Influence of Solvation Factors on Acidity. Volumes of Ionization ($\Delta \bar{V}_i^\circ$) of the Meta and Para Isomers of Nitrophenol and Formylphenol in Water at 25°[1–4]

Sir:

Hepler[5,6] has reported that while the acidities of *m*- and *p*-nitrophenol differ by more than one pK_a unit, the enthalpies of ionization are almost identical (4.90 and 4.65 kcal/mol, respectively). The entropies of ionization for the meta and para isomers, however, are −21.8 and −17.1 cal/(deg mol), respectively. Following the reasoning suggested by other workers in the area,[6–9] Hepler attributes the difference in acidity to solvation suggesting that the entropy of ionization ($\Delta \bar{S}_i^\circ$) qualitatively reflects the relative degree of solvent orientation around the solute species involved in the equilibrium. It is argued that *m*-nitrophenoxide is more effective in orienting solvent molecules since the negative charge is more localized on the oxygen than in the *p*-nitrophenoxide case where the negative charge may be delocalized over the entire molecule (electromeric interaction). The entropies of ionization of *m*- and *p*-cyanophenol (−21.8 and −20.0 cal/(deg mol), respectively) and *m*- and *p*-formylphenol[4,6] (−23.4 and −20.2 cal/(deg mol), respectively) are also consistent with the above interpretation based upon the assumption that solvation differences are more important for the ionized forms of the acids than for the un-ionized.[6] We wish to report data which bear on this explanation.

The volume changes on ionization ($\Delta \bar{V}_i^\circ$) of *m*- and *p*-nitrophenol and *m*- and *p*-formylphenol have been determined in water at 25°. Table I contains the infinite dilution partial molar volumes of the un-ionized and ionized forms of the acids along with the $\Delta \bar{V}_i^\circ$ values. The partial molar volumes were determined from high-precision density measurements by means of a magnetic float densitometer as described by Millero.[10] The apparent molar volumes of the un-ionized forms of the acids were corrected for ionization by the method of King[11] and extrapolated to infinite dilution. The apparent molar volumes of the sodium salts were determined in excess sodium hydroxide to prevent hydrolysis, the apparent molar volume data being corrected with the known NaOH values.[12] In dilute solution the apparent molar volumes varied with $I^{1/2}$ according to the Debye-Hückel limiting law for 1:1 electrolyte.[13]

Table I. Partial Molar Volume and Volumes of Ionization[a] in Water at 25°[b,c]

Acid	$\bar{V}^\circ_{HA}$	$\bar{V}^\circ_{Na^+A^-}$ [d]	$\bar{V}^\circ_{H^+A^-}$ [e]	$\Delta\bar{V}^\circ$
m-Nitrophenol	99.71	85.67	86.87	−12.84
p-Nitrophenol	98.23	85.71	86.91	−11.32
m-Formylphenol	97.87	83.32	84.52	−13.35
p-Formylphenol	96.94	83.53	84.73	−12.21

[a] Ionization process: $HA \rightleftarrows H^+ + A^-$. [b] All volumes are in units of milliliters/mole. [c] As an experimental check of the method and procedures, the $\Delta \bar{V}_i^\circ$ of phenol was determined (−18.01 ± 0.20). This compares favorably with the literature value (−17.3 ± 1.0): S. D. Harmann and S. C. Lim, *Aust. J. Chem.*, **7**, 329 (1954). [d] The difference between the lowest observed apparent molar volume for each salt and the $\bar{V}^\circ$ was less than 0.1 ml/mol in all cases. [e] Found from the values in the previous column by adding $\bar{V}^\circ_{H^+} - \bar{V}^\circ_{Na^+} = +1.20$ ml/mol.[11]

