

## On the Conformation of 1,1,2,2-Tetraphenylethane and the Applicability of $^3J_{\text{HD}}$ to Conformational Analysis

Sir:

Ingold and coworkers have shown that the highly hindered tetrasubstituted ethanes  $[(\text{Me}_3\text{C})_2\text{CH}]_2$  and  $[(\text{Me}_3\text{Si})_2\text{CH}]_2$  adopt a gauche conformation exclusively,<sup>1</sup> while in the less hindered  $(\text{Me}_2\text{CH})_2$  the gauche and anti rotational isomers are present in a 2:1 (i.e., statistical) ratio.<sup>2</sup> 1,1,2,2-Tetraalkylethanes therefore prefer the gauche conformation, a preference which increases with increasing size of the alkyl groups.<sup>3</sup> One might reasonably expect a similar preference for tetraarylethanes, but this expectation is not fulfilled: in sharp contrast to the findings of Ingold et al., empirical force field (EFF) calculations<sup>5</sup> on the parent compound, 1,1,2,2-tetraphenylethane (TPE), predict a ground state with an anti  $C_2$  conformation, and with the lowest energy gauche conformer,  $\sim 5$  kcal/mol less stable than the anti form. A serious question is thus raised concerning the validity of the EFF calculations.

We now report experimental evidence which fully confirms the earlier computational results<sup>6</sup> and vindicates the soundness of the EFF approach as applied to the calculation of tetraarylethane structures.<sup>5,7</sup> We also show that an apparently abnormally low vicinal  $^3J_{\text{HD}}$  coupling constant for the ethano fragment of TPE- $d_1$  is due to efficient quadrupolar relaxation and could lead to erroneous conclusions regarding the conformation of TPE.

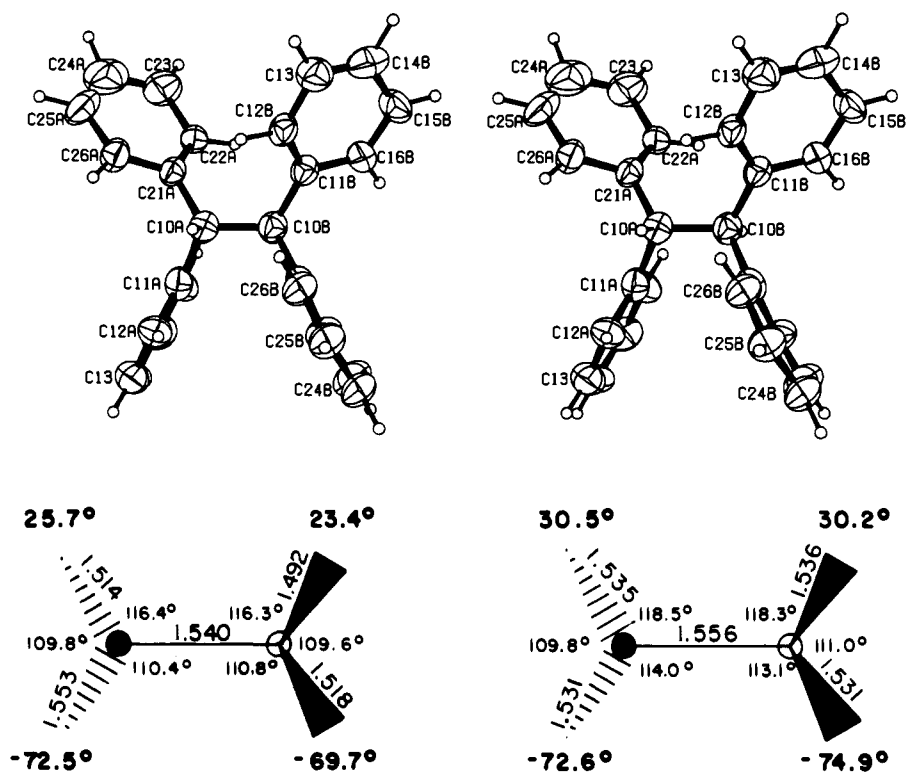
The crystal and molecular structure of TPE was determined by x-ray diffraction. Crystals of TPE, obtained from acetone, are monoclinic with  $a = 17.686(6)$ ,  $b = 5.974(3)$ ,  $c = 17.781(6)$  Å;  $\beta = 91.35(3)^\circ$ ; and  $d_{\text{calcd}} = 1.182$  g cm $^{-3}$  for  $Z = 4$ . Intensity data were measured on a Hilger-Watts four-circle

diffractometer (Ni-filtered Cu  $K\alpha$  radiation,  $\theta$ - $2\theta$  scans, pulse height discrimination). Of the 1921 accessible reflections for  $\theta < 152^\circ$ , 1541 were considered to be observed ( $I > 2.5\sigma(I)$ ). All refinements were carried out by full matrix least squares. The final model structure, which was treated as a twofold statistical disorder of the molecules in space group  $A2/a$ , yielded the structure in Chart I, with  $R = 0.056$  and  $wR = 0.068$  for the observed reflections.<sup>8</sup>

