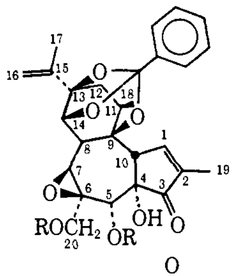
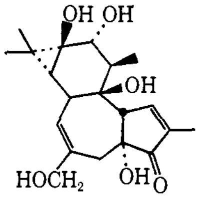
residual degradation effects even after correction for averaged dI/dt and clear evidence of some packing disorder indicate that high precision is not to be expected.



1a, R = $\mathrm{BrCH_2\overset{O}{\overset{\|}{C}}}$—
b, R = H



2

The structure **1b** implied for daphnetoxin itself shows striking similarities, both in the skeleton and in the sites of functional groups to phorbol (**2**), the diterpene parent of the toxic esters of croton oil.[14–16] Comparisons of the physical properties of the two compounds show the expected correspondences, especially in the nmr spectra. Furthermore, the absolute configuration of daphnetoxin bisbromoacetate, as shown both by parallel structure-factor calculations[17] including Br anomalous dispersion in P3$_1$21 and P3$_2$21 to *R*'s of 10.9 and 11.1%, respectively, and by the comparison of 40 pairs of observed and calculated $F_{hkl}/F_{\bar{h}\bar{k}\bar{l}}$, all of which were in accord with P3$_1$21, is as shown in **1** and is the same as found crystallographically for phorbol.[16a] Figure 1 shows a stereoscopic view of the molecule in the proper hand. Strikingly, the CD curve of daphnetoxin, $[\theta]_{342}$ + 3050, $[\theta]_{243}$ − 8300, is nearly enantiomeric with that reported for phorbol.[18] Comparison of the atomic parameters for the one phorbol derivative for which these have been reported[16b] with those for **1a**, however, suggests that the α,β-unsaturated keto systems have opposite chirality in the two molecules despite the configurational identity. Both systems then agree with the CD correlation proposed for cyclopentenones by Snatzke.[19]

The structure of daphnetoxin, although unique in detail, is similar in its high degree of oxygen bridging to a number of other highly toxic nitrogenous and nonnitrogenous compounds.[20] The orthobenzoate structure in particular, although without exact analogy, is strongly reminiscent of the hemilactal structure of tetrodotoxin.[20a] The similarity to phorbol is clearly of chemotaxonomic interest in view of the much disputed phylogenetic placing of the Thymeleaceae,[21] especially since one of the numerous proposals posits on the grounds of pollen morphology a close connection to the crotonoid members of the Euphorbiaceae.[21d,22]

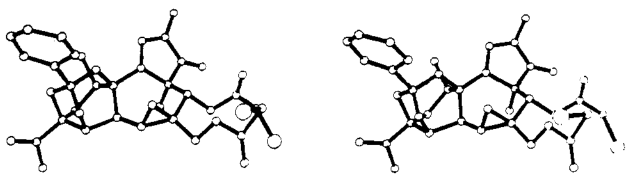


Figure 1. A stereoview of daphnetoxin bisbromoacetate.

Acknowledgment. This work was supported in part by a grant (GM-12095) from the National Institutes of Health, Institute of General Medical Sciences. We are indebted to Dr. A. Horita and Mrs. A. Hamilton for their kind assistance in performing the toxicity tests on mice.

---

(14) E. Hecker, H. Bartsch, H. Bresch, M. Gschwendt, E. Härle, G. Kreibich, H. Kubinyi, H. U. Schairer, Ch. v. Szczepanski, and W. H. Thielmann, *Tetrahedron Lett.*, 3165 (1967), and references cited therein.

(15) (a) R. C. Pettersen, G. Ferguson, L. Crombie, M. L. Games, and D. J. Pointer, *Chem. Commun.*, 716 (1967); (b) L. Crombie, M. L. Games, and D. J. Pointer, *J. Chem. Soc., C*, 1347 (1968).

(16) (a) W. Hoppe, F. Brandl, I. Strell, M. Röhrl, I. Gassmann, E. Hecker, H. Bartsch, G. Kreibich, and Ch. V. Szczepanski, *Angew. Chem. Intern. Ed. Engl.*, **6**, 809 (1967); (b) R. C. Pettersen, G. I. Birnbaum, G. Ferguson, K. M. S. Isham, and J. G. Sime, *J. Chem. Soc., B*, 980 (1968); (c) W. Hoppe, K. Zechmeister, M. Röhrl, F. Brandl, E. Hecker, G. Kreibich, and H. Bartsch, *Tetrahedron Lett.*, 667 (1969).

