$$d[Fe(phen)_3^{2+}]/dt = k_{obsd}[Fe(phen)_3^{3+}][Fe^{2+}] \quad (3)$$

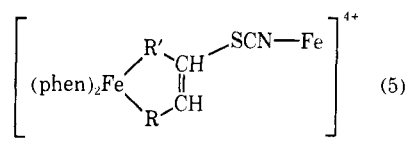
$$k_{obsd} = k_0 + k_1(X^-) + k_2(X^-)^2 + \ldots \quad (4)$$

added anions have very different effects on the rates of the $Fe(phen)_3^{3+}$–Fe^{2+} and Fe^{3+}–Fe^{2+} reactions.[8] In particular, added thiocyanate has a much larger effect on the former reaction than on the latter. Moreover, the ratio of k_1 for azide compared to thiocyanate is only 0.4 for the $Fe(phen)_3^{3+}$–Fe^{2+} reaction, while this ratio is 3×10^4 for the Fe^{3+}–Fe^{2+} reaction. Spectrophotometric and kinetic analysis of the reaction products showed that $FeNCS^{2+}$ is formed quantitatively in the thiocyanate-catalyzed $Fe(phen)_3^{3+}$–Fe^{2+} reaction.

The thiocyanate catalysis of the reduction of the phenanthroline and bipyridine complexes is undoubtedly due in part to the larger driving force for these reactions (because $FeNCS^{2+}$ is more stable than $FeNCS^+$). The magnitude of this factor may be estimated from the effect of thiocyanate on the reduction of Fe^{3+} by Fe^{2+}. The *outer-sphere* reduction of Fe^{3+} by $FeNCS^+$ proceeds about 30 times faster than the reduction of Fe^{3+} by Fe^{2+}.[9] Thus, if the reaction of $Fe(phen)_3^{3+}$ with Fe^{2+} ions were of a comparable weak-interaction, outer-sphere variety, we would expect the rate constant for the $Fe(phen)_3^{3+}$–$FeNCS^+$ reaction to be about 30 times larger than the rate constant for the $Fe(phen)_3^{3+}$–Fe^{2+} reaction. Evidently this is not the case, as may readily be ascertained by dividing k_1 for thiocyanate (2.0×10^9 M^{-2} sec^{-1}) by the stability constant of $FeNCS^+$ (6.5 M^{-1})[9] and comparing the second-order rate constant for the reaction between $Fe(phen)_3^{3+}$ and $FeNCS^+$ thus calculated with k_0 (3.40×10^4 M^{-1} sec^{-1}).[10-13]

The above considerations as well as comparisons with the effects of chloride, azide, and thiocyanate on reactions of known mechanism[14,15] strongly suggest that a new mechanism is operating in the thiocyanate (and azide and iodide) catalyzed reduction of the phenanthroline and bipyridine complexes. An attractive possibility is that the thiocyanate-catalyzed reaction proceeds *via* a bridged intermediate formed by nucleophilic attack of the sulfur atom of SCN^- on a carbon of the ligand ring system bearing a partial positive charge (eq 5).[16] These carbon atoms are presumably good sites for nucleophilic attack as a consequence of electron withdrawal by the central ferric ion. An alternative mechanism involves the addition of the thiocyanate (through the sulfur atom) to the π system of the ligand rather than addition to an

$$Fe(phen)_3^{3+} + SCN^- + Fe^{2+} \longrightarrow$$



(5)

electrophilic carbon atom. This type of addition can perhaps more readily account for the observation (Table I) that replacement of the hydrogen atoms in the 4 and 4′ positions of bipyridine by methyl groups does not significantly alter the value of k_1/k_0.

