Kinetics and Mechanisms of Hydrolysis of Cyclic Sulphinamidates. Part 2.[1] The Breakdown of the Intermediate Ions formed through the Ring Opening of 3-Phenyl-3,4-dihydro-1,2,3-benzoxathiazin-2-one

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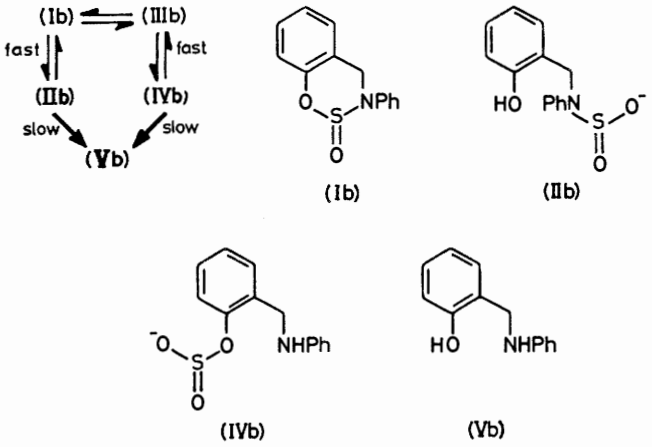
The first step in the ring opening of 3-phenyl-3,4-dihydro-1,2,3-benzoxathiazin-2-one (Ib) is very fast and gives rise to two different intermediate ions depending on the pH of the solutions. Above pH 11, this step proceeds through the cleavage of the ring sulphur–oxygen bond and leads to the formation of *N*-(*o*-hydroxybenzyl)-*N*-phenylsulphinamidate ion (IIb). Below pH 9, the S–N bond is the easiest to break and α-anilino-*o*-tolyl hydrogensulphite ion (IVb) is obtained. The results for the hydrolysis of sulphinamidate ion (IIb) show that the phenol is much more reactive than the phenolate ion and that the reaction occurs *via* hydroxide ion attack on the sulphinyl group. Two mechanisms account for the decomposition of the hydrogensulphite ion: (i) in slightly alkaline media ($7 < pH < 9$), hydroxide ion and base-assisted water attack on the species possessing a non-protonated nitrogen; (ii) at lower pH, acid attack at the oxygen atom bound to the aromatic ring, concerted with the opening of its bond to the sulphur atom. This mechanism is operative for both species of (IVb), which have similar reactivity.

THE hydrolysis of 3-phenylperhydro-1,2,3-oxathiazin-2-one at 70° was reported in Part 1.[1] In acidic or slightly alkaline media, 3-*N*-phenylaminopropyl hydrogensulphite ion (IVa) was obtained; its very slow decomposition to 3-*N*-phenylaminopropan-1-ol (Va) was not investigated. In strongly alkaline media, the amino-alcohol (Va) was obtained directly; however, 3-hydroxypropyl *N*-phenylsulphinamidate (IIa) an intermediate which did not build up in the medium, was involved in the reaction mechanism (Scheme 1 of ref. 1).



SCHEME 1

As aryl sulphates hydrolyse much more rapidly than their alkylated homologues [2] in acidic solutions, 3-phenyl-3,4-dihydro-1,2,3-benzoxathiazin-2-one (Ib) was synthesised [3] so as to obtain a sufficiently fast transformation of the corresponding intermediate (IVb) (see Scheme 1). Moreover the benzo fusion should stabilize the open-chain intermediate ion (IIb) as a phenol function is formed which should delay its decomposition. The ring opening of (Ib) to (IVb) was fast and the breakdown of (IVb) which predominates over the pH range 2—9, could be investigated. Besides, (IIb), which was found to build up in the reaction medium between pH 11 and 14, was the major intermediate in this pH range. Between pH 9 and 11 both (IIb) and (IVb) are present and the two hydrolysis reactions compete; the concentration of each of these species varies as a function of pH, but, as yet, we have been unable to interpret the results.

EXPERIMENTAL

The kinetics of hydrolysis were followed spectrophotometrically by recording at 256 nm the increase in absorbance ($pH > 4$) and at 240 nm the decrease in absorbance ($pH < 3.3$) which both correspond to the appearance of the final product. All reactions exhibited good first-order kinetics with respect to the substrates.

