, OEt, J = 7.2 Hz), 1.35 (s, 3 H, C_3-CH_3), 2.84, 3.17 (AB q, 2 H, C_2-H, J = 15.0 Hz), 3.62 (q, 2 H, OEt, J = 7.2), 3.80 (s, 3 H, $COOCH_3$), 4.83 (s, 1 H, C_4-H), 5.50 (AB q, 2 H, β-lactam), 7.60-8.0 (m, 4 H, aromatic)	
6β-OH (fraction 6)[a]	200 194-195[c]			
14[a,d]	106-108	1798, 1780, 1730-1740 (two peaks)	3.70, 4.18 (AB q, 2 H, α-CH_2Cl, J = 11.5 Hz), 4.19, 4.55 (AB q, 2 H, β-CH_2Cl, J = 12.0 Hz), 3.83 (s, 3 H, CO_2CH_3), 5.16 (s, 1 H, C_3-H), 5.67 (d, 1 H, C_5-H), 5.75 (d, 1 H, C_6-H), 7.80 (m, 4 H, aromatic)	429 (M^+), 400, 392, 358, 341, 314, 242, 206, 187, 146, 142
15[a]	189-190	1788, 1775, 1740, 1728	2.76, 3.56 (AB q, 2 H, C_2-H), J = 15.0 Hz), 3.73 (AB q, 2 H, CH_2Cl, J = 9.5 Hz), 3.82 (s, 3 H, CO_2CH_3), 4.80 (s, 1 H, C_4-H), 5.47 (d, 1 H, C_5-H), 5.67 (d, 1 H, C_6-H), 7.60-8.0 (m, 4 H, aromatic)	
16[a,e]	169-171	1800, 1780, 1730 (two peaks)	3.55 (AB q, 2 H, C_2-H, J = 18.0 Hz), 3.90 (s, 3 H, $COOCH_3$), 4.45, 4.87 (AB q, 2 H, C_3-CH_2, J = 11.0 Hz), 5.14 (d, 1 H, C_6-H), 5.80 (d, 1 H, C_7-H), 7.83 (m, 4 H, aromatic)	392 (M^+), 346, 329, 305, 270, 206, 187, 172, 160, 132, 104

[a] Satisfactory combustion analysis data (±0.3%) were provided for these compounds. [b] Taken from ref 7a. [c] Taken from ref 19. [d] This compounds shows $[\alpha]^{24.5}_D$ +243.5 ± 4.7° (c 0.604, CH_3CN). [e] This compound shows $[\alpha]^{24.5}_D$ +5.1 ± 1.1° (c 0.396, CH_3CN).

cleavage consuming additional base. Thus, the straight line obtained up to the first half-life time was used to obtain the rate constant shown in Table I.

Product Analysis. First, 1 mmol (390 mg) of penam chlorides (5α-Cl and 5β-Cl) dissolved in 50 mL of aqueous ethanol was heated at 60 °C for 2 h as in the kinetic measurement. After the reaction was completed, the mixture was immediately poured into cold water, extracted three times with ethyl acetate, dried over magnesium sulfate, filtered, and condensed under reduced pressure, giving oily products which were separated by preparative TLC and characterized as shown below.

Solvolysis products from 5α-Cl gave two pure compounds, fraction 1 (125 mg, 36.7%) and fraction 2 (87 mg, 21.8%), isolated. The fraction 1 compound was identified as **6β-phthalimido-2α-(hydroxymethyl)-2β-methylpenam-3α-carboxylic acid lactone (13A)**: mp 239 °C; IR ($CHCl_3$) 1813 (γ-lactone C=O), 1795 (β-lactam C=O), 1780, 1728 (phthalimido C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ (s, 3, $C_{2\beta}$-CH_3), 4.37 and 4.60 (AB q, 2, $C_{2\alpha}$-CH_2, J = 10.0 Hz), 5.36 (s, 1, $C_{3\alpha}$), 5.47 and 5.95 (2 d, 2, $C_{5\alpha}$, $C_{6\alpha}$), 7.97 (m, 4, aromatic); mass spectrum, m/e 344 (M^+), 316, 231, 218, 205, 204, 203, 187, 170, 132, 104. Anal. Calcd for $C_{16}H_{12}O_5N_2S$: C, 55.80; H, 3.51; N, 8.14; S, 9.32. Found: C, 55.91; H, 3.85; N, 7.89; S, 9.47.