Regardless of whether the oxidation–reduction reactions proceed by nucleophilic attack on a carbon atom or by π-complex formation (or some other mechanism), these studies show that added anions have very different effects on the rate of reduction of phenanthroline and bipyridine iron(III) complexes than they have on "ordinary" electron-transfer reactions. This difference in the reactivity patterns might be used to obtain information about the electron-transfer site in more complex systems. Thus the thiocyanate catalysis of the reduction of cytochrome c by chromous ions suggests that in this reaction the porphyrin ring system is the electron-transfer site. Similarly, the relatively large effect of thiocyanate on the rate of reduction of iron(III) and manganese(III) tetrapyridylporphines[17] raises the possibility that in this reaction, too, the electron-transfer site is the porphyrin ring rather than the central metal atom. These and related electron-transfer reactions are currently under active investigation in this laboratory.[18]

Acknowledgment. The authors wish to express their appreciation to Dr. Stanley Seltzer for helpful discussions.

(8) The oxidation of free azide, iodide, or thiocyanate ions by the iron(III) complexes is sufficiently slow under the conditions used in these studies as not to interfere with the reduction of the iron(III) complexes by ferrous ions.

(9) T. J. Conocchioli and N. Sutin, *J. Amer. Chem. Soc.*, **89**, 282 (1967).

(10) The ratio of k_1 for thiocyanate compared to chloride is also relatively small in other outer-sphere reactions. This ratio is only about 10 for the outer-sphere oxidation of Cr^{2+} by Fe^{3+} ions[11,12] and approximately 30 for the oxidation of U^{3+}.[13]

(11) G. Dulz and N. Sutin, *J. Amer. Chem. Soc.*, **86**, 829 (1964).

(12) A. Haim and N. Sutin, *ibid.*, **87**, 4210 (1965).

(13) R. T. Wang and J. H. Espenson, *ibid.*, **93**, 380 (1971).

(14) N. Sutin, *Accounts Chem. Res.*, 1, 225 (1968).

(15) M. Orhanovic, H. N. Po, and N. Sutin, *J. Amer. Chem. Soc.*, **90**, 7224 (1968).

(16) Although the possibility of adjacent attack of the Fe^{2+} on the sulfur atom of the coordinated thiocyanate cannot be excluded, it is unlikely that this occurs to any significant extent under the conditions used in this work, since $FeNCS^{2+}$ is formed quantitatively in the reaction (and no $CrSCN^{2+}$ is formed in the reaction of $Fe(bipy)_3^{3+}$ with Cr^{2+} in the presence of thiocyanate).

(17) P. Hambright and E. B. Fleischer, *Inorg. Chem.*, **4**, 912 (1965).

(18) Preliminary results indicate that the $Co(phen)_3^{3+}$–Fe^{2+} reaction is also catalyzed by added thiocyanate ions.

Norman Sutin*

Chemistry Department, Brookhaven National Laboratory
Upton, New York 11973

Arthur Forman

Medical Research Center, Brookhaven National Laboratory
Upton, New York 11973

Received August 9, 1971

Ground-State Substituent Effects. I. Deuterium and Methyl

Sir:

Theoretical interest has been directed toward the problem of substituent effects on cyclopropyl rings, especially those involved in Cope rearrangements.[1-3] Remarkably large displacements by substituents have been observed in norcaradiene–cycloheptatriene[4] and bullvalene[5] equilibria.[6] However, these systems are

(1) (a) R. Hoffmann, *Tetrahedron Lett.*, 2907 (1970); (b) R. Hoffmann and W.-D. Stohrer, to be published.

(2) H. Günther, *Tetrahedron Lett.*, 5173 (1970).

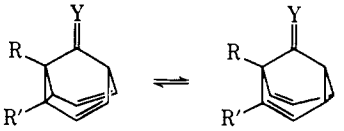
(3) (a) M. J. S. Dewar and W. W. Schoeller, *J. Amer. Chem. Soc.*, **93**, 1481 (1971); (b) M. J. S. Dewar and D. H. Lo, *ibid.*, in press.

(4) H. J. Reich, E Ciganek, and J. D. Roberts, *ibid.*, **92**, 5166 (1970); G. E. Hall and J. D. Roberts, *ibid.*, **93**, 2203 (1971); E. Ciganek, *ibid.*, **93**, 2207 (1971); A. Cairncross, to be published.