Examination of Table I reveals that $\Delta \bar{V}_i^\circ$ is more negative for *m*-nitrophenol and *m*-formylphenol as compared to their corresponding para isomers. This appears to be consistent with the qualitative explanation of the entropy data cited above, in that the more negative the $\Delta \bar{S}_i^\circ$ the more electrostriction is expected in the ionization process. Indeed, this type of behavior is qualitatively what might be predicted in view of the general correlation between $\Delta \bar{S}^\circ$ and $\Delta \bar{V}^\circ$ reported by Hepler for the ionization in water of a wide variety of structurally different acids.[14] Quite surprisingly, the partial molar volumes of the isomeric sodium salts were found to be almost identical (within experimental error) indicating that *the origin of the* $\Delta \bar{V}_i^\circ$ *difference lies exclusively with the un-ionized forms.* This appears to be in direct contradiction to the interpretation given above for the origin of the difference in entropy changes. Based upon the data presented in this communication, it appears that *the solvation contribution to differences in acidity of isomeric phenols may have their primary origin in solvation differences in the un-ionized forms.*

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(1) Part IV in the series, "Thermodynamics of Acid-Base Equilibria."

(2) Part III: C. L. Liotta, E. M. Perdue, and H. P. Hopkins, Jr., *J. Amer. Chem. Soc.*, in press.

(3) Part II: C. L. Liotta, D. F. Smith, Jr., H. P. Hopkins, Jr., and K. Rhodes, *J. Phys. Chem.*, **76**, 1909 (1972).

(4) Part I: C. L. Liotta, K. H. Leavell, and D. F. Smith, Jr., *ibid.*, **71**, 3091 (1967).

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(9) E. J. King and G. W. King, *J. Amer. Chem. Soc.*, **78**, 1089 (1956).

(10) F. J. Millero, *Rev. Sci. Instrum.*, **38**, 1441 (1967).

(11) E. J. King, *J. Phys. Chem.*, **73**, 1220 (1969).

(12) L. G. Hepler, J. M. Stokes, and R. H. Stokes, *Trans. Faraday Soc.*, **61**, 20 (1965).

(13) O. Redlich, *J. Phys. Chem.*, **67**, 496 (1963).

(14) L. G. Hepler, *ibid.*, **69**, 965 (1965).

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On the Conformation of Derivatives of 2,2,5,5-Tetramethylcyclohexane-1,3-dione

Sir:

A knowledge of the conformational properties of cyclohexane derivatives with ring carbons sp^2 hybridized is fundamental in organic chemistry. While cyclohexanone exists in a chair conformation, some of its alkyl derivatives have been found to exist predominantly in a twist-boat form.[1] Furthermore, it has been recognized for some time that cyclohexane-1,4-

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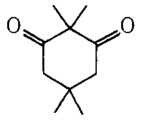
(1) (a) H. Hanack, "Conformational Theory," Academic Press, New York, N. Y., 1965, p 275; (b) D. L. Robinson and D. W. Theobald, *Quart. Rev., Chem. Soc.*, **21**, 314 (1967).

dione exists as a twist–boat both in solution and in the solid state[2] and recently it has been suggested that a derivative of cyclohexane-1,3-dione also exists as a twist–boat.[3] Because of the indirect nature of the evidence presented, we wish to report on our investigation of related compounds. Our results have an important bearing on the conformational properties of derivatives of cyclohexane-1,3-dione in general. Because of problems related to enolization of 1,3-diketones[4] our initial report is concerned with 2,2,5,5-tetramethylcyclohexane-1,3-dione (**1**) and two of its derivatives **2** and **3** which were prepared from **1** by a Wittig reaction.[5]



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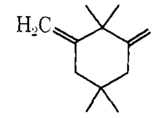

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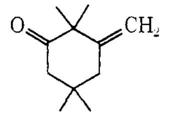


3

A low-temperature investigation of the pmr spectrum of **1** down to −160° did not reveal any spectral change other than slight broadening of the peaks which could be due to increased viscosity. On the other hand, both **2** and **3** were shown to have temperature-dependent spectra as illustrated in Figure 1.

The 100-MHz pmr spectrum of the nonolefinic protons of **2** at +25° consists of three peaks (Figure 1): a singlet (two methyls on C_5) at δ 0.86, a singlet (two methyls on C_2) at δ 1.26, and another singlet (methylene on C_4 and C_6) at δ 2.16. As the temperature is decreased each of the methyl signals splits up to give a doublet (separations 34.8 and 12.9 Hz), whereas the methylene signal separates into an AB quartet characterized by a chemical-shift difference of 54.2 Hz and a geminal coupling constant of −13.0 Hz at −139°.

