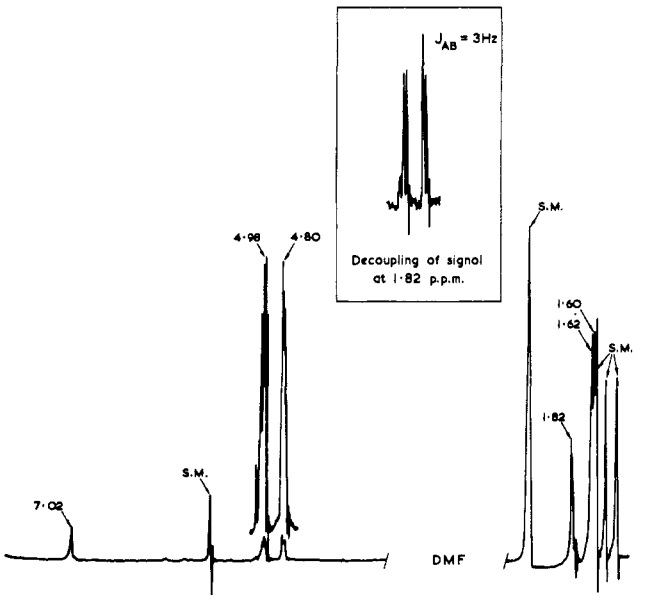
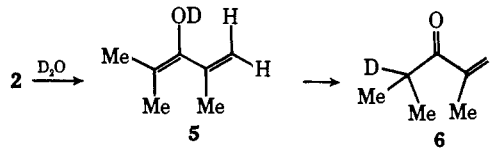


Figure 1. Nmr spectrum (δ^{TMS}) of 2,4-dimethyl-1,3-pentadien-3-ol (**2**) in dimethylformamide (S. M. = starting material **1**).

benzoic acid (0.003 *M*), it became clear that ketone **3** arose from an intermediate, the concentration of which reached a maximum (>0.5 *M*) after *ca.* 15 hr at 25°. At this point and during the preceding 6 hr the ratio of intermediate–ketone **3** amounted to *ca.* 4:1, and the formation of ketone was complete after *ca.* 30 hr at 25°. The nmr spectrum [$\delta^{TMS}_{CCl_4}$ 1.61 (s, 3 H), 1.60 (s, 3 H), 1.80 (br, s, 3 H), 4.77 (1 H) and 4.92 (1 H) (AB quartet with further fine structure which could be removed cleanly by decoupling the signal at 1.80 ppm), 6.10 (s, 1 H)] and the ir spectrum [intense broad bond at 3390 cm^{-1}; OH stretching] suggested the intermediate to be 2,4-dimethyl-1,3-pentadien-3-ol (**2**).

The most reasonable chemical proof for this enol was thought to be its transformation into the enol ether **4** by methylation with diazomethane in diethyl ether. However, several attempts to obtain **4** by this route were not successful. Apparently, the enolic proton is not acidic enough to allow O-methylation and it is instructive that the chemical shift of the OH proton of enol **2** (δ 6.10 ppm) is closer to that of ordinary alcohols (*e.g.*, methanol ($\delta^{TMS}_{CCl_4}$ 4.00)) than to conventional enols (acetylacetone, 15 ppm).

Nevertheless, the enolic proton of **2** could be exchanged rapidly and quantitatively by brief shaking of the solution of **2** in CCl_4 with an excess of D_2O. The deuterioenol **5** so produced rearranged into the



deuterioketone **6**, which was isolated (mass spectrum *m/e* 113.0948; calcd for $C_7H_{11}OD$, 113.0951). Significantly, while **2** rearranged into **3** within 15 hr in CCl_4, the rearrangement of the deuterioenol **5** proceeded more slowly and required *ca.* 250 hr. Independently, the enol **2** was generated in dimethylformamide from a 2 *M* solution of the precursor **1** in the presence of 0.003 *M* benzoic acid (*cf.* Figure 1). In this instance the concentration of the enol reached its maximum after *ca.* 50 hr and formation of the ketone **3** was complete after 120 hr.

We conclude that thermodynamically unstable enols[4] can be handled perhaps more easily than has been hitherto assumed, especially if as in the present instance the double bond is fully alkylated and delocalized further by conjugation. It also seems advantageous to generate the enol in a solvent such as dimethylformamide which in being polar and aprotic stabilizes the enol *via* hydrogen bonding without supplying any protons itself, which would catalyze the rearrangement into the ketone.