(5) (a) G. Schröder and J. F. M. Oth, *Angew. Chem., Int. Ed. Engl.*, **6**,

not ideal for a systematic study of these phenomena. In the former, the equilibrium in the parent system lies too far to one side,[4] and in the latter, all substituents except fluorine[5b,c] prefer attachment to olefinic sites.[5] A twofold-degenerate system would be much better for this purpose.[7]

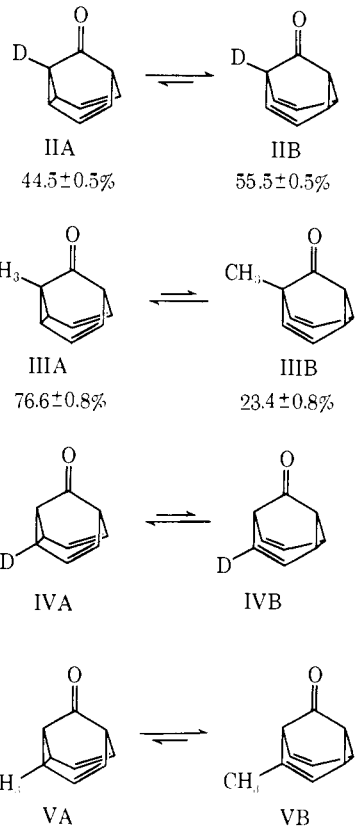
We have chosen the barbaralyl[8] systems I for quantitative study of substituent effects on equilibria. At normal temperatures, a rapid Cope rearrangement between two structures, identical except for the substituent, is operative. The activation energies (8.6 kcal/mol for I, Y = H_2[8a] and 9.6 kcal/mol for I, Y = O[8c]) are sufficiently high that the equilibria can be slowed in the nmr time scale if this is necessary for analytical purposes. The activation energy for semibullvalene interconversions is too low for this purpose.[3,9] Both barbaralyl and semibullvalenyl systems are well arranged so that differences in steric environments around the substituents are minimal.



IA IB

By selecting appropriately substituted barbaralyl derivatives, one can measure competition between attachment to cyclopropane (C_1) and aliphatic (C_5) positions (IA *vs.* IB, R′ = H, R = X) as well as between cyclopropane (C_2) and olefinic (C_4) positions (IA *vs.* IB, R = H, R′ = X). This initial report describes the synthesis and behavior of the deuterated and methylated barbaralones II–V.

1-Deuteriobarbaralone (II) was obtained from ethyl diazoacetate-d_1 and benzene, using a previously published procedure.[8a,10] 1-Methylbarbaralone (III) was



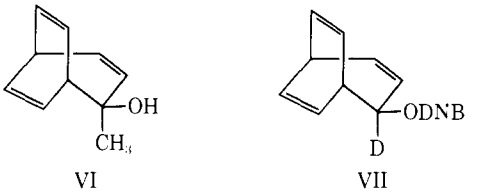
IIA 44.5±0.5% IIB 55.5±0.5%

IIIA 76.6±0.8% IIIB 23.4±0.8%

IVA IVB

VA VB

synthesized by the same procedure,[8a] the methyl group being introduced in a later step by using diazoethane instead of diazomethane. 2-Methylbarbaralone (V) was obtained by CrO_3–pyridine oxidation of the methylbarbaralol product that resulted when 4-methylbicyclo[3.2.2]nonatrien-4-ol (VI) was treated under mild conditions with dilute acid. Finally, 2-deuteriobarbaralone



VI VII

(IV) was synthesized as a 2:1 mixture with II by solvolysis of 4-deuteriobicyclo[3.2.2]nonatrien-4-yl 3,5-dinitrobenzoate (VII).[11]

Equilibrium data were obtained from pmr spectra of the substituted barbaralones. Advantage was taken of the temperature dependence of the barbaralone equilibrium[8c] in order to determine the positional preference of deuterium in the system. At low temperatures, pmr decoupling studies showed that the cyclopropyl proton at C_1 corresponded to a unique absorption at τ 7.54, thereby allowing a crude quantitative estimate of the equilibrium in II by integration of this signal. Excess deuterium (~54%) preferred attachment to the bridgehead (IIB) over the cyclopropyl (IIA) position. More accurate data were obtained by analysis of the normal-temperature 220-MHz spectrum of II.[12] The presence of deuterium in II removes

414 (1967); (b) J. F. M. Oth, R. Merényi, H. Röttele, and G. Schröder, *Tetrahedron Lett.*, 3941 (1968); (c) H.-P. Löffler and G. Schröder, *Angew. Chem., Int. Ed. Engl.*, 7, 736 (1968).