(17) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).

(18) E. Hecker, C. v. Szczepanski, H. Kubinyi, H. Bresch, E. Härle, H. V. Schairer, and H. Bartsch, *Z. Naturforsch.*, **21b**, 1204 (1966). These are the n–π* and π–π* bands of the cyclopentenone chromophore. The additional CD band at 270 nm in phorbol does not appear in daphnetoxin.

(19) G. Snatzke in "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," G. Snatzke, Ed., Heyden and Son, London, 1967, pp 217–8.

(20) *Inter alia* (a) tetrodotoxin, R. B. Woodward, *Pure Appl. Chem.*, **9**, 49 (1964); (b) batrachotoxin, T. Tokuyama, J. Daly, and B. Witkop, *J. Amer. Chem. Soc.*, **91**, 3931 (1969); (c) picrotoxinin, H. Conroy, *ibid.*, **79**, 5550 (1957).

(21) (a) A. Engler, "Syllabus der Pflanzenfamilien," Vol. II, 12th ed, Gebruder Borntraeger, Berlin, 1964, pp 316–321; (b) J. Hutchinson, "The Genera of Flowering Plants," Vol. II, Oxford, 1967, pp 239–271; (c) A. Cronquist, "The Evolution and Classification of Flowering Plants," Houghton Mifflin, Cambridge, Mass., 1968, pp 238–241; (d) A. Takhtajan, "Die Evolution der Angiospermen," Gustav Fischer Verlag, Jena, 1959, pp 216–217.

(22) G. Erdtman, "Pollen Morphology and Plant Taxonomy," Vol. I, Hafner, New York, N. Y., 1966, pp 175, 431–433.

George H. Stout, Wayne G. Balkenhol
Mitchell Poling, Gary L. Hickernell
Department of Chemistry, University of Washington
Seattle, Washington 98105

Received November 29, 1969

Intermolecular Methyl Transfers in the Methylation of Anisole

Sir:

We wish to report a study of the methylation of anisole which reveals that the major reaction pathway involves initial alkylation on oxygen followed by intermolecular transfer of a methyl group to oxygen or carbon.

Reaction of 0.1 *M* methyl chloroformate with silver hexafluoroantimonate[1] and a fivefold excess of anisole in chlorobenzene for 10 hr at room temperature gives a 24 ± 3% yield[2] of methylanisoles with an *ortho*:*meta*:*para* isomer distribution of 35:5:60.[3] Reaction of methyl-d_3 chloroformate with anisole under the same conditions gives a 26 ± 3% yield of methylanisoles with an isotope distribution of 72 ± 6% **1**, 25 ± 3% **2**, 3 ± 1% **3**, and <1% **4**. Recovered excess anisole con-

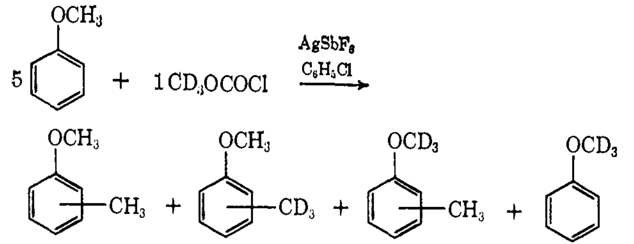
---

(1) P. Beak, R. J. Trancik, and D. A. Simpson, *J. Amer. Chem. Soc.*, **91**, 5073 (1969).

(2) Yields are based on initial methyl chloroformate unless otherwise specified.

