

Table I. Complexation of Na⁺/K⁺ by Neutral Ligands^a

	K picrate, %	Na picrate, %
5	10	33
7	5	25
8	5	28
18-crown-6	100	100
blank	0.7	0.4

^a Determined by measuring A_{360} (nm) of a stirred chloroform solution, 10 mM in ligand, 10 mM picrate after 30 min.

In fact, as indicated in Figure 1, the Ca²⁺ transport properties were in exactly that order, as measured in the standard U-tube test system. Secondly, the transport capability of **15**, particularly, compares very favorably with the best known Ca²⁺ ionophores, A-23187 and X-537A. It is of interest also to compare the transport efficiencies of **15** and **9** with a crown ether possessing a directional carboxyl ligand such as **16**.²⁶ Although the bridging components differ (binaphthyl vs. bicyclooctane) it is apparent that a cyclic ligand system is less efficient, since, as depicted in Figure 1, nearly 7 equiv of **16** are required to approach the transport capabilities of **15**.²⁸

Although nonionizable ligands such as **5**, **7**, and **8** do not exhibit Ca²⁺ translocation in this system, they do bind monovalent ions as seen in the solubilization of sodium and potassium picrate (Table I). We are continuing our investigation into synthetic ionophores and will report the interesting biological properties of these ligands in due course.

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- Y. F. Shealy and J. D. Clayton (*J. Am. Chem. Soc.*, **91**, 3075 (1969)), M. C. Thorpe and W. C. Coburn, Jr. (*J. Org. Chem.*, **34**, 2576 (1969)), for examples of norbornenediols and tetraols. Furthermore, examination of the 7s,7a protons in **4** relative to the diol (reaction g) and the cyclic carbonate (reaction h) show the expected coalescing of the AB of **4** (7s, 1.68, m; 7a, 2.08, d, $J = 9$ Hz) to a broad multiplet in the more symmetrical diol (1.74, 7a and 7s) and back to the AB of the carbonate with both 7a and 7s showing similar W coupling with the endo protons (1.70 and 2.15, br d, $J = 12$ Hz).
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 - (22) Satisfactory (a) ¹H NMR and elemental analysis/mass spectral data or (b) ¹H and ¹³C NMR and elemental analysis-mass spectral data were obtained for this compound.
 - (23) ¹H NMR (CDCl₃): **4**, 6.38, 6.25 (4 H, dd, $J = 3.5$ Hz), 5.95 (2 H, m), 5.42 (2 H, s), 4.52 (4 H, s); **6**, 7.12, 6.42, 6.26 (4 H, dd, $J = 3.5$ Hz), 5.98 (2 H, s), 5.42 (1 H, s), 3.82 (3 H, s); **14**, 7.6-7.1 (4 H, m), 6.33 and 6.22 (4 H, dd), 3.76 (3 H, s).
 - (24) Prepared by alkylation of *m*-hydroxybenzaldehyde with α -bromomethyl acetate (NaH, THF) followed by oxidation (KMnO₄, C₆H₆, 18-crown-6)²⁵ to the acid (45%; mp 117-119°; IR (mull) 3200-2600, 1770, 1690 cm⁻¹)^{22a} and chlorination in thionyl chloride.
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 - (28) Transport is a function of ionophore concentration. For example, changing the concentration of A-23187 from 100 μ g/mL to 200 μ g/mL to 500 μ g/mL produces percent transport (1 h) of 29, 54, and 72%, respectively. Similarly, ligand **15** exhibits percent transport of 11 (20 μ g/mL), 21 (50 μ g/mL), 52 (100 μ g/mL), and 78% (500 μ g/mL) after 16 h in one experiment.

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On the Mechanism of Friedel-Crafts Acylation and Sulfonylation Reactions

Sir:

There is general agreement that the transition state for the attack of a weak electrophile on an aromatic substrate resembles a benzenium ion or σ complex. The nature of the reaction pathway for the attack of a strong electrophile, on the other hand, is less certain. Highest energy transition states resembling either a σ complex or a π complex have been proposed.¹

As part of our systematic study of the mechanisms of electrophilic aromatic substitutions, we undertook a statistical analysis of acylation studies² reported by Olah to be supportive of the π -complex mechanism, i.e., those proposed to involve strong but selective electrophiles. We included the studies of the similar sulfonylation reaction in our analysis.³ From the reported k_T/k_B values and toluene product isomer percentages, we calculated partial rate factors and attempted to correlate the results according to the Brown-Stock selectivity relationship. A graph of calculated values is given in Figure 1.

The linear regression analysis of this plot yielded a slope and intercept, together with their 95% confidence limits, of 1.30 ± 0.20 (standard deviation, ± 0.10) and 0.05 ± 0.34 . The linear correlation was 0.9437. These values are in remarkable agreement with those obtained for 47 reactions by Brown and Stock;^{1a} i.e., the slope was 1.31 ± 0.10 (standard deviation) and the intercept 0.007.