Acknowledgment. We thank Mr. B. K. Carpenter and Professor F. Sondheimer for a discussion and Schering A. G. Berlin and the Dr. Carl-Duisberg Stiftung for financial support.

(4) I. A. Kaye, M. Fieser, and L. F. Fieser (*J. Amer. Chem. Soc.*, **77**, 5936 (1955)) have suggested the formation of a fairly stable enol derived from α-amyrin in which the OH group is attached to a nonhydrogenatable double bond. This observation, which appears to have escaped all further compilation, can only be retrieved on careful scrutiny of the experimental part (*cf.* 3β,12-dihydroxy-Δ^{12}-ursene on p 5938). Nevertheless, this work has apparently been confirmed by Professor D. Arigoni and his collaborators. We thank Professor Arigoni for this information.

A referee has drawn our attention to the transient formation of the enol (or enolate ion) of α-ketoisovaleric acid (*cf.* R. Steinberger and F. H. Westheimer, *ibid.*, 73, 429 (1951)); however, in this instance the enolic double bond is conjugated with a carboxyl group.

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On the Mechanism of Intermolecular Aromatic Substitution by Arylnitrenes

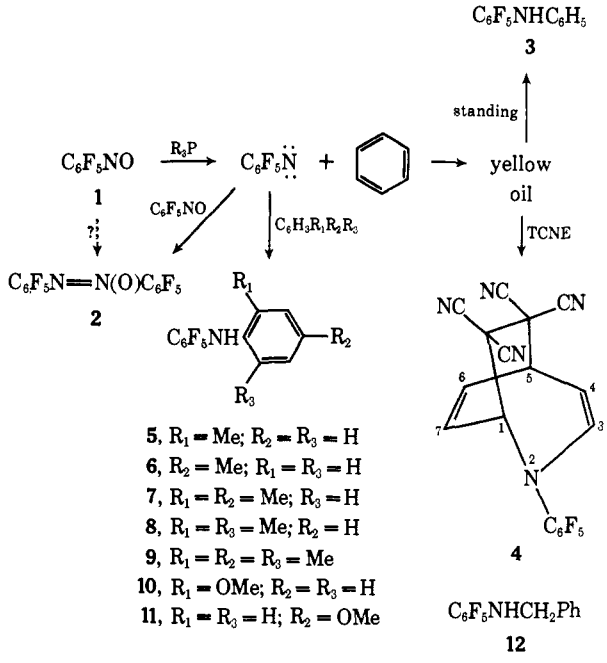
Sir:

We wish to report studies on the mechanism of intermolecular aromatic substitution of activated substrates by electrophilic nitrenes.[1] Ethoxycarbonyl-[2] and cyanonitrene[3] react with benzene to give both N-substituted azepines and anilines, the latter probably arising from the former either thermally or through acid catalysis. With sulfonylnitrenes formation of the *N*-sulfonylazepine is the kinetically controlled process while the *N*-sulfonylanilines are products of thermodynamic control.[4] Intramolecular cyclizations of some *o*-azidodiphenylmethanes give fused seven-membered ring compounds.[5] We now report examples in which benzene and substituted benzenes containing weak electron-donating substituents undergo intermolecular substitution by an arylnitrene, and the trapping of some *N*-arylazepines.

Since the *N*-arylazepines anticipated from a kinetically controlled addition of ArN to Ar'H were not ex-

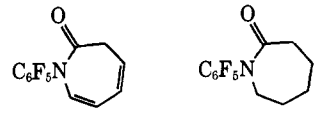
(1) R. A. Abramovitch and E. F. V. Scriven, *Chem. Commun.*, 787 (1970).
(2) W. Lwowski, T. J. Maricich, and T. W. Mattingly, Jr., *J. Amer. Chem. Soc.*, **85**, 1200 (1963); R. J. Cotter and W. F. Beach, *J. Org. Chem.*, **29**, 751 (1964); K. Hafner and C. König, *Angew. Chem.*, **75**, 89 (1963).
(3) F. D. Marsh and H. E. Simmons, *J. Amer. Chem. Soc.*, 87, 3529 (1965).
(4) R. A. Abramovitch and V. Uma, *Chem. Commun.*, 797 (1968).
(5) L. Krbechek and H. Takimoto, *J. Org. Chem.*, **33**, 4286 (1968); G. R. Cliff and G. Jones, *Chem. Commun.*, 1705 (1970).