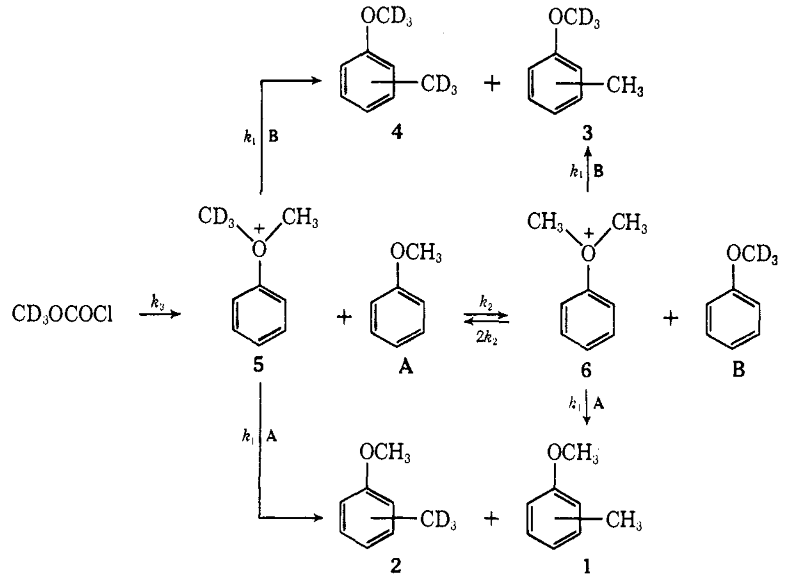
(3) Thermodynamic and kinetic evidence shows that the relative yield of *ortho* methylanisole is not deceptively low because of equilibration to *meta* and *para* isomers or selective reaction of the *ortho* isomer. Equilibration would lead to considerably more *meta* compound than the 5% observed.[4] Separate reactions of each of the methylanisoles with a solution made by reaction of *n*-propyl chloroformate with silver hexafluoroantimonate in chlorobenzene, at room temperature for 10 hr, gave recovery of the *ortho*, *meta*, and *para* isomers of 89, 71, and 31%, respectively.

(4) D. A. McCaulay, "Friedel-Crafts and Related Reactions," Vol. II, G. A. Olah, Ed., Interscience Publishers, New York, N. Y., 1965, Chapter XXIV.



18.6 ± 0.7% **1** 6.4 ± 0.5% **2** 0.9 ± 0.2% **3** 13.5 ± 3.2%

Scheme I



tains 13.5 ± 3.2% anisole-O-methyl-d_3.[2] The isotope distribution was determined by proton and deuteron magnetic resonance spectroscopy and mass spectrometry.

The products obtained may be accounted for by initial formation of methyl, methyl-d_3-phenyl oxonium ion (**5**) which partitions equally between transfer of a methyl to oxygen or carbon of anisole in subsequent second-order reactions. Based on the assumptions that isotope effects can be disregarded, that **5** is formed in a first-order process from methyl-d_3 chloroformate, and that the ratio of rate constants $k_1:k_2:k_3$ is 25:25:1, the scheme shown (Scheme I) predicts an isotope distribution for the methylanisoles of 65 ± 1% **1**, 24 ± 1% **2**, 5 ± 1% **3**, and 1.0 ± 0.5% **4**, as well as 15% methylanisole-d_3.[5,6] Although a better fit to the data might be obtained by including the acid-catalyzed self-alkylation of anisole[7,8] or by using a lower rate for production of **5**, the results do not warrant a more precise treatment. It is clear that the proposed scheme accounts for the major pathway of this reaction. Even though minor contributions from other processes, including direct attack of the electrophilic methyl on the ring or intramolecular rearrangement of the oxonium ions **5** and **6** cannot be excluded, such pathways do not by themselves account for the isotopic distribution observed.

Oxonium ions are well-characterized stable species with precedent as reactive intermediates,[9,10] and n complexes between the catalyst and substrate are well known in Friedel–Crafts reactions.[11] Electrophilic aromatic substitution reactions which give unusually large fractions of *ortho* product[12] or show deviation from expected reactivities[13] have been postulated to involve initial n complex formation. Accordingly, increased amounts of *ortho* product have been rationalized by intramolecular rearrangement of the electrophilic group from the substituent to the ring.[8,12,14] The present results indicate that a large fraction of *ortho* product is not a necessary or sufficient criterion for the intermediacy of an n complex[15] in electrophilic aromatic substitution

---

(5) The scheme was analyzed with the aid of an analog computer. The results are not very sensitive to as much as 10% variation in rate constants. Isotope effects reported for solvolyses of methyl-d_3 halides and esters vary from 0.97 to 1.00 kH/kD per deuterium; A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(6) Identity methyl transfers analogous to the interconversion of **5** and **6** have been reported; P. Beak, J. Bonham, and J. T. Lee, Jr., *J. Amer. Chem. Soc.*, **90**, 1569 (1968).