Even Olah's individual points show little deviation from Brown and Stock's line. Of the 24 reactions plotted, only 3 are outside the 95% confidence limits (± 0.20), while 14 lie within

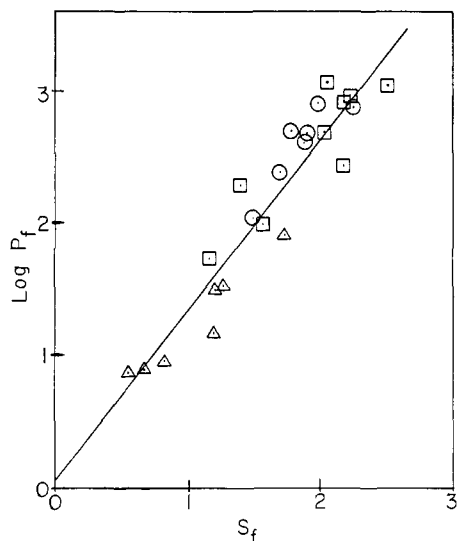


Figure 1. Relationship between $\log p_f$ and selectivity factor, S_f , for acylation and sulfonylation reactions: acetylation (O), ref 2, Table I; benzoylation (\square), ref 2, Table II; sulfonylation (Δ), ref 3, Table I.¹¹

one standard deviation (± 0.10). Clearly, this sulfonylation and acylation data is in excellent agreement with the Brown selectivity relationship and therefore is strongly supportive of a σ -complex mechanism.

Rys, Skrabal, and Zollinger⁴ have applied regression analysis to Olah's nitration data and have found the correlation to π -complex stabilities is really no better than the correlation to σ -complex stabilities required by Brown's theory. Neither correlation is satisfactory.

Although Olah's argument for the π -complex mechanism has been weakened considerably by the results of these regression analyses, we decided to study the benzoylation reaction using our improved vacuum line techniques and thoroughly dried solvents. This approach in both ethylation⁵ and benzoylation⁶ studies yielded reproducible results substantially different from that previously reported.

We now report noncompetitive kinetic results for the AlCl_3 catalyzed reaction between the strong electrophile 2,4-dichlorobenzoyl chloride and benzene or toluene in nitromethane at 20 °C. Thoroughly dried Spectrograde CH_3NO_2 gave inconsistent kinetic data for low AlCl_3 concentrations.⁷ When the CH_3NO_2 was purified by low temperature recrystallization,⁸ the 2-nitropropane impurity was reduced to $<0.03\%$. Consistent and reproducible kinetic data were then obtained for all reactions, including AlCl_3 concentrations as low as 0.02 M. For both toluene and benzene, third-order kinetics were found, i.e., first order in AlCl_3 , 2,4-dichlorobenzoyl chloride, and aromatic hydrocarbon. The third-order rate constant however did show a tendency to decrease as the initial AlCl_3 concentration was increased in a manner very similar to that observed by Brown and Young.⁹ A rate constant ratio k_T/k_B of 480 ± 120 was calculated using the k_3 values for benzene, $(5.4 \pm 0.4) \times 10^{-3} \text{ M}^{-2} \text{ s}^{-1}$, and toluene, $2.6 \pm 0.5 \text{ M}^{-2} \text{ s}^{-1}$, at 0.03 M AlCl_3 concentration. For toluene, the isomeric distribution is $8.4 \pm 0.3\%$ ortho, $0.4 \pm 0.1\%$ meta, and $91.2 \pm 0.9\%$ para.

Not surprisingly, these results fit the selectivity relationship. What is surprising, however, is the marked substrate and positional selectivity of 2,4-dichlorobenzoyl chloride. In systematically varying the ring substituents in benzoyl chloride, Olah found k_T/k_B values ranging from 16 to 233.² As expected, his highest ratios occurred with electron-donating groups: *p*- CH_3 , *p*-F, 2,4,6-trimethyl, and *p*- CH_3O . With the much stronger electrophile, 2,4-dichlorobenzoyl chloride,¹⁰ we obtain a k_T/k_B value along with product isomer percent-

ages expected of a very weak electrophile. At present we are unable to explain this unusual result.

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- (11) Reactions with percent meta product isomer percentages listed as ~ 0 and ~ 1 were not included in the statistical analysis.
- (12) Teaching-Research Postdoctoral Fellow, 1974-76. Supported by Research Corporation.
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On "Anomalous" Selectivities in Electrophilic Aromatic Substitutions

Sir:

The selectivity relationship¹ for electrophilic aromatic substitutions (EAS) quantitatively accounts for the relationship between substrate and positional selectivities in a large number of EAS.² According to this principle, and its interpretation through the Hammond postulate, as the reactivity of an electrophile decreases, both the substrate and positional selectivities increase. However, Olah and co-workers have reported a class of reactions which appear to give high positional but low substrate selectivity. They suggested that these reactions do not follow the selectivity relationship because they involve, first, as rate-determining step—that determining substrate selectivity—the formation of a π complex, followed by a second faster step, which determines positional selectivity.³ These "anomalous" cases have been given several theoretical rationales.⁴⁻⁷ However, we report here that few of these reactions show "anomalous selectivities", and, for that reason, some previous rationales of such selectivities do not correctly identify the factors influencing selectivities in "early" transition states of EAS.

Brown and co-workers established that the vast majority of