packed with a silica gel slurry (75 mL) in petroleum ether. The column was eluted with petroleum ether to provide pure (*E*)-1-[^{125}I]diiodo-1-alkene, which cochromatographed with respective cold authentic sample. Recovery of the ^{125}I after column chromatography was generally 90%.

General Procedure E. Synthesis of Alkyl (*E*)-18-[^{125}I]-Iodotellura-17-octadecenoate Analogues 10a,c,d (Scheme II). The dialkyl ditelluraalkanedioate substrate (**7a**, **7c**, or **7d**; 0.1 mmol) was dissolved in EtOH (5 mL, and the corresponding sodium tellurol (**8a**, **8c**, or **8d**) was generated by $NaBH_4$ reduction under argon atmosphere. The [^{125}I]diiodoalkene substrate (**6a**, **6b**, or **6c**), obtained as described in procedure D, was dissolved in EtOH (2 mL) and added to the reaction mixture. The solution was stirred for 1 h in the dark at room temperature under argon atmosphere, diluted with 0.9% saline solution (25 mL), and extracted with Et_2O (2 × 25 mL). The ether portion was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated under argon at ~70 °C. The residue (syrup) was dissolved in petroleum ether and applied to a column packed with a silica gel slurry (~65 mL) in petroleum ether. The column was eluted with petroleum ether (ca. 180 mL) to remove the unreacted [^{125}I]diiodoalkene. The column was then eluted with C_6H_6, and fractions (18 mL each) were collected. The fractions (generally 3 to 7) containing the product, (*E*)-18-[^{125}I]iodotellura-17-octadecenoate (compared with cold authentic sample on TLC, SiO_2 GF in benzene), were collected and evaporated to provide (60 ± 5%) of the alkyl (*E*)-18-[^{125}I]-iodotellura-17-octadecenoate.

General Procedure F. Preparation of (*E*)-18-[^{125}I]Iodotellura-17-octadecenoic Acid Analogues (10a,c,d). The hydrolysis was performed as described in general procedure C. The ^{125}I-labeled fatty acid ester (**9a**, **9c**, or **9d**) obtained from general procedure E was dissolved in EtOH (10 mL) and refluxed for 1 h with 1 N NaOH (1 mL). Following dilution with H_2O (~50 mL), the mixture was cooled to room temperature and extracted with Et_2O. The ether extract was discarded, and the aqueous portion was adjusted to pH 1 with 1 N HCl and extracted with ether (2 × 25 mL). The ether portion was washed with H_2O and dried over anhydrous Na_2SO_4. Evaporation of the ether portion under argon at ~40 °C provided the ^{125}I-labeled fatty acid **10a**, **10c**, or **10d**, which was stored under argon at <0 °C.

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Registry No. **1a**, 14916-79-1; **1b**, 31333-13-8; **1c**, 51887-25-3; **2a**, 63478-76-2; **2b**, 10160-28-8; **2c**, 18202-11-4; **3a**, 87462-63-3; **3b**, 87462-64-4; **3c**, 87462-65-5; **4a**, 87462-66-6; **4b**, 87462-67-7; **4c**, 87462-68-8; **5a**, 87462-69-9; **5b**, 87462-70-2; **5c**, 87462-71-3; **6a**, 87462-72-4; **6a** (^{125}I labeled), 87462-75-7; **6b**, 87462-73-5; **6b** (^{125}I labeled), 87462-76-8; **6c**, 87462-74-6; **6c** (^{125}I labeled), 87462-77-9; **7a**, 87462-78-0; **7b**, 81579-34-2; **7c**, 87462-79-1; **8a**, 87462-80-4; **8c**, 87462-81-5; **9a**, 87462-82-6; **9c**, 87462-83-7; **10a**, 87462-84-8; **10c**, 87462-85-9; **10d**, 87462-86-0; **10a** (^{125}I labeled), 87462-87-1; **10b** (^{125}I labeled), 87462-88-2; **10c** (^{125}I labeled), 87462-89-3.