(7) As much as 20% of the methylanisoles formed could be produced by acid-catalyzed self-alkylation of anisole; addition of an amount of anisole equivalent to that initially present in the above reactions to a solution made by reaction of n-propyl chloroformate with silver hexafluoroantimonate in chlorobenzene gives 5% methylanisoles.[4]

(8) Acid-catalyzed inter- and intramolecular rearrangements of aryl alkyl ethers have been studied; N. M. Collinane, R. A. Woolhouse, and G. B. Carter, *J. Chem. Soc.*, 2995 (1962); M. J. S. Dewar and N. A. Puttnam, *ibid.*, 4080, 4086 (1959); H. Hart and R. J. Elia, *J. Amer. Chem. Soc.*, **76**, 3031 (1954); D. S. Tarbell and J. C. Petropoulos, *ibid.*, **74**, 244 (1952).

(9) H. Meerwein, "Methoden der organischen Chemie," Vol. 6, No. 3, 1965, pp 325–365. Dimethylphenyl oxonium hexachloroantimonate has been reported: F. Klages, A. Meuresch, and W. Steppich, *Ann.*, **592**, 81 (1955).

(10) See, for example, A. Streitwieser and S. Andreaddes, *J. Amer. Chem. Soc.*, **80**, 6553 (1958); D. E. Applequist and D. E. McGreer, *ibid.*, **82**, 1965 (1960); P. Caruso and L. Friedman, unpublished data cited in footnote 9a, L. Friedman and J. F. Chlebowski, *J. Org. Chem.*, **33**, 1633 (1968); R. T. Channon, G. W. Kirby, and S. R. Massey, *J. Chem. Soc., C*, 1215 (1969); D. Bethell and V. Gold, "Carbonium Ions," Academic Press, New York, N. Y., 1967, p 168.

(11) G. Olah and M. W. Meyer, "Friedel–Crafts and Related Reactions," Vol. I, G. A. Olah, Ed., Interscience Publishers, New York, N. Y., 1964, Chapter VII.

(12) P. Kovacic and J. J. Hiller, *J. Org. Chem.*, **30**, 1581 (1965); P. Haberfield and D. Paul, *J. Amer. Chem. Soc.*, **87**, 5502 (1965); R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzeneoid Compounds," Elsevier Publishing Co., New York, N. Y., 1965, pp 303–305, and references cited therein; D. E. Pearson, R. D. Wysong, and C. V. Breder, *J. Org. Chem.*, **32**, 2358 (1967).

(13) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 133–134 (1963).

(14) M. J. S. Dewar, "Molecular Rearrangements," P. de Mayo, Ed., John Wiley & Sons, Inc., New York, N. Y., 1963, pp 306–344, and references cited therein.

(15) The favorability for n-complex formation and intermolecular rearrangement observed in this case cannot be extrapolated without

and suggest that substituents bearing *n* electrons can exert a leveling effect on electrophilic reactivity.

Acknowledgment. We are grateful to the Public Health Service (GM12595 and GM37395) and the Alfred P. Sloan Foundation for support.

further study. However, in circumstances where a nucleophilic solvent or counterion is available to effect alkyl transfer, it seems possible that even the "intramolecular" rearrangements[6,12] might involve double displacements and intimate ion pairs.

David A. Simpson, Stanley G. Smith, Peter Beak
Department of Chemistry, University of Illinois
Urbana, Illinois 61801

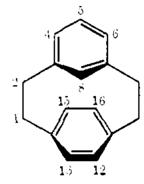
Received November 20, 1969

Barriers to Ring Rotation in [2.2]Metaparacyclophane and Derivatives[1]

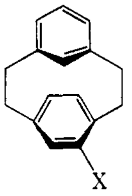
Sir:

With both nmr and stereochemical techniques we have studied the ring rotation and condensation potentialities of [2.2]metaparacyclophane[2] (I) and its derivatives in connection with our electrophilic substitution studies.[3] Others[4] have reported recently that I undergoes ring inversion at rates observable on the nmr time scale. Our work differentiates between one-ring and two-ring inversion possibilities.

Acetylation of I[2] at −25° in dichloromethane with acetyl chloride and aluminum chloride gave a mixture of IIa,[5] mp 67–68° (20%), and IV, mp 87–88.6° (37%). The structural assignment of IIa was based on its nmr (see below) and mass spectrum, and the reactions IIa → IIb[5] → I, which involved oxidation of IIa with sodium hypobromite to give acid IIb (80%), followed by decarboxylation by heating IIb to 237° with copper carbonate–quinoline (40%). The structural assignment of IV was based on its uv, ir, and nmr (both ^{1}H and ^{13}C) spectra, and on the production of 1,2,3-benzenetricarboxylic acid when oxidized with alkaline potassium permanganate in water at reflux for 8 hr (50%). Compounds IIc–IIf,[5] prepared from IIb by conventional reactions, gave the following melting points: IIb, 163–163.5°; IIc, 75–76.2°; IId, 88–90°; IIe, 73–79°; IIf, 42–44°.

