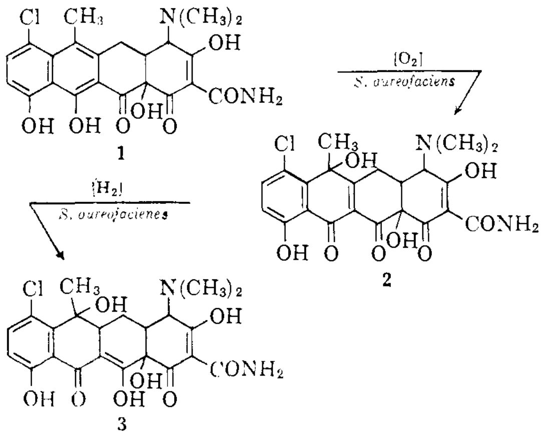
6-methylation, 12a-hydroxylation, 2-acetyl to 2-carboxamide conversion, nor 2-nitrile hydrolysis (CN → $CONH_2$) was observed. In addition, no biological transformation products were detected from the following compounds: apoterramycin[4]; dedimethylaminotetracycline[5]; 4a,12a-anhydrotetracycline[6]; isoaureomycin[7]; dedimethylamino-12a-deoxytetracycline[5]; and 12a-deoxytetracycline.[8]

The observed rehydration of 5a,6-anhydro-12a-deoxytetracycline to 12a-deoxytetracycline, unaccompanied by 12a-hydroxylation, demonstrates that neither of these compounds is an intermediate in the biosynthetic pathway and that the presence of 12a-hydroxyl is unimportant in the rehydration reaction.[9]

The rehydration of the 5a,6-anhydrotetracyclines is probably the net result of a biological oxidation and then a biological reduction. Thus the apparent rehydration of 5a,6-anhydro-7-chlorotetracycline (**1**) to 7-chlorotetracycline (**3**) would be the result first, of oxidative hydroxylation to yield 7-chloro-5a,11a-dehydrotetracycline (**2**) followed by biological reduction[10] of the 5a,11a double bond yielding **3**. This was confirmed by the conversion of Cl^{36}-5a,6-anhydro-7-chlorotetracycline to Cl^{36}-7-chloro-5a,11a-dehydrotetracycline by *S. aureofaciens* S1308, a mutant blocked for the reduction of **2** to **3**. We therefore conclude that oxidative hydroxylation of 5a,6-anhydrotetracyclines at C-6 and reduction of the resulting 5a,11a-dehydrotetracyclines are the final two steps in the biosynthetic pathways to the tetracyclines.[11,12]



1

2

3

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[4] F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *J. Am. Chem. Soc.*, **75**, 5455 (1953).

[5] A. Green, R. G. Wilkinson and J. H. Boothe, *ibid.*, **82**, 3946 (1960).

[6] K. Blackwood, H. H. Rennhard and C. R. Stephens, *ibid.*, **82**, 745 (1960).

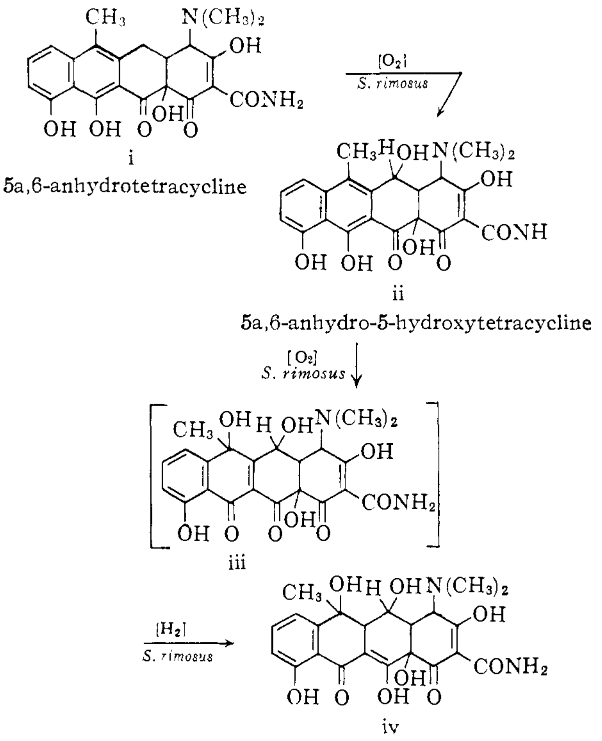
[7] C. W. Waller, B. L. Hutchings, R. W. Broschard, A. A. Goldman, W. J. Stein, C. F. Wolf and J. H. Williams, *ibid.*, **74**, 4981 (1952).

[8] A. Green and J. H. Boothe, *ibid.*, **82**, 3950 (1960).