Electronic Structures of Cephalosporins and Penicillins. 15. Inductive Effect of the 3-Position Side Chain in Cephalosporins

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Induction appears to be the primary means by which the side chain at position 3 of the cephem nucleus influences the chemical reactivity of the β-lactam ring. In vitro antibacterial activity data suggest that when the cephalosporin is in the active site of the target bacterial enzymes, the presence of a leaving group in the side chain can promote inhibition.

It has long been known that electron-withdrawing groups on the 3-position of cephalosporins enhance antibacterial activity.[1] Linear relationships between inductive σ_I constants for several 3-substituents and various other physicochemical properties that reflect the reactivity of the β-lactam ring toward nucleophiles have been discussed.[2-4] As indicated in Figure 1, a number of properties of, or related to, the β-lactam ring are now known to correlate with antibacterial activity of the compounds.[4-10] These include the theoretical transition-state energy (TSE), the net atomic charge on the β-lactam carbonyl oxygen [$Q(O_9)$], and the overlap population of the β-lactam carbonyl [$n(C_8{=}O_9)$] (all computed for model cephem structures), as well as experimental alkaline hydrolysis rates and carbon-13 chemical-shift differences for C_3 and C_4 measured for cephalosporins.[4,10,11]

Intuitively, it is reasonable that because of the intervening enamine system, the inductive effects of the 3-position side chain would have a very important, even dominant, influence on the β-lactam ring. However, without adequate data, it is difficult to conclude definitely that the effect of the substituent is *purely* inductive.[3,12]

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0022-2623/84/1827-0063$01.50/0

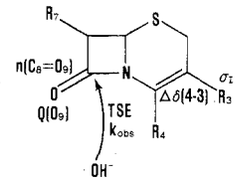


Figure 1. Some properties of cephalosporins related to each other and to in vitro Gram-negative activity. Typically, R_7 is an acylamino side chain that has a minor influence on the chemical reactivity of the molecule, except in the case of phenylglycyl, which undergoes intramolecular reactions (ref 2 and 8). Biological activity depends strongly on R_7. The R_4 side chain is carboxyl and is essential for activity.

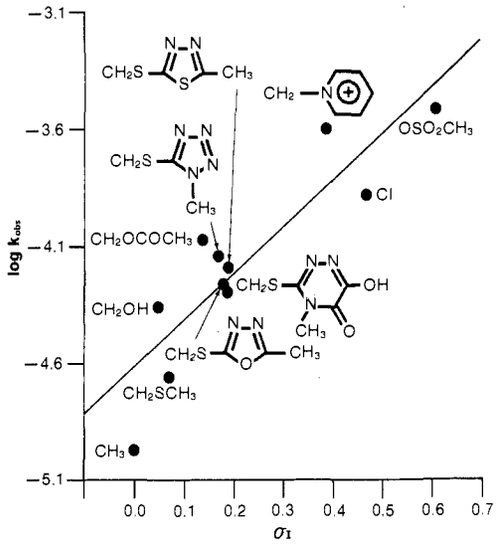
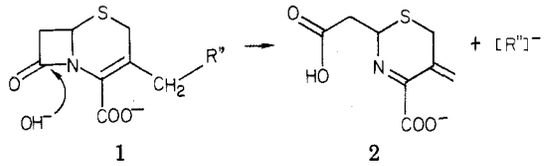


Figure 2. Relationship between log k_{obsd}, measured at pH 10 for 7-(thien-2-ylacetyl)cephalosporins, and inductive substituent constants for the 3-R side chains shown.

In the case of cephalosporins with side chains of similar inductive effect, resonance or hyperconjugative effects may differentiate the reactivities. In the case of cephalosporins with leaving groups R″ at the 3′-position, the following mechanism can occur.[13,14]