RESULTS

Effect of pH *on the Hydrolysis of Sulphinamidate Ion* (IIb) ($11 < pH < 14$).—The u.v. spectrum of the final product was identical with that of *N*-*o*-hydroxybenzylaniline, run at the same concentration, suggesting that the product has this structure. The pH dependence of the u.v. absorbance of (IIb) (pK_a *ca.* 10.2) is the same as that of *N*-*o*-hydroxybenzylaniline. This variation is not consistent with a cyclic sulphinamidate structure which is unable to ionise in this pH range, but is readily explicable in terms of the open-chain *N*-*o*-hydroxybenzyl-*N*-phenylsulphinamidate structure (IIb) which contains a phenol function; it can be assumed that the $N(Ph)SO_2^-$ group which is far away from the phenol function, has a negligible effect on its pK_a, and the observed value of *ca.* 10.2 is therefore compatible with this structure.

Also, if the ring opening of (Ib) like that [1] of 3-phenylperhydro-1,2,3-oxathiazin-2-one, is assumed to proceed through hydroxide ion attack on the sulphur atom, leading to sulphinamidate ion (IIb), the leaving group would be a phenol for (Ib) whereas it would be an alcohol for (Ia). The rate constant ratio would then be approximately equal to that of the acidity constants, *i.e.* 10^5—10^6. The expected value of k_{OH} for the hydrolysis of (Ib) ($8.43 \times 10^{-3} \times 10^5$ l mol^{-1} s^{-1}, *i.e. ca.* 10^3 l mol^{-1} s^{-1}) would be too large to be measured using conventional techniques. As a matter of fact, kinetic measurements could be carried out, and the rate of hydrolysis was found to be pH independent [k_{obs} 5.0

[1] Part 1, P. Maroni, M. Calmon, L. Cazaux, P. Tisnès, G. Sartoré, and M. Aknin, preceding paper.

[2] J. L. Kice and J. M. Anderson, *J. Amer. Chem. Soc.*, 1966, **88**, 5242.

[3] L. Cazaux and P. Tisnès, *J. Heterocyclic Chem.*, 1976, **13**, 665.

$\times 10^{-3}$ s^{-1} (Table 1)]. Therefore, such a rate constant does not pertain to a ring cleavage reaction. So, as opposed to

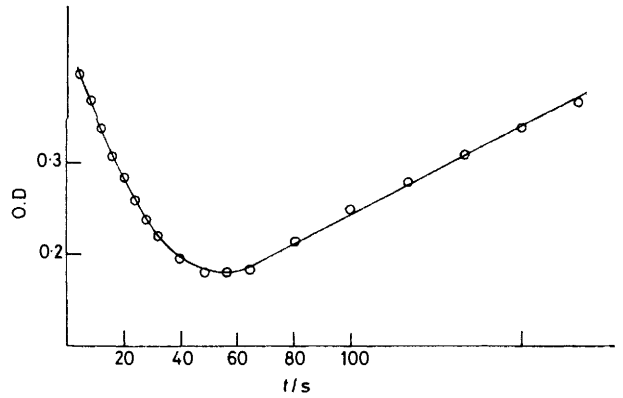


FIGURE 1 Plot of the observed optical density *versus* time for the hydrolysis of 3-phenyl-3,4-dihydro-1,2,3-benzoxathiazin-2-one ($2 < pH < 9$; 25°; μ 1.0, KCl)

3-phenylperhydro-1,2,3-oxathiazin-2-one, the hydrolysis was not that of the cyclic compound (Ib) but of the open-chain intermediate (IIb) as shown by the pK_a value. All attempts at isolating the intermediate, in particular the use of phase transfer catalysts for its extraction from the reaction medium, failed. The rate constants for the hydrolysis of (IIb) at various pH values are listed in Table 1.