(6) Significant effects have also been observed in the cyclooctatriene–bicyclo[4.2.0]octadiene equilibria by R. Huisgen, G. Boche, A. Dahmen, and W. Hechtl, *Tetrahedron Lett.*, 5215 (1968). A thermochemical study of the effects of esters and nitriles on the stability of strained rings indicates that the effects are minor [H. K. Hall, Jr., and J. H. Baldt, *J. Amer. Chem. Soc.*, **93**, 140 (1971)], *e.g.*, the hypothetical reaction *i*-C_3H_7–CN + c-C_3H_6 → C_3H_8 + c-C_3H_5–CN is actually endothermic by a slight amount (ΔH_{isom} = 0.3 kcal/mol). This apparent discrepancy with the very large effect of cyano groups on the norcaradiene–cycloheptatriene equilibria can be reconciled by distinguishing between *total stabilizing effects* (as measured by combustion studies) and the *specific bond weakening and strengthening effects* on the individual cyclopropane ring bonds suggested by theory.[1-3] See C. J. Fritchie, Jr., *Acta Crystallogr.*, 20, 27 (1966). Finally, H. E. O'Neal and S. W. Benson, *J. Phys. Chem.*, 72, 1866 (1968), have concluded that fluorine substitution destabilizes both cyclopropane rings and olefins by about 5 kcal.

(7) After our work had commenced, we became aware of calculations on substituent effects in the semibullvalenyl series.[1b,3b] A recent paper has even suggested that the MINDO/2 method would be preferable to experiment for similar purposes.[3a] Saunders and coworkers have used degenerate cationic rearrangement systems for the measurement of deuterium isotope effects on equilibria: M. Saunders, M. H. Jaffe, and P. Vogel, *J. Amer. Chem. Soc.*, **93**, 2558 (1971); M. Saunders and P. Vogel, *ibid.*, **93**, 2559, 2561 (1971).

(8) (a) W. v. E. Doering, B. M. Ferrier, E. D. Fossel, J. H. Hartenstein, M. Jones, Jr., G. Klumpp, R. M. Rubin, and M. Saunders, *Tetrahedron*, **23**, 3943 (1967). In this report, Doering and coworkers recognized the possibility of using fluxional molecules such as bullvalene for qualitaive evaluation of substituent effects. (b) J. C. Barborak, J. Daub, D. M. Follweiler, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 7760 (1969); (c) J. B. Lambert, *Tetrahedron Lett.*, 1901 (1963); (d) H. Tsuruta, K. Kurabayashi, and T. Mukai, *ibid.*, 3775 (1967).

(9) H. E. Zimmerman and G. L. Grunewald, *J. Amer. Chem. Soc.*, **88**, 183 (1966).

(10) All new compounds met usual standards of analysis. Mass spectral and nmr analysis of deuterated compounds and their precursors showed >98% D in indicated positions.

(11) J. C. Barborak and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 3184 (1970).

the degeneracy, and the result is a *two-peak* spectrum for H_2, H_4, H_6, and H_8. The ratio of the separation of these peaks (37 ± 1 Hz) to the total separation of the H_2, H_8 and H_4, H_6 signals in frozen barbaralone (669 ± 2Hz) provides the IIA ⇄ IIB equilibrium value of 44.5 (± 0.5) *vs.* 55.5 (±0.5)%, respectively.