1 2

One would expect that the differing nucleofugalities[15] of

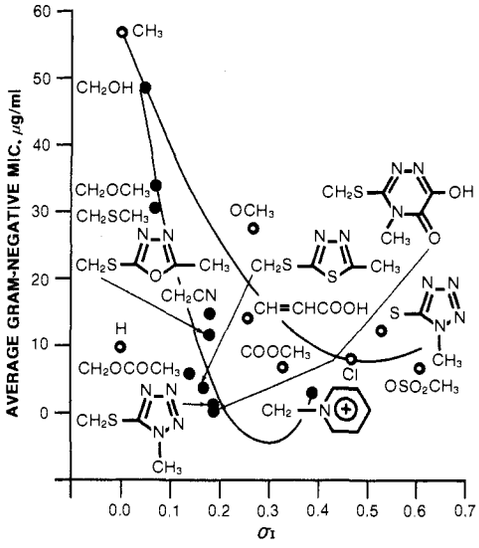


Figure 3. Relationship between average Gram-negative MICs of 7-(thien-2-ylacetyl)cephalosporins and inductive substituent constants for the 3-R side chain. Two separate parabolic curves are fit to points for the nonleaving groups (open circles) and to the points for side chains with potential leaving groups (filled circles). The 3-H point is excluded from the fit of these curves. The Gram-negative organisms used to determine the MICs are *Shigella sonnei, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes,* and *Salmonella heidelberg.*

the leaving groups would influence to some extent the feasibility of a base-catalyzed, concerted reaction.

Consider first the nonenzymatic opening of the β-lactam ring. Alkaline hydrolysis rate constants are available for a closely related series of 3-substituted 7-(thien-2-ylacetyl)cephalosporins.[2,11,16] The σ_I values for the corresponding 3-R groups are known.[17-23] It should be noted that the σ_I values from trimethylammonium, which were previously used[2,3] for pyridiniomethyl, are lower than the value actually measured for pyridiniomethyl.[22] As seen in Figure 2, an excellent corrlation is obtained between the two properties, alkaline hydrolysis rate and σ_I. Electron-withdrawing groups promote the reactivity of the β-lactam ring, and only about 22% of the variance (r^2) in the hy-

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(14) It should be emphasized that the *base*-catalyzed, concerted mechanism 1 → 2 is the only reaction discussed in reference 13. In *acid*-catalyzed hydrolysis, which is investigated in ref 12, the inductive effect of the 3-R substituent is expected to impede, rather than enhance, the hydrolysis rate because an electron-withdrawing 3-R group will lower the basicity of the β-lactam oxygen and nitrogen. This expectation is consistent with the experimental k_H values for the few cephalosporins with different 3-position side chains reported in reference 12. Furthermore, since the rate of acid-catalyzed hydrolysis increases monotonically with decreasing pH and since the β-lactam nitrogen and oxygen have extremely low basicities (ref 12), protonation of one of these atoms may be the rate-determining step. One other possibility is that if a potential leaving group R″ is basic enough to be protonated in the rate-determining step, then departure of HR″ could be concerted with attack of a nucleophile at the β-lactam carbonyl carbon.
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(23) In cases where σ_I values are for R″ groups, one can estimate the corresponding CH_2R'' values by dividing these values by a factor of 2.8 as recommended in reference 17. For instance, after taking into account the intervening methylene group, the $OCOCH_3$ and SCH_3 values in reference 19 can be scaled for CH_2OCOCH_3 and CH_2SCH_3.

drolysis rates is left unexplained by induction.

$$\log k_{obsd} = 1.989\sigma_I - 4.62$$

$$n = 11, r = 0.89, s = 0.21, p = 0.0003$$

One can see in Figure 2 that a straight line ($r^2 = 0.999$, $p = 0.0161$) could be fit through the points for methyl, chloro, and mesylate. These three groups cannot participate in the mechanism **1** → **2**. It is interesting to note, therefore, that *all* the other data points in Figure 2 fall *above* this (undrawn) line. With the available data, therefore, it remains difficult to exclude the possibility that groups capable of partipicating in the leaving group mechanism may hydrolyze faster than on the basis of induction alone. The standard error of the slope of the drawn regression line is just about large enough (±0.348) that one cannot conclude with confidence that separate lines should be drawn through the points for nonleaving and leaving groups.