decrease followed by a slower increase, suggesting the appearance and the disappearance of an intermediate. The final product was identified by u.v. and n.m.r. spectroscopy as being *N*-*o*-hydroxybenzylaniline: the u.v. spectrum of the hydrolysis product was identical with that of an authentic sample of *N*-*o*-hydroxybenzylaniline run at the same concentration. The u.v. spectrum of this intermediate varies with pH, suggesting a protonation–deprotonation equilibrium. Its pK_a' value, which was estimated spectrophotometrically to be 4.6, is close to those of the amino function of *N*-*o*-hydroxybenzylaniline (4.7) and of the intermediate (IVa) (4.8) formed in the course of the hydrolysis of *N*-phenylperhydro-1,2,3-oxathiazin-2-one.[1] An open-chain α-anilino-*o*-tolyl hydrogensulphite ion structure can thus be considered; as with (IIb) the intermediate (IVb) could not be isolated. Both reactions have pseudo-first-order kinetics, but the first step was very fast and could not be followed long enough for subsequent analysis in every case. The second reaction, corresponding to the absorbance increase, is the conversion of the intermediate α-anilino-*o*-tolyl hydrogensulphite ion (IVb) into *N*-*o*-hydroxybenzylaniline (Vb). This second step was not studied for the saturated heterocycle (Ia).[1]

In all the buffers investigated general catalysis was important. In acetate buffer, general acid catalysis masked that of hydronium ion, so that, even at low buffer concentration, the accuracy of the extrapolation to zero buffer concentration was poor. In other pH ranges, the constants

TABLE 1

Rate constants for the hydrolysis of *N*-*o*-hydroxybenzyl-*N*-phenyl sulphinamidate ion (IIb) at 25 °C (μ 1.0, KCl)

$10^3[OH^-]$/M	1 000	600	250	100	20	10	9	8	7	5	2
pH	14	13.80	13.40	13	12.30	12	11.95	11.90	11.84	11.70	11.30
$10^4 k_{obs}/s^{-1}$	6	5.4	5.1	5.2	4.6	4.8	5	5.1	4.8	4.8	4.6
$4 + \log k_{obs}$	1.78	1.73	1.71	1.72	1.66	1.68	1.70	1.71	1.68	1.68	1.66

The deuterium oxide solvent isotope effect obtained for three different concentrations of NaOH and NaOD (25°; μ 1.0, KCl) gave k_{OH}/k_{OD} 1.25 ± 0.05. The thermodynamic parameters measured between 25 and 50° yielded

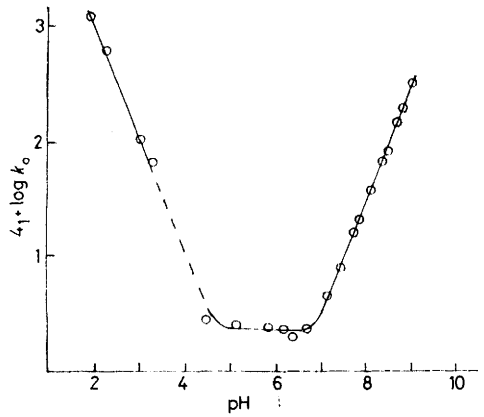


FIGURE 2 pH–Rate profile for the hydrolysis of α-anilino-*o*-tolyl hydrogensulphite ion (IVb) in the absence of buffer (25°; μ 1.0, KCl)

the following activation parameters: E_a 14.6×10^4 kcal mol^{-1} and $\Delta S^{\ddagger}$ −21 cal mol^{-1} K^{-1}.

Effect of pH *on the Hydrolysis of Hydrogensulphite Ion* (IVb) ($2 < pH < 9$).—In all the buffers investigated, a plot of the optical density against time (Figure 1) exhibits a fast

k_0' for hydronium ion catalysis were easily obtained. A plot of log k_0' *versus* pH is shown in Figure 2: the high level of catalysis observed in acetate buffer prevented an accurate drawing of the junction between pH 3.3 and 4.5. In tris(hydroxymethyl)aminomethane buffer, the plot of log k_0' *versus* pH is linear (slope + 1), and general base catalysis was observed above pH 7. However, in this buffer, as the pH increases further ($pH > 8.5$), the catalysis becomes more complex; this can be assigned to a significant involvement of the other open-chain intermediate (IIb). In more acidic solutions ($pH < 7$), general acid catalysis was observed (Table 2, Figure 3). In monochloroacetate buffer, hydro-

TABLE 2

Catalytic constants for the hydrolysis of α-anilino-*o*-tolyl hydrogensulphite ion (IVb) (25°; μ 1.0, KCl)

k_{BH}/l mol^{-1} s^{-1}	log k_{BH}	pK_{BH}	Buffer
12	1.08	−1.74	H_3O^+
1.8×10^{-2}	−1.75	4.80	Acetate
6.5×10^{-3}	−2.19	6.50	Phosphate
2.9×10^{-6}	−5.55	15.74	H_2O

lysis was followed at 14° because the reaction rates are very high (k_{BH} 5.2 × 10^{-2} l mol^{-1} s^{-1}).