The fraction 2 compound was identified as **methyl 6β-phthalimido-2β-methyl-2α-(ethoxymethyl)penam-3α-carboxylate (5α-OEt)**: mp 113–114 °C; IR ($CHCl_3$) 1795, 1780, 1740, 1725 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77 (s, 3, $C_{2\beta}$-CH_3), 1.17 (t, 3, OCH_2CH_3, J = 7.0 Hz), 3.34 and 3.56 (q, 2, OCH_2CH_3, J = 7.0 Hz), 3.60 (s, 2, $C_{2\alpha}$-CH_2), 3.80 (s, 3, $COOCH_3$), 4.66 (s, 1, $C_{3\alpha}$), 5.61 (m, 2, $C_{5\alpha}$, $C_{6\alpha}$), 7.83 (m, 4, aromatic); mass spectrum, m/e 404 (M^+), 376, 358, 345, 317, 290, 285, 271, 258, 257, 244, 218, 187, 172, 132, 104. Anal. Calcd for $C_{19}H_{20}O_6N_2S$: C, 56.42; H, 4.98; N, 6.93; S, 7.93. Found: C, 56.61; H, 5.07; N, 6.70; S, 8.19.

Solvolysis products from 5β-Cl gave four pure compounds, fraction 3 (13 mg, 3.6%), fraction 4 (42 mg, 10.7%), fraction 5 (106 mg, 26.5%), and fraction 6 (135 mg, 36.2%), isolated. The fraction 3 and 4 compounds were identified as methyl 7β-phthalimido-3-methyl-3-cephem-4α-carboxylate (7) and methyl 7β-phthalimido-3β-chloro-3α-methyl-cepham-4α-carboxylate (6β-Cl), respectively, by using authenitc samples. 7: mp 166–167 °C (lit.[7] mp 167–168 °C). 6β-Cl: mp 194–196 °C (lit.[7] mp 194–196 °C).

The fraction 5 compound was identified as **methyl 7β-phthalimido-3β-ethoxy-3α-methylcepham-4α-carboxylate (6β-OEt)**: amorphous; IR ($CHCl_3$) 1795, 1780, 1730 (two peaks) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (t, 3, OCH_2CH_3, J = 7.2 Hz), 1.35 (s, 3, $C_{3\alpha}$-CH_3), 2.84 and 3.17 (AB q, 2, C_2, J = 15.0 Hz), 3.62 (q, 2, OCH_2CH_3, J = 7.2 Hz), 3.80 (s, 3, $COOCH_3$), 4.83 (s, 1, $C_{4\alpha}$), 5.50 (q, 2, $C_{6\alpha}$, $C_{7\alpha}$), 7.60–8.0 (m, 4, aromatic).

The fraction 6 compound was identified as **methyl 7β-phthalimido-3β-hydroxy-3α-methylcepham-4α-carboxylate (6β-OH)** by comparison with the sample obtained from the experiment described below: mp 200 °C (lit.[19] mp 194–195 °C). Anal. Calcd for $C_{17}H_{16}O_6N_2S$: C, 54.24; H, 4.29; N, 7.44; S, 8.52.

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Found: C, 54.22; H, 4.17; N, 7.56; S, 8.45.

The solvolysis products from 6β-Cl were confirmed by comparison of TLC and IR data with those of authentic samples.