The chemical reactivity data are interesting, but more relevant in the case of cephalosporins are the biological data. When a cephalosporin is reversibly bound to the active site of β-lactam binding proteins,[8,24] the proximity of various functionalities near the 3-R side chain may promote simultaneous departure of a leaving group and β-lactam acylation of a nucleophilic functionality in the active site. For instance, a relatively poor leaving group, like hydroxyl, is expelled in enzymatic β-lactam hydrolysis even though it is not expelled in the nonenzymatic reaction.[25]

A concerted nature of the acylation reaction might make the cephalosporin more active than expected from just an inductive effect of the 3-R group. The data compared in Figure 3 address this possibility. Besides the 3-substituents in Figure 2, some additional substituents can be included in Figure 3 because of the availability of σ_I values[21-23] and average Gram-negative minimum inhibitor concentration (MIC) data.[8] Antibacterial activity is expressed in terms of MIC for reasons discussed previously.[8,11,26]

At first sight, the data points in Figure 3 appear almost random. With all the data combined, only 25 and 42% of the variance is accounted for by linear and parabolic regression equations, respectively. However, if one views the 3-hydrocephem data point as an active outlier, as will be discussed later, then the remaining data in the figure fall into well-defined sets. One set of 3-R groups cannot operate through the leaving group mechanism and consists of R = CH_3, OCH_3, CH=CHCOOH, Cl, 5-methyl-1,2,3,4-tetrazol-5-ylthio, and OSO_2CH_3. The other set consists of 3-CH_2R'' structures, where R'' is a group capable of undergoing **1** → **2**.

Two parabolic equations are drawn in Figure 3. These give better statistics than the two corresponding linear equations.

3-R

$$MIC = 192.575\sigma_I^2 - 195.16\sigma_I + 56.9$$

$$n = 7, r = 0.95, s = 6.8, p = 0.0085$$

$$MIC = -75.43\sigma_I + 45.6$$

$$n = 7, r = 0.85, s = 10.7, p = 0.0164$$

3-CH_2R''

$$MIC = 819.877\sigma_I^2 - 475.18\sigma_I + 64.2$$

$$n = 10, r = 0.94, s = 6.2, p = 0.0004$$

$$MIC = -123.37\sigma_I + 35.6$$

$$n = 10, r = 0.72, s = 12.2, p = 0.0188$$

The curve fit to the 3-CH_2R'' data points in Figure 3 is obviously dependent on one point (pyridinium) for preferring a parabolic rather than linear equation. However, the 4-carboxamidopyridinium derivative has similar activity[8] and probably would have a σ_I value similar to that measured for pyridinium. Thus, an additional point for supporting the parabolic curve could be added.

TSEs are known to correlate parabolically with MICs.[6,7] It is not surprising, therefore, that about 53% of the variance of the TSEs for all 18 cephalosporins in Figure 3 is explained by the σ_I values in a linear regression ($p = 0.0006$). If methoxy and mesylate, for which the TSEs predict a smaller activating effect on the β-lactam ring than would be expected from the σ_I values, are arbitrarily excluded, then 78% of the variance is explained ($p = 0.0000$). The σ_I values for these oxygen-linked substituents do not reflect the back-donating effect of the oxygen lone pairs; the TSEs, on the other hand, show this deactivating resonance effect. The overall high correlation between σ_I and TSE means that the TSE is mainly reflecting the inductive effect of the 3-substituent.

There are no hydrolysis rate data known for 3-hydrocephalosporins, which would be useful in understanding the exceptional activity imparted by this substituent. However, there is information available for ceftizoxime in regard to its cell-wall permeability, β-lactamase resistance, affinity for penicillin-binding proteins, and intrinsic inhibitory activity against peptidoglycan biosynthesis.[27] The outstanding activity of this 3-hydrocephalosporin appears to be due to a combination of desirable properties. Its resistance to β-lactamase hydrolysis and its binding to PBPs associated with lysis and filament formation derive mainly from the 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino] side chain. However, the superiority of ceftizoxime at penetrating into the periplasmic space of bacterial cells may stem not only from the 7-position side chain but also from the 3-hydro substituent. The low MIC shown by the 3-hydro-7-(thien-2-ylacetyl)cephalosporin in Figure 3 could conceivably be due in part to an exceptionally high concentration at the target enzymes.