The room temperature spectrum of the nonolefinic protons of **3** shows four peaks: a singlet (two methyls on C_5) at δ 0.93, a singlet (two methyls on C_2) at δ 1.26, a singlet (methylene next to C=O) at δ 1.93, and a singlet (methylene next to =CH_2) at δ 1.87. A spectral change similar to that of **2** takes place at slightly lower temperatures such that the spectrum at −160° consists of four partially overlapping methyl lines and two partially overlapping AB quartets.

Free energies of activation ($\Delta G^{\neq}$) were calculated from the spectral changes using the standard procedure[6] with a transmission coefficient of 1. The splitting of the high-field methyl signal of **2** into a doublet separated by 34.8 Hz led to a $\Delta G^{\neq}$ = 7.6 kcal/mol at −120°, the coalescence temperature. The corresponding change for **3** (singlet to a doublet separated by 39 Hz) gave a $\Delta G^{\neq}$ = 5.9 kcal/mol at −149°. The higher energy barrier for **2** over **3** parallels the order found for 2,2,5,5-tetramethylmethylenecyclohexane and 2,2,5,5-tetramethylcyclohexanone[7] whose $\Delta G^{\neq}$ values are 10.0 and 8.1 kcal/mol, respectively.

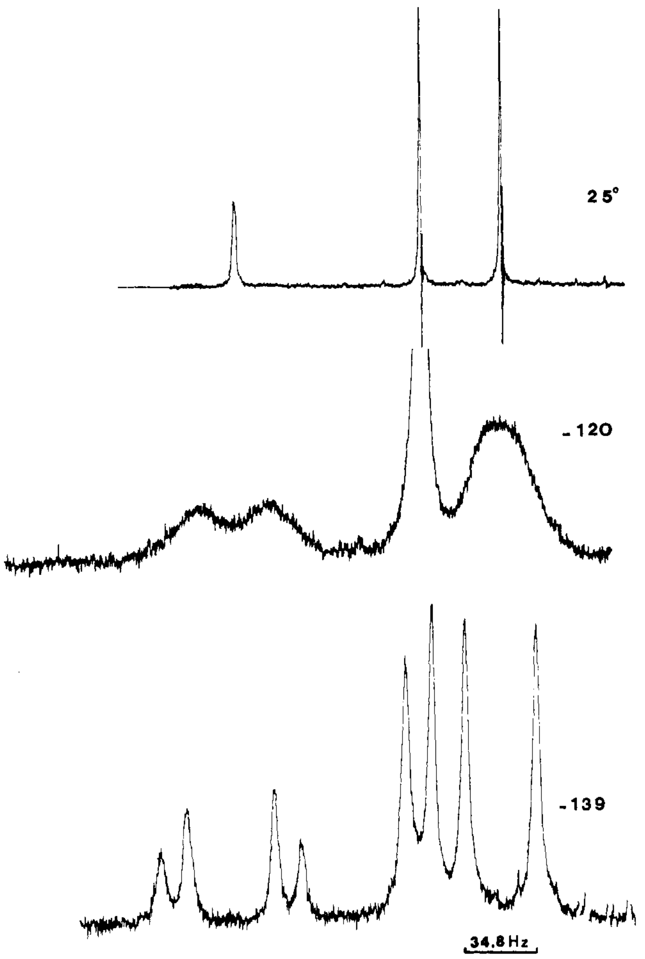
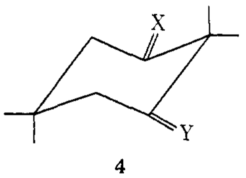


Figure 1. The 100-MHz pmr spectra of compound **2** dissolved in chlorodifluoromethane at several temperatures.