Thermal Isomerization of 5α-Cl and 5β-Cl in Me_2SO. Samples of 0.6 g of both penam chlorides, 5α-Cl and 5β-Cl, were dissolved in 20 mL of purified Me_2SO and kept at 100 °C for 1 h for complete isomerization. Next, the reaction mixture was poured into cold water and extracted twice with ethyl acetate. The organic layer was repeatedly washed with water to remove Me_2SO completely, dried over anhydrous magnesium sulfate, filtered, and condensed under reduced pressure to leave crude product mixtures from both chlorides, which showed three TLC spots of almost the same R_f values. Their NMR and IR spectra were also very similar, suggesting formation of the same products. Separation of both reaction mixtures on preparative TLC plates yielded 6β-Cl as a major product (270 mg from 5β-Cl and 310 mg from 5α-Cl) and almost the same amounts of minor products 7 and 6β-Cl (20–30 mg of 7 and 25 mg of 6β-OH from both chlorides), confirming the formation of the same products from both. The formation of 6β-OH could not be suppressed even by an attempted complete removal of water from the Me_2SO using an activated alumina column and molecular sieves. The structural elucidation of 7 and 6β-OH was straightforward by comparison of melting point and spectral data with the reported values.[7,19] The structure of 6β-Cl was previously reported by us.[9]

Methyl 6β-Phthalimido-2α,2β-bis(chloromethyl)penam-3-carboxylate (14). The oxidation of 0.6 mmol of 5β-Cl (235 mg) with *m*-chloroperbenzoic acid by a conventional method afforded the *R* sulfoxide, which was successively subjected, without purification, to thermal sulfoxide rearrangement in the presence of equimolar amounts of acetyl chloride and pyridine, using a reported method.[9] After the usual workup, the resultant crude crystalline product was recrystallized from a solvent mixture of dichloromethane and ether to afford a pure sample of the title compound in an isolated yield of ca. 40% (102 mg): mp 106–108 °C; $[\alpha]^{24.5}_D$ +243.5 ± 4.7° (*c* 0.604, CH_3CN); IR ($CHCl_3$) 1798, 1780, 1730–1740 (two peaks) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 and 4.18 (AB q, 2, $C_{2\alpha}$-CH_2Cl, J = 11.5 Hz), 4.19 and 4.55 (AB q, 2, $C_{2\beta}$-CH_2Cl, J = 12.0 Hz), 3.83 (s, 1, $C_{3\alpha}$), 5.67 (d, 1, $C_{5\alpha}$), 5.75 (d, 1, $C_{6\alpha}$), 7.80 (m, 4, aromatic); mass spectrum, *m/e* 429 (M^+), 400, 392, 358, 341, 314, 242, 206, 187, 160, 146, 142. Anal. Calcd for $C_{17}H_{14}O_5N_2SCl_2$: C, 47.56; H, 3.29; N, 6.53; O, 18.63; Cl, 16.34. Found: C, 47.75; H, 3.64; N, 6.04; O, 18.48; Cl, 16.34.

The *R* sulfoxide derived from 5α-Cl, having the cis S–O bond with respect to the C_2–CH_2Cl bond, did not produce 14 at all as reported by Spry[6] with similar systems having the acetoxy substituent in place of the chlorine.

Methyl 7β-Phthalimido-3α-(chloromethyl)-3β-hydroxycepham-4α-carboxylate (15). 14 (1 mmol, 429 mg) was dissolved in 25 mL of 80% aqueous Me_2SO containing an equimolar amount of $AgClO_4$ (207 mg) and kept at 45 °C for 3 h. After the same workup, except for filtration through a Celite layer, used in the thermal rearrangement of penam chlorides in Me_2SO, the resultant crude crystalline product was recrystallized from a mixed solvent of acetone and ether and gave a pure sample of **15** in 78.0% yield (320 mg): mp 189–190 °C; IR ($CHCl_3$) 1788, 1775, 1740, 1728 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.76, 3.56 (AB q, 2, C_2, J = 15.0 Hz), 3.73 (q, 2, $C_{3\alpha}$-CH_2Cl, J = 9.5 Hz), 3.82 (s, 3, CO_2CH_3), 4.80 (s, 1, $C_{4\alpha}$), 5.47 (d, 1, $C_{6\alpha}$), 5.67 (d, 1, $C_{7\alpha}$), 7.60–8.0 (m, 4, aromatic). Anal. Calcd for $C_{17}H_{15}N_2O_6SCl$: C, 49.70; H, 3.68; N, 6.82; S, 7.79; Cl, 8.63. Found: C, 49.82; H, 3.75; N, 6.62; S, 8.17; Cl, 8.33.