Another reason for 3-hydro being an outlier in Figure 3 is that the 3-hydro group cannot hyperconjugatively donate electron density into the cephem ring, an effect known to decrease the reactivity of the β-lactam.[6,28] The σ_I values do not reflect this resonance effect.

As an alternative to the grouping of points in Figure 3, one may want to classify all CH_2R'', including CH_3, into

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one set and the remaining so-called "direct" 3-R, excluding H, into a second set. With this possibility, the parabolic curve through the CH_2R'' points remains about the same ($r = 0.96$, $p = 0.0000$), but the MICs of the remaining direct 3-R points are practically independent of the σ_I value ($r = 0.64$, $p = 0.4547$ for a parabolic curve). Intuitively, it is difficult to understand why activity for the direct substituents should be independent of the inductive effect. Hence, the initial way of classifying the substituents is preferred, at least until additional data are available.

Curves representing the lowest MIC achievable at a particular σ_I value would be of interest because the curves should define the best activity that can be obtained with that degree of electron-withdrawing effect. Poorer activity than represented by such a boundary curve could be due to any number of factors.[8] Often the biological activity of poorly active compounds is not well documented because the compounds are not as well studied as more active compounds.

The significant message from Figure 3 is that those cephalosporins with a leaving group (lower curve) can have much better Gram-negative activity than those with a directly attached R group (upper curve). It should be noted that none of the leaving groups have significant antibacterial activity in their own right,[29] so this is not a factor in differentiating the two types of side chain. Also, there is no known general distinction between the direct 3-R and 3-CH_2R'' compounds in regard to relative resistance to β-lactamases or relative ability to penetrate into the periplasmic space of bacterial cell walls.[8,30,31] The superior activity of cephalosporins with leaving groups is therefore believed to be due, in part at least, to a better ability to acylate the active sites that normally transform the X-D-alanyl-D-alanine substrate in peptidoglycan biosynthesis.

Whereas this paper is principally concerned with electronic effects, some comments about molecular shape are needed for perspective. The three-dimensional shape of an inhibitory molecule can be one of the important factors in determining how well it fits into the active site of each lethal target enzyme.[8,32] One study involving model enzyme systems of limited relevance to the target enzymes found that for a heterogeneous set of antibiotics containing different β-lactam nuclei, goodness of fit was *more* important than chemical reactivity.[33] This is reasonable because of the wide variety of β-lactams that were being compared. On the other hand, for a series of related structures where molecular shape is invariant in the sterically important regions, such as apparently with the 3-substituted 7-(thien-2-ylacetyl)cephalosporins, chemical reactivity becomes a dominant determinant of antibacterial activity.[34]

One may antipicate that when the three-dimensional structures of biologically essential transpeptidases and carboxypeptidases are known, a rational mechanism for cooperative departure of a leaving group and opening of the β-lactam will become evident. Unfortunately, the serine-containing bacterial enzymes have so far shown no homology to serine proteases for which crystallographic atomic coordinates are available,[35] and the X-ray studies on model bacterial enzymes are only now on the verge of revealing the active sites at atomic resolution.[36,37]

It is known that once a β-lactam antibiotic molecule has reached an active site, associated with it first reversibly and then covalently, the normal turnover of the bacterial enzyme is inhibited. The reason for the inhibition of turnover may lie in the fact that the 4-carboxylate group of a cephalosporin, which hydrogen bonds to one part of the active site, is still attached via the C_6–C_7 bond to the portion of the antibiotic molecule that is covalently bound to the enzyme through C_8. The tentacular functionalities in the active site normally have some freedom to move about and transfer on interloping substrate to an external nucleophile, such as another polypeptide or water, for release. However, such movement is restricted when the residues in the receptor are bridged by the inhibitor molecule. A consequent cascade of events leads to the aberrant cell walls that are observed microscopically.[38]

Acknowledgment. The author expresses his thanks to W. H. W. Lunn for helpful comments, to J. M. Indelicato for generously providing unpublished data, and to J. L. Ott for the MICs.

Registry No. Cephalosporin, 11111-12-9.

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