[9] Although C. E. Holmlund, W. W. Andres and A. J. Shay [(*ibid.*, **81**, 4750 (1959)] were able to demonstrate the 12a-hydroxylation of 12a-deoxytetracycline by *Curvularia lunata*, they too were unable to demonstrate a similar 12a-hydroxylation by *S. aureofaciens*.

[10] J. R. D. McCormick, N. O. Sjolander, P. A. Miller, U. Hirsch, N. H. Arnold and A. P. Doerschuk, *ibid.*, **80**, 6460 (1958).

[11] Similarly, the last steps in the biosynthesis of 5-hydroxytetracycline would appear as:



i

5a,6-anhydrotetracycline

ii

5a,6-anhydro-5-hydroxytetracycline

iii

iv

5-hydroxytetracycline

although at this time experimental evidence for the intermediate iii is lacking.

[12] NOTE ADDED IN PROOF.—A. I. Scott and C. T. Bedford [*J. Am. Chem. Soc.*, **84**, 2271 (1962)] have now reported the photoöxidation of 5a,6-anhydro-7-chlorotetracycline to the 6-hydroperoxide and the reduction of this product to 7-chloro-5a,11a-dehydrotetracycline in simulation of the biosynthetic process.

LEDERLE LABORATORIES
AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK

J. R. D. MCCORMICK
PHILIP A. MILLER
SYLVIA JOHNSON
NANCY ARNOLD
NEWELL O. SJOLANDER

RECEIVED JUNE 7, 1962

A REINVESTIGATION OF THE APPLICABILITY OF THE SELECTIVITY RELATIONSHIP TO SE REACTIONS OF BIPHENYL AND FLUORENE

Sir:

The non-adherence of the rates of electrophilic aromatic substitution reactions in the *para* position of biphenyl to the Selectivity Relationship recently has been clearly demonstrated.[1] The anomalously small activation by the phenyl group, and the increase in its activating ability with increase in electron demand of the attacking electrophile have been rationalized on the basis of the variable noncoplanar configuration of the two benzene rings.[1] This theory is supposedly further substantiated by the much greater reactivity of fluorene and the adherence of the latter compound to the Selectivity Relationship in SE reactions. In fact, a reinvestigation of the available data for SE reactions of fluorene[1] shows an apparent *deviation* from the Selectivity Relationship *analogous to that of biphenyl* (see Fig. 1).

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[1] L. M. Stock and H. C. Brown, *J. Am. Chem. Soc.*, **84**, 1242 (1962), and H. C. Brown, *et al.*, *ibid.*, **84**, 1229, 1233, 1236 and 1238 (1962).

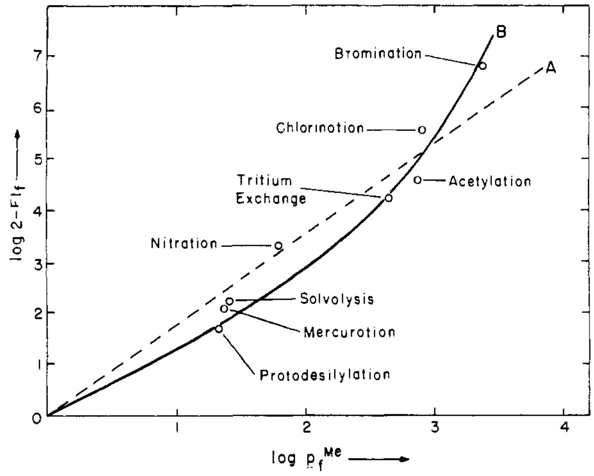

Fig. 1.—Log 2 − Fl_f *vs.* log p_f^{Me} for S_E reactions.

In Fig. 1, line A is the best least-squares straight line through the available points which passes through the origin.[2] The standard deviation of points from this line is 0.6. It can be seen that the arbitrary curve B fits enough better to suggest that the data, although scattered, may contain a trend similar to that shown by data for biphenyl. If biphenyl and fluorene really differ with regard to the Selectivity Relationship, a plot of log 2−Fl_f *vs.* log p_f^{Ph} should show a marked curvature. However, (see Fig. 2) the best least-squares line with zero intercept[2b] shows that the data fit a more reasonable linear relationship than line A, Fig. 1. The standard deviation of points from the line is 0.4. Two points for nitration in acetic anhydride are shown in Fig. 2. The point farthest from the line corresponds to a value p_f^{Ph} = 11, obtained by Dewar.[3] The point closer to the line is obtained from an average of the values, p_f^{Ph} = 32.6 and 38.0, obtained by Simamura[4] and Norman.[5] The least-squares line in Fig. 2 was obtained from an average of these two points.[6]