The analysis of the low-temperature spectra of **2** and **3** provides information on the conformation of these molecules in solution. The spectrum of **2** at −139° reveals that its stable conformation must contain methyl groups in four different environments (one for each line) while the observation of only one AB for the C_4 and C_6 methylene protons suggests that a plane of symmetry passes through C_2 and C_5. These requirements are in accord with a chair conformation of structure **4a**, but not with any viable twist–boat forms. For example, the twist–boat **5a** can be ruled out since the twofold axis of symmetry through C_2 and C_5 bisects the *gem*-dimethyl angle leading to only two different types of methyl groups and hence to only two spectral lines instead of the observed four.



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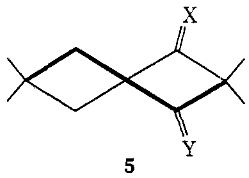

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a, X = Y = CH_2
b, X = O; Y = CH_2

Symmetry arguments are less conclusive for **3** because of the different substituent on each side of the

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(2) (a) N. L. Allinger, H. M. Blatter, L. A. Frieberg, and F. M. Karkowski, *J. Amer. Chem. Soc.*, **88**, 2999 (1966); (b) P. Groth and O. Hassel, *Acta Chem. Scand.*, **18**, 923 (1964); (c) A. Bossel and C. Romers, *Acta Crystallogr.*, 17, 1217 (1969).

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ring, but the striking similarity in the spectral characteristics of **2** and **3** suggests that it is highly probable that **3** also exist in a chair conformation (**4b**). It is very tempting to carry this analogy over to **1** for which no spectral change was observed but caution is suggested in light of the recently observed change from a twist–boat conformation for cyclohexane-1,4-dione to a chair for 1,4-dimethylenecyclohexane.[8] On the other hand, the negative results for **1** and 2,2-dibenzyl-5,5-dimethylcyclohexane-1,3-dione[3] do not necessarily rule out a chair conformation since cyclohexanone, which exists as a chair, does not give rise to a spectral change down to −170°.[9]

Our work certainly indicates that more information is necessary in this area of chemistry and our objective will now be a systematic study of various derivatives of cyclohexane-1,3-dione in an attempt to determine all the relevant factors influencing conformation.

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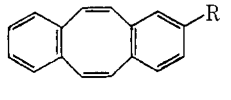
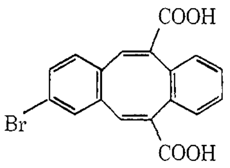
Ring Inversion in Di- and Tetrabenzocyclooctatetraenes

Sir:

Recent studies have dealt with the effect of fused benzene rings on the inversion barrier of cyclooctatetraene.[1-3] In this connection, we wish to report that the barrier ($\Delta G^{\ddagger}$) to ring inversion for **1a**, 12.3 ± 0.2 kcal/mol at −5°, is substantially lower than the racemization barrier of 27 kcal/mol earlier reported by us for **2**,[4] a finding which is consistent with the failure of our attempts to resolve **1c**.[5]



1a, R = CF$_2$H
b, R = Br
c, R = COOH
d, R = CHO



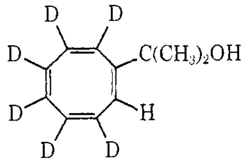
2

Decarboxylation of **2** with copper–chromium oxide catalyst[6] in quinoline at 205° yielded **1b**, mp 78–79°, which was converted to **1c** by the Grignard synthesis (gaseous carbon dioxide). The acid, mp 264–268° dec, on treatment with thionyl chloride gave the acid chloride, mp 140–142°, which, upon reduction with lithium tri-*tert*-butoxyaluminum hydride,[7] yielded **1d**, mp 127–129°; $\delta^{\mathrm{TMS}}_{\mathrm{CDCl_3}}$ 9.87 (s, C*H*O), 7.78–6.95 (m, aromatic H), 6.76 (br s, olefinic H). An excess of sulfur tetrafluoride was condensed into a stainless steel bomb containing a methylene chloride solution of **1d** and a catalytic amount of water. Reaction at room temperature for 22 hr gave **1a**, mp 71–72°; $\delta^{\mathrm{TMS}}_{\mathrm{CDCl_3}}$ 7.50–6.92 (m, aromatic H), 6.75 (s, olefinic H), 6.52 (t, $^2J_{FH}$ = 56.4 Hz, CF$_2$*H*).[8]