pected to be stable under the conditions of thermolysis of the corresponding azides (130–150°) we proposed to trap such azepines by producing the nitrene at low temperatures from ArNO and $(EtO)_3P$. Using *p*-cyano- or *p*-CF_3-nitrosobenzene and substrates such as *N,N*-dimethylaniline or *sym*-trimethoxybenzene, such intermediates could neither be detected nor trapped, though aromatic substitution was observed.[6] On the other hand, pentafluorophenylnitrene, generated from C_6F_5NO (**1**) and $(EtO)_3P$ in benzene at 0°, gave the expected decafluoroazoxybenzene (**2**) as the major product together with an oil which, at room temperature, gave pentafluorodiphenylamine (**3**) (1.8%).[7] If the oil was immediately treated with tetracyanoethylene (TCNE) the (4 + 2) adduct (**4**) of *N*-pentafluoro-1*H*-azepine was obtained (2.0%), mp 191–195° dec. Its nmr spectrum agreed with those reported for the *N*-carbethoxyazepine–TCNE[8] and the *N*-mesylazepine–TCNE adducts.[4] The low yields of **3** and **4** are undoubtedly due to the low reactivity of the singlet nitrene toward benzene, compared with its tendency to relax into the triplet state and give other products (mainly **2** plus tars).[9] Thermolysis and photolysis of $C_6F_5N_3$ in C_6H_6 gave comparable yields of **3** but attempts to trap an azepine failed.



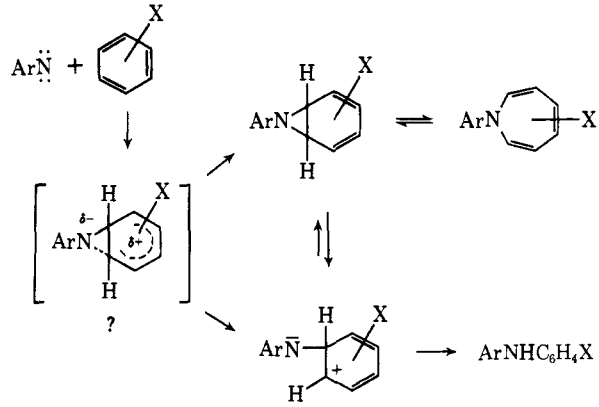
With the more nucleophilic toluene, **2** was again obtained (32.8%) together with **5** (10.2%), **6** (2.2%), and **12** (1.6%). The intermediate yellow material was less stable than in the case of benzene, and its reaction with TCNE gave a 1:1 adduct (4.8%) together with smaller amounts of **5** (1.4%), **6** (0.6%), and **12** (0.5%). The nmr of the adduct suggests that it is a mixture of the C_4-Me and C_7-Me derivatives of **4**, both arising from 3-methyl-*N*-pentafluorophenyl-1*H*-azepine formed at the expense of the ortho substitution product **5**. *m*-Xylene and C_6F_5N at −25° gave **2** (24%), **7** (18.2%), and **8** (12.3%). No yellow intermediate was observed, but when TCNE was added immediately to the cold reaction mixture the (4 + 2) 1:1 adduct was isolated (9.7%). Four methyl resonances were observed and, assuming no bridgehead methyl groups,[8b] it is concluded that a mixture of 4,6- and 3,7-dimethyl-**4** was formed. C_6F_5N and mesitylene at −25° gave only **2** (18.5%) and **9** (32.0%). No azepines could be detected or trapped, due to the destabilization of the azepine by the electron-releasing methyl groups and that no adduct can be formed from *N*-pentafluorophenyl-2,4,6-trimethyl-1*H*-azepine which does not involve formation of a bridgehead methyl.[8b]

Striking evidence for the addition–ring expansion was obtained from the deoxygenation of **1** with $(EtO)_3P$ in anisole. This gave **2** (5.3%), **10** (2.7%), **11** (4.3%), and azepinone (**13**) (15.9%): bp 128–130° (0.4 mm); $\nu_{C=O}$ 1700 cm^{-1}. Catalytic reduction of **13** gave **14**,



$\nu_{C=O}$ 1678 cm^{-1}. The *lowering* of the carbonyl frequency on hydrogenation of **13** to **14** and the nmr spectra confirm structure **13**. The nmr of the crude reaction mixture suggests that **13** is formed on silica gel chromatography from 2-methoxy-1-pentafluorophenyl-1*H*-azepine.

Two pathways appear possible for the intermolecular attack of an aromatic nucleus by an arylnitrene



The extent to which each will be followed depends on the nature of Ar, X, and the reaction conditions.

(6) R. A. Abramovitch, S. R. Challand, and E. F. V. Scriven, unpublished results.

(7) Since the nitroso compound is mainly monomeric in solution the azoxy derivative does not arise by the deoxygenation of the dimer.