Although our analysis of the effects of deuterium at C_2–C_4 positions (IV) is complicated by partial isotopic scrambling (only two-thirds of the sample is IV, the rest being II),[11] we were able to ascertain from normal- and low-temperature pmr spectra that a deuterium isotope effect did exist, favoring attachment of deuterium to the cyclopropanoid positions C_2 (IVA).[13]

Substitution of methyl for hydrogen in the barbaralyl system has, as expected, a more pronounced effect. Methyl at C_1 was found by pmr[14] to shift the equilibrium in the direction of substitution on cyclopropyl rather than aliphatic; quantitatively, 76.6 ± 0.8% of the mixture of isomers is represented by structure IIIA. Preference of methyl for a vinylic rather than cyclopropyl position is clearly demonstrated in the pmr spectrum of V, in which isomer B is preferred (>75%).

Although equilibrium deuterium isotope effects have been observed only recently, it has long been known that deuterium prefers attachment to C_{sp^3} over C_{sp^2}.[15] Our investigation extends such equilibrium studies to cyclopropyl C_{sp^2}, the ordering C_{sp^3}(aliphatic) > $C_{\sim sp^2}$(cyclopropyl) > C_{sp^2}(vinylic) being observed.[16]

Our data indicate an inverse ordering for methyl attachment: olefinic > cyclopropane > aliphatic. That methyl groups prefer double bonds is well known and is in accord with available thermodynamic data, *e.g.*, eq 1. Our results contrast with available enthalpy data on ethylcyclopropane, eq 2, which indicate ethyl attachment to prefer aliphatic to cyclopropane positions.[17]

$$\text{c-}C_3H_5\text{-H} + i\text{-}C_3H_7\text{-}CH_3 \longrightarrow \text{c-}C_3H_5\text{-}CH_3 + i\text{-}C_3H_7\text{-H} \quad (1)$$
exothermic, $\Delta H_{isom} = 1.59$ kcal/mol[17]

$$\text{c-}C_3H_5\text{-Et} + i\text{-}C_3H_7\text{-H} \longrightarrow \text{c-}C_3H_5\text{-H} + i\text{-}C_3H_7\text{-Et} \quad (2)$$
exothermic, $\Delta H_{isom} = 0.46$ kcal/mol[17]

A fuller discussion of these effects will be presented later, as well as an assessment of the influences of other substituents, especially of the π-donor and -acceptor types for which theoretical predictions are available.[1-3]

Acknowledgments. This work was supported by grants from the National Institutes of Health (No. AI-07766); the National Science Foundation; the Petroleum Research Fund, administered by the American Chemical Society; and Hoffmann-La Roche, Nutley, N. J.

(12) We gratefully acknowledge the assistance of Professor A. Allerhand of Indiana University in obtaining 220-MHz nmr spectra.

(13) W. v. E. Doering and J. B. Lambert, *Tetrahedron*, **19**, 1989 (1963), did not report observing a deuterium isotope effect in the rearrangement of α-thujene, in which the C–D moiety alternated between vinylic and cyclopropyl position. See also W. v. E. Doering and E. K. G. Schmidt, *ibid.*, **27**, 2005 (1971).

(14) Chemical shifts were measured using the standard audio-sideband technique from an oscillator accurate to 0.1 Hz.

(15) K. Humski, R. Molojčič, S. Borčič, and D. E. Sunko, *J. Amer. Chem. Soc.*, **92**, 6534 (1970), and references therein.

(16) W. Grimme, private communication, has found the same ordering in the thermally degenerate bicyclo[5.1.0]octa-2,4-diene system.

(17) P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Amer. Chem. Soc.*, **92**, 2377 (1970); S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *Chem. Rev.*, **69**, 279 (1969).

(18) National Institutes of Health Postdoctoral Fellow, 1969–1970.
(19) Shell Fellow in Chemistry, 1970–1971.