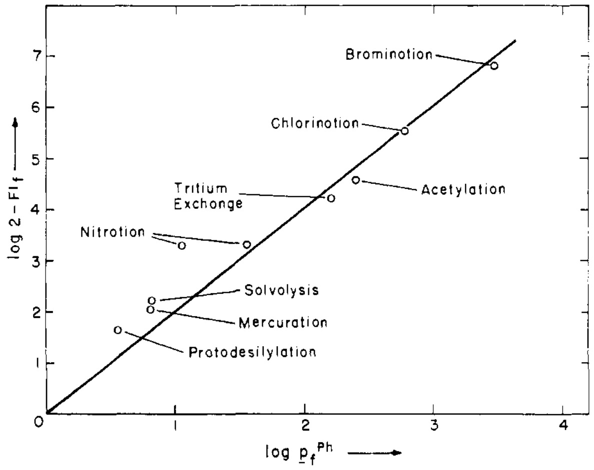

Fig. 2.—Log 2 − Fl_f *vs.* log p_f^{Ph} for S_E reactions.

On the basis of the available data we are led to the conclusion that σ^+_{2-Fl} is at least as good, and probably a better linear function of σ^+_{p-Ph} as of σ^+_{p-Me}, and that apparently fluorene does not fit the Selectivity Relationship much better than biphenyl.

It is reasonable to attribute the much lower reactivity of biphenyl as opposed to fluorene to the deviation from planarity in the biphenyl system. However, since biphenyl and fluorene (on the basis of available data) both show greater participation of the phenyl substituent as the electron demand of the attacking reagent becomes larger, it is unreasonable to say that biphenyl is a special case due to its nonplanar geometry. *A priori* the 0.4 kcal.[1] barrier to rotation in biphenyl should be no more special than ionization potentials of other types of substituents which are of the order of 7–11 electron volts. In every case, maximum stabilization of transition states depends upon an energy balance. Thus, in general, it would be expected that the different electron demand of various electrophiles would solicit a correspondingly variable response by the substituent group. This idea has been discussed by a number of workers and has most recently been demonstrated and discussed by Knowles, Norman and Radda.[8]

Acknowledgment.—The author wishes to acknowledge the helpful assistance and counsel of Professor George S. Hammond.

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[2] (a) The form of the relationship used in Fig. 1 is log 2 − Fl_f = ($\sigma^+_{2-Fl}/\sigma^+_{p-Me}$) log p_f^{Me}.[1] 2 − Fl_f is the partial rate factor for substitution in one of the 2-positions of fluorene and p_f^{Me} is the partial rate factor for substitution in the para position of toluene. (b) The requirement that the line pass through the origin is discussed by Brown [*J. Am. Chem. Soc.*, **77**, 2300 (1955)].

[3] F. B. Deans, C. Eaborn and D. E. Webster, *J. Chem. Soc.*, 3031 (1959); P. B. D. de La Mare and M. Hassan, *ibid.*, 3004 (1957); M. J. S. Dewar, T. Mole and E. W. T. Warford, *ibid.*, 3576 (1956).

[4] O. Simamura and Y. Mizuno, *Bull. Chem. Soc., Japan*, **30**, 196 (1957).

[5] C. J. Billing and R. O. C. Norman, *J. Chem. Soc.*, 3885 (1961).

[6] Nitration data for fluorene[7] are referred to benzene through Dewar's nitration data[3] for biphenyl, which disagree with those of Simamura[4] and Norman.[5]

[7] M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 3079 (1958).

[8] J. R. Knowles, R. O. C. Norman and G. K. Radda, *J. Chem. Soc.*, 4885 (1960).

CONTRIBUTION NO. 2843
GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA ROBERT C. NEUMAN, JR.

RECEIVED MAY 19, 1962

ISOMERS OF $B_{20}H_{18}^{-2}$

Sir:

There are to date no known isomers among molecular or ionic species containing only boron and hydrogen, presumably owing to facile rearrangement of both B and H geometries in electron deficient situations. We wish to report an isomer of $B_{20}H_{18}^{-2}$ ion as the first example.

It has been reported[1] recently that Fe^{+3} oxidation of the $B_{10}H_{10}^{-2}$ ion, the proposed[2] structure of which has now been proven,[1] produces centrosymmetric[3] $B_{20}H_{18}^{-2}$ (ion A; m. p. of $HNEt_3^+$ salt, 173–174°). The B^{11} nuclear magnetic resonance

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[1] A. Kaczmarczyk, R. D. Dobrott and W. N. Lipscomb, *Proc. Nat. Acad. Sci. U. S.*, **48**, 729 (1962).

[2] W. N. Lipscomb, A. R. Pitochelli and M. F. Hawthorne, *J. Am. Chem. Soc.*, **81**, 5833 (1959).

[3] B. Dickens and W. N. Lipscomb, X-ray diffraction study in progress.