DISCUSSION

Hydrolysis of Sulphinamidate Ion (IIb) ($11 < pH < 14$).—From the conjugate acid–base couple, two possible mechanisms can account for the pH-independent

rate constants (Scheme 2). For hydroxide ion attack (mechanism 1) the rate constant is $k_{obs} = k_{OH}[OH^-]a_H/(K_A + a_H)$; in the pH range under consideration, $K_A \gg a_H$, giving $k_{obs} = k_{OH}K_W/K_A$. Such a mechanism

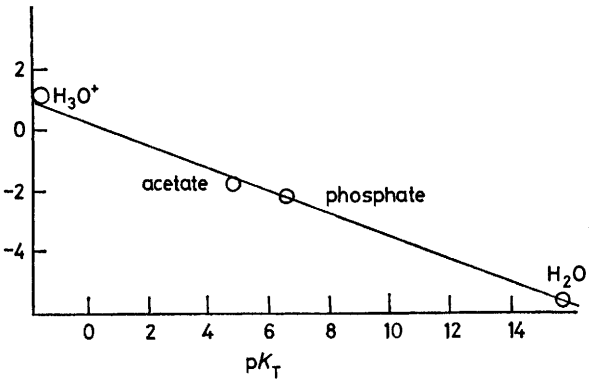
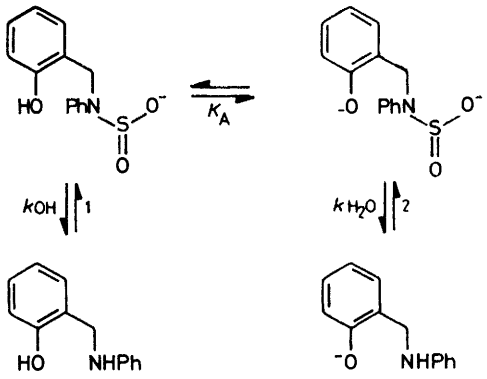
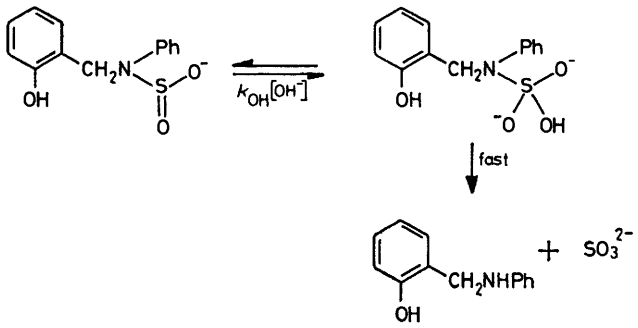


FIGURE 3 Brönsted plot of the catalytic constants for the hydrolysis of α-anilino-*o*-tolyl hydrogensulphite ion (IVb) at 25° (μ 1.0, KCl)



SCHEME 2

is consistent with the isotopic effect of 1.25. Thus, making use of the value measured by Bender [4] for the ionization constant of phenol $K_A^{H_2O}/K_A^{D_2O} = 4.02$, and the ratio $K_W^{H_2O}/K_W^{D_2O} = 7.5$,[5] it is possible to calculate the isotope effect on k_{OH}, namely $k_{OH}/k_{OD} = 0.66$. This value is in good agreement with the reverse isotope effect expected for nucleophilic hydroxide ion attack. This result, as well as the value of $\Delta S^{\ddagger}$ (−21 cal mol^{-1} K^{-1}) support a mechanism (Scheme 3) of the same type as the one considered by Bender [6] for the hydrolysis of carboxylates and as that put forward [1] for the hydrolysis of 3-phenylperhydro-1,2,3-oxathiazin-2-one (Ia) in strongly alkaline media. As for (Ia),[1] the possibility of a concerted hydroxide ion attack cannot be excluded. One possible explanation for the large difference in reactivity between the phenolate ion and the phenol with respect to the hydroxide ion could be the existence of a phenolate