(8) (a) J. E. Baldwin and R. A. Smith, *J. Amer. Chem. Soc.*, **87**, 4819 (1965); (b) L. A. Paquette, D. E. Kuhla, J. H. Barrett, and L. M. Leichter, *J. Org. Chem.*, **34**, 2888 (1969).

(9) Tar formation in the low conversion photolysis of PhN_3 solutions has been attributed to singlet phenylnitrene substituting into phenyl azide to give $PhNHC_6H_4N_3$, which photolyzes and substitutes further, and so on, even though most of the PhN_3 is not decomposed.[10] When we deoxygenated PhNO (monomeric species) in benzene with $(EtO)_3P$ in the presence of PhN_3, the latter was recovered essentially quantitatively; azoxybenzene and the ubiquitous tars were formed. Even with a 5*M* excess of PhN_3 only a very small amount of azobenzene was formed, but no product of aromatic substitution of the phenyl azide was observed. This is not surprising since PhN_3 ($\sigma_{p\text{-}N_3}^+ = -0.54$)[11] would be expected to be somewhat less susceptible than $PhOCH_3$ ($\sigma_{p\text{-}OCH_3}^+ = -0.78$) to electrophilic attack, and even more electrophilic arylnitrenes, *e.g.*, *p*-CNC_6H_4N and *p*-$NO_2C_6H_4N$, generated either from the azide or the nitroso compound, do not insert into either benzene or anisole.[1,6] An alternate origin of the tars will have to be found.

(10) A. Reiser and L. J. Leyshon, *J. Amer. Chem. Soc.*, **93**, 4051 (1971).

(11) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, Amsterdam, 1965, p 287.

Acknowledgment. We thank the National Science Foundation (Grant No. GP-18557) for support of this work.

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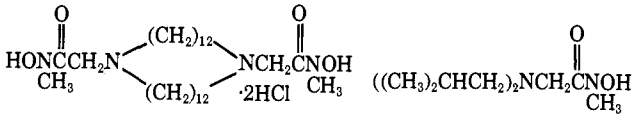
Nucleophilic and Metal Ion Acceleration of Ester Hydrolysis in a Hydrophobic Complex. A Reactive Enzyme Model System

Sir:

We wish to report the synthesis and preliminary characterization of macrocyclic *N*-methylhydroxamic acid (I), the first homolog of a projected series of simple macrocyclic and macrobicyclic amines with appended catalytic functionalities, *i.e.*, binding sites with proximate active sites.[1] The ease in incremental variation of ring size and rigidity, charge, and functional group together with its steric relationship to the binding site suggests that an unambiguous explanation for the large rate acceleration, described below, is possible. It is hoped that the adaptability of this system will enable a better assessment of the relative importance of the factors involved in the complexation and acylation steps of proteolytic enzymes.



I

II

In order to separate the influence of binding on reaction rates from any intrinsic functional group specificity, a specificity constant, k_r, was defined as the ratio of k_I, the apparent second-order rate constant for the reaction of I with a series of *p*-nitrophenyl carboxylates, to k_{II}, the second-order rate constant for the reaction of II with the respective carboxylate. For this purpose k_r will be a valid indicator if compounds I and II are similar in physical properties and if II represents a normally reactive hydroxamic acid. Both requirements are confirmed by the following observations. (1) The λ_{max} of their infrared carbonyl absorption is the same and the *N*-methyl and α-methylene hydrogens of the hydroxamate group have identical chemical shifts. (2) In a 5% $FeCl_3$–0.1 *N* HCl solution the ϵ at 540 nm of I is twice that of II and approximately equal to that of α-aminohydroxamic acids under similar conditions.[2] (3) The first pK_a of I is 6.8 ± 0.1 while that for II is 7.0 ± 0.2, determined spectrophotometrically. (4) A Brønsted plot for the reaction of *N*-methylacetohydroxamic acid,[3,4] *N*-methyl-1-methoxyacetohydroxamic acid,[4] and II with *p*-nitrophenyl acetate (*p*-NPA) affords an excellent linear correlation with a slope of 0.68, close to the value found for the reaction of moderately basic oxygen anions with *p*-NPA.[5] (5) A linear correlation exists between the logarithm of the rate constants for the hydroxide-accelerated hydrolysis of the ethyl carboxylates of Table I and the reaction of II with the *p*-nitrophenyl esters of these acids.[6] (6) Consistent with previous studies on the reactivity of *N*-methylhydroxamic acids, at ester concentrations greater than "catalyst" concentration, both I and II displayed kinetically biphasic reactivity—burst kinetics[7] —with all *p*-nitrophenyl esters except that of chloroacetic acid. Titration of I by measurement of the burst size indicates that only one hydroxamate group per molecule of I is active.[8] (7) The release of *p*-nitrophenol from *p*-nitrophenyl hexanoate in the presence of I showed a dependence on one group with pK_a = 6.7 ± 0.1. As a consequence of these observations, any departure of the reactions accelerated by I from the corresponding acceleration by II must arise from some unique property of compound I's aliphatic portion, not its functional groups, or the special reactivity of II.