J. C. Barborak,[18] Sarangan Chari,[19] P. v. R. Schleyer*
Department of Chemistry, Princeton University
Princeton, New Jersey 08540
Received April 21, 1971

Nucleic Acid Related Compounds. III. A Facile Synthesis of 5-Fluorouracil Bases and Nucleosides by Direct Fluorination[1]

Sir:

We wish to report the preparation of 5-fluorouracil (**2a**), 5-fluoro-1-methyluracil (**2b**), 5-fluorouridine (**2c**), and 5-fluoro-2′-deoxyuridine (**2d**) from the corresponding uracils (**1a–d**) as examples of the first direct synthesis of the biochemically and therapeutically important fluoropyrimidines and nucleosides.

Since the first publication[2] on the preparation of 5-fluorouracil (**2a**) by construction of the pyrimidine ring beginning with ethyl fluoroacetate, all syntheses of analogous bases and nucleosides[3] have employed this basic approach—construction of the appropriate 5-fluoropyrimidine from a fluoro-substituted aliphatic fragment followed by transformations on the base and/or sugar after standard nucleoside-coupling procedures.[4]

These *de novo* procedures[3] have been employed to give an assortment of 5-fluoropyrimidine compounds which have been studied in great detail in biological systems.[4,5] As well, 5-fluorouracil (**2a**) and 5-fluoro-2′-deoxyuridine (**2d**) are employed as standard clinical drugs for certain solid tumors and viral infections.[5]

In order to explore the biochemical and therapeutic properties of selected fluoronucleosides with modified carbohydrate moieties without the necessity of recourse to relatively inaccessible and expensive 5-fluorouracil nucleosides or bases as starting materials,[3] we sought a direct method for introduction of fluorine into preformed nucleosides. Treatment of *dl*-1-methyl-5-bromo-6-methoxy-5,6-dihydrouracil[6] with silver fluoride and with various other fluoride nucleophiles gave only 1-methyluracil, unlike an analogous approach to 5-mercaptouracils using the same heterocycle and hydrosulfide.[6]

(1) This work was generously supported by the National Cancer Institute of Canada.

(2) R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Amer. Chem. Soc.*, **79**, 4559 (1957).

(3) See, for example, (a) M. Hoffer, R. Duschinsky, J. J. Fox, and N. Yung, *ibid.*, **81**, 4112 (1959); (b) N. C. Yung, J. H. Burchenal, R. Fecher, R. Duschinsky, and J. J. Fox, *ibid.*, **83**, 4060 (1961); (c) D. C. Remy, A. V. Sunthankar, and C. Heidelberger, *J. Org. Chem.*, **27**, 2491 (1962); (d) M. Prystaš and F. Šorm, *Collect. Czech. Chem. Commun.*, **29**, 2956 (1964); (e) M. Prystaš and F. Šorm, *ibid.*, **30**, 1900 (1965); (f) G. J. Durr, *J. Med. Chem.*, **8**, 253 (1965); (g) J. J. Fox, N. Miller, and I. Wempen, *ibid.*, **9**, 101 (1966); (h) R. Duschinsky, T. Gabriel, W. Tautz, A. Nussbaum, M. Hoffer, E. Grunberg, J. H. Burchenal, and J. J. Fox, *ibid.*, **10**, 47 (1967); (i) I. Wempen, N. Miller, E. A. Falco, and J. J. Fox, *ibid.*, **11**, 144 (1968); (j) K. Undheim and M. Gacek, *Acta Chem. Scand.*, **23**, 294 (1969); (k) T. A. Khwaja and C. Heidelberger, *J. Med. Chem.*, **13**, 64 (1970), and references therein.

(4) C. Heidelberger, *Progr. Nucl. Acid. Res. Mol. Biol.*, **4**, 1 (1965), especially p 4.

(5) For reviews, see H. E. Kaufman, *Progr. Med. Virol.*, **7**, 116 (1965); C. Heidelberger, *Annu. Rev. Pharmacol.*, **7**, 101 (1967); W. H. Prusoff, *Pharmacol. Rev.*, **19**, 209 (1967); H. G. Mandel, *Progr. Mol. Subcellular Biol.*, **1**, 82 (1969); C. Heidelberger, *Cancer Res.*, **30**, 1549 (1970).