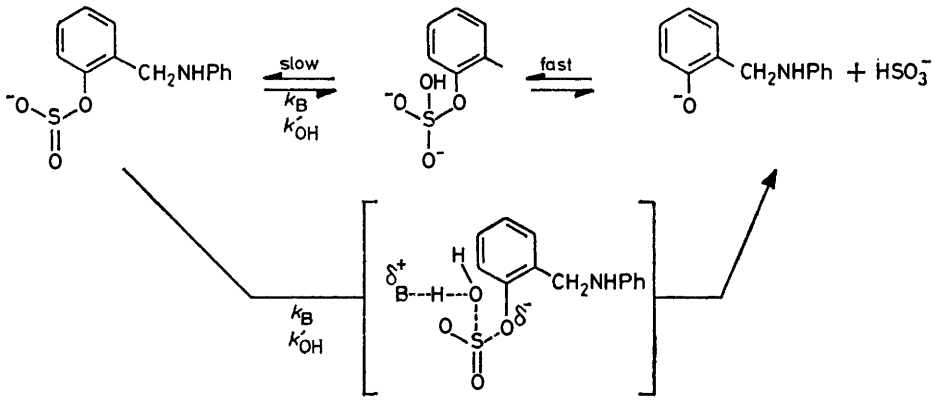


SCHEME 3

conformation in which the negatively charged group is close to the electrophilic sulphur of the NSO_2^- group, thus decreasing the reactivity of the sulphur atom and hindering the approach of the hydroxide ion.

Water attack (mechanism 2) on the phenolate by intramolecular general base catalysis would lead to $k_{obs} = k_{H_2O}[H_2O]$. For such a mechanism, according to Bruice and Benkovic,[7] an isotopic effect of 1.8—2.8 is to be expected, which is in disagreement with the observed value of 1.25.

Hydrolysis of Hydrogensulphite Ion (IVb) (2 < pH < 9).—In slightly alkaline media (7 < pH < 9), a mechanism for hydroxide ion attack on the sulphinyl



SCHEME 4

[4] M. L. Bender and M. S. Silver, *J. Amer. Chem. Soc.*, 1963, **85**, 3306.
[5] P. Salomaa, *Acta Chem. Scand.*, 1971, **25**, 367.
[6] M. L. Bender, *Chem. Rev.*, 1960, **60**, 53.
[7] T. C. Bruice and S. J. Benkovic, 'Bioorganic Mechanisms,' Benjamin, New York, 1966, vol. I, ch. 1, p. 157.

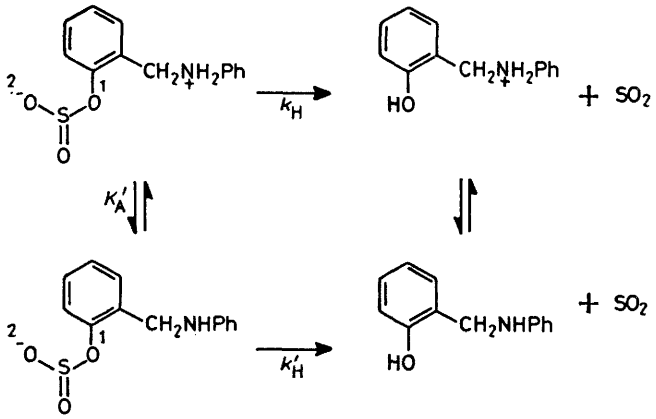
group of the hydrogensulphite function is proposed. This mechanism which operates on the amine form of the substrate, may be a stepwise or a concerted process (Scheme 4). The corresponding rate equation is (1)

$$k_{obs}[S_t] = k'_{OH}[OH^-][S_t]K'_A/(K'_A + a_H) + k_B[B][S_t]K'_A/(K'_A + a_H) \quad (1)$$

where $[S_t]$ is the total substrate concentration, K_A' the protonation constant of the amine function, k_{OH}' and k_B' are the constants for base attack on the substrate species possessing a non-protonated nitrogen. Over the pH range considered, $K_A' \gg a_H$, and equation (1) reduces to (2) with k_{OH}' 2.9×10^3 and k_B 7×10^{-2} l mol^{-1} s^{-1}. Equation (2) is in agreement with the linear relationship (slope + 1) seen in Figure 3 and with the observed general base catalysis.