Methyl 7β-Phthalimido-3-(chloromethyl)-3-cephem-4-carboxylate (16). To a benzene solution of 0.146 mmol of **15** (60 mg dissolved in 2 mL of benzene) and 0.438 mmol of pyridine was added 0.438 mmol of thionyl chloride dropwise at room temperature under stirring, and the mixture was heated at 80 °C for 10 min while gas evolution was observed. Next, the reaction mixture was quickly poured into cold 3% aqueous sodium bicarbonate solution, extracted with ethyl acetate twice, dried over magnesium sulfate, filtered, and condensed under reduced pressure, leaving an oily product mixture (58 mg) which showed two spots on TLC analysis. The preparative TLC separation of this mixture afforded a higher R_f fraction compound (12 mg, 19.1%), which was found to be **14** by comparison of its melting point and spectral data with those of the authentic sample, and also the pure lower R_f fraction compound (40 mg, 52.3%), which was determined to be **16** on the basis of the spectral and analytical data: mp 169–171 °C; $[\alpha]^{24.5}_D$ +5.1 ± 1.1° (*c* 0.396, CH_3CN); IR ($CHCl_3$) 1800, 1780, 1730 (two peaks) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.55 (AB q, 2, C_2, J = 18.0 Hz), 3.90 (s, 3, $COOCH_3$), 4.45 and 4.87 (AB q, 2, $C_{3\alpha}$-CH_2Cl, J = 11.0 Hz), 5.14 (d, 1, $C_{6\alpha}$), 5.80 (d, 1, $C_{7\alpha}$), 7.83 (m, 4, aromatic); mass spectrum, *m/e* 392 (M^+), 346, 329, 305, 270, 206, 187, 172, 160, 132, 104. Anal. Calcd for $C_{17}H_{13}N_2O_5SCl$: C, 51.99; H, 3.34; N, 7.13; S, 8.15; Cl, 9.03. Found: C, 51.79; H, 3.45; N, 7.06; S, 8.19; Cl, 9.11.

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Registry No. 5α-Cl, 39067-79-3; 5α-OEt, 73805-78-4; 5β-Cl, 51415-59-9; 6β-Cl, 40146-21-2; 6β-OH, 51815-69-1; 6β-OEt, 73816-18-9; 7, 38584-05-3; 11, 753-89-9; 12 (X = Cl), 931-78-2; 13A, 73805-79-5; 14, 73805-80-8; 15, 73805-81-9; 16, 73805-82-0; 17-OH, 58346-65-9; 18-OH, 54288-61-8.

Organic Semiconductors Based on Diaminodicyanothiophene and Diaminodicyanoselenophene

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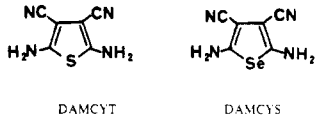
Several new derivatives of 2,5-diamino-3,4-dicyanothiophene (DAMCYT) as well as of the new compound 2,5-diamino-3,4-dicyanoselenophene (DAMCYS) are described. Conversions of a disulfinyl derivative and an *N,N*-bis(chlorothio) derivative to conducting polymers are reported.

In our continuing effort[1] to emulate polythiazyl[2] [$(SN)_x$], we decided to prepare polymers with the backbone shown in Figure 1. These polymers could be envisioned as alternating sulfur diimides and diaminothiophenes (diaminoselenophenes). The latter are expected to be extremely unstable and have not been described in the literature. On the other hand, diaminodicyanothiophene (DAMCYT) is a known compound,[3] but DAMCYS (the



DAMCYT DAMCYS

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