At −50° the 94.1-MHz ^{19}F nmr spectrum of **1a** (CFCl$_3$) consists of the AB portion of an ABX system (ν_A 50.39, ν_B 49.80 ppm downfield from C$_6$F$_6$ as internal reference; $^2J_{HF_A} \cong {}^2J_{HF_B} = 56.4$ Hz, $^2J_{FF} = 296$ Hz).[9] Upon warming the sample, the ABX spectrum collapses to an A$_2$X pattern. The temperature-dependent spectrum was analyzed as two overlapping AB systems,[10] and rates were determined by line-shape analysis, which yielded the value for the ring inversion barrier of **1a** reported above.

The present work fully bears out our conjecture of 10 years ago[4] that "nonbonded interaction of carboxyl groups and benzene hydrogens in the transition state [for the racemization of **2**] is likely to contribute significantly to the destabilization of the transition state." Although the mechanism of enantiomerization is still in doubt,[11] the observed barrier for **2** must be a lower limit to the ring inversion process. The very much higher value of this barrier, as compared to that of **1a**, is a consequence of repulsive interactions in the transition state.[13]

The barriers observed for ring inversion in the cyclooctatetraene derivative **3**, $\Delta G^{\ddagger}_{-2}$ = 14.7 kcal/mol,[15] and the benzocyclooctatetraene derivative **4**, $\Delta G^{\ddagger}_{-30}$ = 13.4 kcal/mol,[2] differ but slightly from that of **1a**. It thus appears that in the absence of substitution patterns which are capable of giving rise to strong nonbonded interactions, the overall effect of benzene fusion on the structural rigidity of the cyclooctatetraene ring is quite minor.[16] Where steric factors are operative,



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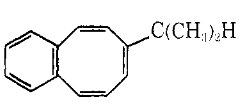

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(1) H. P. Figeys and A. Dralants, *Tetrahedron Lett.*, 3901 (1971).

(2) G. W. Buchanan, *ibid.*, 665 (1972).

(3) L. B. Anderson and L. A. Paquette, *J. Amer. Chem. Soc.*, **94**, 4915 (1972).

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(8) Acceptable elemental analyses were obtained for all new compounds. Mass spectra were likewise consistent with the assigned structures.

(9) Since only the four central lines of the spectrum were observed, $^2J_{FF}$ was obtained from the proton-decoupled AB spectrum. Such behavior for the CF$_2$H group has been previously noted. See, for example, J. W. Rakshys, Jr., S. V. McKinley, and H. H. Freedman, *J. Amer. Chem. Soc.*, **93**, 6522 (1971).

(10) G. M. Whitesides and J. D. Roberts, *ibid.*, **87**, 4878 (1965).

(11) Originally, the racemization of **2** was simply viewed[4] as proceeding through a conformational tub inversion, by way of a planar transition state. Subsequently, Stiles and Burckhardt[12] suggested an alternative mechanism by way of an intermediate [2 + 2] cycloaddition product.

(12) M. Stiles and U. Burckhardt, *J. Amer. Chem. Soc.*, **86**, 3396 (1964).

(13) Ground-state stabilization of **2** by, for example, intramolecular H-bonding interactions between the two carboxyl groups, may be ruled out by the observation[14] that the barriers to racemization of the sodium salt and the dimethyl ester of **2** differ by no more than 1 kcal/mol from that of the parent compound.

(14) H. D. Perlmutter, Ph.D. Dissertation, New York University, 1963.

(15) F. A. L. Anet, A. J. R. Bourn, and Y. S. Lin, *J. Amer. Chem. Soc.*, **86**, 3576 (1964).

(16) Increased rigidity of the cyclooctatetraene ring on annelation with benzene has been suggested as a possible explanation for the failure to generate dianion species of benzo- and dibenzo[*a*,*e*]cyclooctatetraene.[3]