$$k_{obs} = k_{OH}'[OH^-] + k_B[B] \quad (2)$$

In acidic media ($2 < pH < 7$) the low accuracy of the pH–rate profile in acetate buffer makes a thorough discussion difficult. However a mechanism of acid attack at the phenolic oxygen atom O^1 concerted with cleavage of the O^1–S bond seems likely (Scheme 5). The reaction



SCHEME 5

would be readier in acidic media if the O^1 rather than O^2 was protonated, ArOH being a better leaving group than ArO^-. Heterolysis of the ArO–S bond should also be, according to the work of Kice and Anderson [2] on sodium aryl sulphates, easier for $ArOSO_2^-$ than for $ArOSO_2H$. Moreover, if the results of Jencks [8] for the carbonyl group are extended to hydrogensulphites, general acid catalysis would not be necessary for the protonation of O^2, the resulting $ArOSO_2H$ being stable. General acid catalysis would allow, in the case of protonation of O^1, the avoidance of the unstable intermediate and the transition state leading to it.

This mechanism is described by equation (3) where k_H and k_{BH} are the acid-catalysed rate constants of the *N*-protonated species of the substrate and k_{H_2O} is the

$$k_{obs}[S_t] = (k_H a_H + k_{H_2O}[H_2O])[S_t]a_H/(K_A' + a_H) + (k_H' a_H + k_{H_2O}'[H_2O])[S_t]K_A'/(K_A' + a_H) + k_{BH}[BH^+][S_t]a_H/(K_A + a_H) + k_{BH}'[BH^+][S_t]K_A'/(K_A' + a_H) \quad (3)$$

water-catalysed rate constant; k_H', k_{BH}', and k_{H_2O}' are the rate constants relative to the non-protonated substrate. The value of k_H (12 l mol^{-1} s^{-1}) is easily computed from the plot of log k_0' *versus* pH (Figure 2; $pH < 3$); likewise a value of 2.9×10^3 l mol^{-1} s^{-1} is obtained for the constant k_{OH}' corresponding to the base catalysis mechanism operating above pH 7. The mechanisms put forward in the pH range 2—9 lead to equation (4).

$$k_0' = (k_H a_H + k_{H_2O}'[H_2O])a_H/(K_A' + a_H) + (k_H' a_H + k_{H_2O}'[H_2O])K_A'/(K_A' + a_H) + k_{OH}'[OH^-]K_A'/(K_A' + a_H) \quad (4)$$

Using the above values of k_H and k_{OH}' as well as the spectrophotometrically measured pK_A' (4.6), the agreement between the experimental plot (Figure 2) and that calculated from equation (4) is satisfying only if $k_H' \sim k_H = A = 12$ l mol^{-1} s^{-1} and $k_{H_2O}' \sim k_{H_2O} = B = 2.9 \times 10^{-6}$ l mol^{-1} s^{-1}. The two species of substrate (IVb) are therefore likely to have similar reactivities leading to $k_{BH} \sim k_{BH}'$. The electronic effects of the ionisable amine function (pK_A' 4.6) are weak since this function is distant from the reaction centre O^1. Spatial interactions with the protonated nitrogen atom in pseudocyclic conformations would only affect the negatively charged oxygen atom O^2 without significantly modifying the reactivity or accessibility of the reaction centre O^1. Under these conditions, equation (3) becomes (5).

$$k_{obs} = A\,a_H + B[H_2O] + C[BH^+] \quad (5)$$

An intramolecular catalysis involving the anilinium ion, analogous to that reported by Benkovic [9] for salicyl sulphate, would not compete with hydronium ion catalysis significantly, since it would not obey rate equation (5). The slope of the Brönsted plot (Figure 3; α 0.33) is in the range given by Jencks [8] for concerted mechanisms (0.27—0.45). The value of this slope would obviously be more significant had it been obtained from a greater number of buffer catalytic constants. However, though the points for H_3O^+ and H_2O often deviate from the correlation line, the fact that they are correctly aligned with the buffer datum points suggests that a concerted mechanism is most likely.

We thank Dr. M. Calmon for helpful discussions.

[7/1241 *Received*, 13*th July*, 1977]

[8] W. P. Jencks, *Chem. Rev.*, 1972, **72**, 707.
[9] S. J. Benkovic, *J. Amer. Chem. Soc.*, 1966, **88**, 5511.