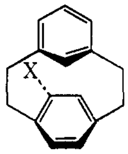


I

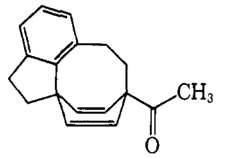


II

IIa, X = COCH$_3$
IIb, X = CO$_2$H
IIc, X = CO$_2$CH$_3$
IId, X = CH$_2$OH
IIe, X = CHO
IIf, X = CH$_3$



III



IV

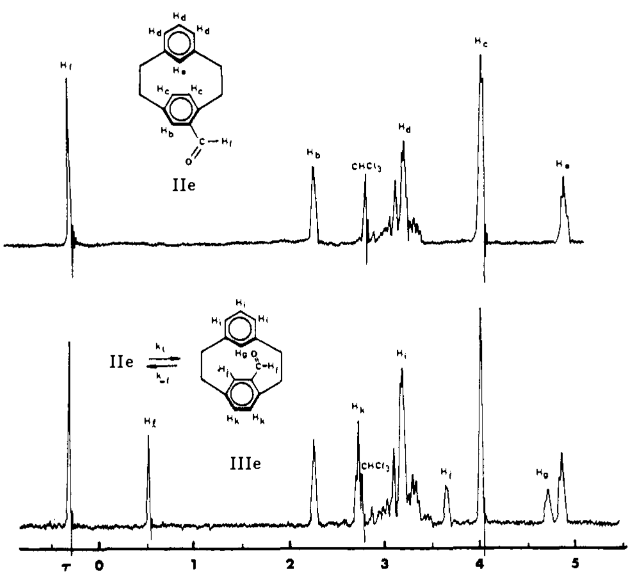


Figure 1. Nmr spectrum of 12-aldehydo[2.2]metaparacyclophane (IIe); top spectrum, at −50°, pure IIe; bottom spectrum, at 37°, equilibrium mixture of IIe and IIIe (CDCl$_3$, 60 MHz, spectrum amplitude not equal for both spectra).

Although IIa–IIf crystallized as single compounds, when dissolved they equilibrated with their corresponding III isomers, a process detected by nmr spectroscopy. For example, Figure 1 shows a spectrum of aldehyde IIe obtained by adding crystalline material to frozen deuteriochloroform, warming the mixture to −50° in an nmr tube, and recording the spectrum. The observed spectrum is that expected for IIe. The solution, when warmed to 37°, gave a nontime dependent curve consistent with that expected for IIe $\rightleftarrows$ IIIe. Peak integrations of the nmr spectra of $(\text{II} \rightleftarrows \text{III})_{\text{equil}}$ at 37° provided the equilibrium constants ($K_{37°}$) listed in Table I. The rate constants k_1 and k_{-1} were determined for IIe $\underset{k_{-1}}{\overset{k_1}{\rightleftarrows}}$ IIIe at −13.5° making use of the two aldehyde proton peaks in the nmr (τ −0.32 for IIa and 0.52 for IIIa) and $k_1 = 1.72 \times 10^{-4}$ sec^{-1} and $k_{-1} = 3.83 \times 10^{-4}$ sec^{-1} ($K_{-13.5°} = 0.45$).[6] The rate constants were also determined at the coalescence tempera-

Table I

X	II:III	$K_{37°}$
CO$_2$CH$_3$	7:1	0.14
COCH$_3$	3.9:1	0.26
CH$_3$	3.3:1	0.31
CH$_2$OH	2.2:1	0.45
CHO	2.1:1	0.48
H	1:1	1.00

---

(1) The authors wish to thank the National Science Foundation for a grant used in support of this research. D. T. H. also wishes to thank the National Science Foundation for a Traineeship, 1965–1969.

(2) D. J. Cram, R. C. Helgeson, D. Lock, and L. A. Singer, *J. Amer. Chem. Soc.*, **88**, 1324 (1966).

(3) A full paper is being prepared.

(4) (a) F. Vögtle, *Chem. Ber.*, **102**, 3077 (1969); (b) S. Akabori, S. Hayashi, M. Nawa, and K. Shiomi, *Tetrahedron Lett.*, 3727 (1969).

(5) Combustion analysis gave carbon and hydrogen values less than 0.2% from theory.

(6) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1961, p 186.