Table I. Comparison of the Effects of I and II on *p*-Nitrophenol Release from *p*-Nitrophenyl Carboxylates at pH 6.80[a]

p-Nitrophenyl ester	k_I, M^{-1} sec^{-1} [b]	k_{II}, M^{-1} sec^{-1}	k_r
Acetate	1.18	0.693	1.7
Propionate	1.32	0.527	2.5
Butyrate	4.00[g]	0.420	9.0
Isobutyrate	2.29	0.230	10
Valerate	3.31	0.340	9.8
Hexanoate	6.35	0.350	15
Octanoate	34.2	0.190	150
Dodecanoate[c]	152[d]	0.02[f]	7600
Chloroacetate[e]	240		

[a] 25°, in aqueous phosphate buffer, μ = 0.088, containing 10.55% methanol–1.75% acetonitrile (v/v). [b] 9.5 × 10^{-6} *M* I employed in all determinations with substrate in excess, except as indicated. [c] 6 × 10^{-6} *M* dodecanoate. [d] 1.9 × 10^{-5} *M* I. [e] pH 6.37, [I] = 8.7–17 × 10^{-6} *M*. [f] Measured at pH 7.98 (Tris, μ = 0.088, 10.55% methanol, 1.75% acetonitrile (v/v)), and corrected to pH 6.80. [g] Obtained from the inverse of the slope of a Lineweaver–Burk plot.

(1) (a) C. A. Blyth and J. R. Knowles, *J. Amer. Chem. Soc.*, **93**, 3017, 3021 (1971); (b) R. G. Shorenstein, *et al.*, *ibid.*, **90**, 6199 (1968); (c) C. Aso, *et al.*, *Chem. Commun.*, 1483 (1968); (d) R. L. Van Etten, *et al.*, *J. Amer. Chem. Soc.*, **89**, 3242, 3253 (1967); (e) J. C. Sheehan, *et al.*, *ibid.*, **88**, 3455 (1966); (f) I. Photaki, *et al.*, *J. Chem. Soc. C*, 1860 (1968); (g) I. Photaki and S. Moschopedes, *Experientia*, **25**, 903 (1964); (h) J. C. Sheehan and D. N. McGregor, *J. Amer. Chem. Soc.*, **84**, 3000 (1962); (i) D. I. Elmore and J. J. Smyth, *Biochem. J.*, **94**, 563 (1965); (j) K. D. Kopple and D. E. Nitecki, *J. Amer. Chem. Soc.*, **83**, 4103 (1961); **84**, 4457 (1962); (k) T. Maugh II and T. C. Bruice, *ibid.*, **93**, 6584 (1971).

(2) S. Seifter, P. M. Gallop, S. Michaels, and E. Meilman, *J. Biol. Chem.*, **235**, 2613 (1960).

(3) J. Gerstein and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 4655 (1964).

(4) William Gruhn, unpublished results, 1969.

(5) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).

(6) D. P. Evans, J. J. Gordon, and H. B. Watson, *J. Chem. Soc.*, 1439 (1938).

(7) M. L. Bender, F. J. Kezdy, and F. C. Wedler, *J. Chem. Educ.*, **44**, 84 (1967).

(8) For the general scheme

$$I + S \underset{}{\overset{K_s}{\rightleftharpoons}} I \cdot S \xrightarrow{k_2} I' \xrightarrow{k_3} I + P_2$$
$$\qquad\qquad\qquad\quad +$$
$$\qquad\qquad\qquad\quad P_1$$

it has also been shown that

$$B = \frac{I_0(k_2/(k_2 + k_3))^2}{(1 + K_m/S_0)^2}$$

where B is the burst size, I_0 and S_0 are initial I and ester concentrations, respectively, and $K_m = [k_3/(k_2 + k_3)]K_s$. In the case of PNPB where k_2 and K_s have been separated, k_2 is greater than $200k_3$ as judged from the slope of the linear portion of the progress curve. Consequently, $K_m < 5 \times 10^{-6}$ *M* for this substrate, and presumably much less for longer chain acids, so that $B = I_0$.