A comparison of structural parameters (Chart I) reveals striking agreement between values obtained by the x-ray and EFF methods. Not only does the molecule prefer an anti  $C_2$  conformation, as predicted, but more refined structural features such as valence angle distortions and degree of twist of the phenyl rings are also correctly predicted by the EFF calculation. The  $C_{\text{phenyl}}-C_{\text{ethane}}-C_{\text{ethane}}-C_{\text{phenyl}}$  dihedral angles are  $174$  and  $175^\circ$  for the x-ray and EFF methods, respectively. The major differences between the two structures reflect a tendency of the EFF to overestimate steric repulsions as evidenced by an elongated ethane bond and overly distorted  $C_{\text{phenyl}}-C_{\text{ethane}}-C_{\text{ethane}}$  valence angles. A similar tendency to overestimate bond and angle distortions was noted in the EFF structure of trimesitylmethane<sup>9</sup> and appears to be a general deficiency of our force field; however, the correct *trend* in valence angles is reproduced. We note that the anti conformation is also assumed in the crystal by the closely related 1,1,2,2-tetramesitylethane (TME)<sup>10</sup> and 1,1,2,2-tetrakis(2-methoxyphenyl)ethane.<sup>11</sup>

Compelling evidence that the anti conformation of TPE also predominates in solution is provided by the  $^1\text{H}$  NMR (90 MHz FT) spectrum of a sample (in  $\text{CDCl}_3$ ) enriched in  $\text{Ph}_2^{13}\text{CHCHPh}_2$ .<sup>12</sup> The spectrum displays the expected eight lines of the AB portion (methine protons) of an ABX spin system. The  $^3J_{\text{HH}}$  is exhibited four times in this subspectrum, and has a value of 11.3 Hz, consistent only with the anti con-

Chart I<sup>a</sup>



<sup>a</sup> Top: stereoscopic drawing of a molecule of TPE showing the  $C_2$  symmetry of the molecule; the thermal ellipsoids of the carbon atoms are scaled to the 50% probability level; the hydrogen atoms are shown as spheres of a fixed, arbitrary size. Bottom left: crystal structure parameters; boldface numbers represent the degree of twist of the phenyl rings, e.g., looking from  $C_{10B}$  to  $C_{11B}$ , a  $23.4^\circ$  counterclockwise rotation of the  $(C_{12B}-C_{11B}-C_{16B})$  plane eclipses the  $(C_{10A}-C_{10B}-C_{11B})$  plane. Bottom right: calculated<sup>5</sup> EFF structure of TPE; the definition of the ring dihedral angles is chosen to correspond to that used for the crystal structure and differs from the notation employed in ref 5.

formation.<sup>13</sup> This value is invariant over the temperature range 310–370 K (toluene-*d*<sub>8</sub>), in harmony with the predicted<sup>5</sup> strong preference for the anti conformer.<sup>14</sup> The observed value of <sup>1</sup>J<sub>CH</sub>, 129.7 Hz, is also consistent with this type of structure.<sup>17</sup> The value of <sup>2</sup>J<sub>CH</sub> is –5.4 Hz. Similar coupling constants (<sup>3</sup>J<sub>HH</sub> and <sup>1</sup>J<sub>CH</sub>) are obtained by analysis of the <sup>13</sup>C satellite lines of TPE of natural isotopic composition.<sup>18,19</sup>

Spin–spin coupling constants between homotopic protons have also been elucidated by determination of the pertinent proton–deuteron coupling constant and application of the equation<sup>20</sup>

$${}^nJ_{HH} = (\gamma_H/\gamma_D)^n J_{HD} \quad (1)$$

where *n* = number of intervening bonds, and  $\gamma_H/\gamma_D = 6.514$ .<sup>21a</sup> However, <sup>1</sup>H NMR spectra of 1-deuterio-1,1,2,2-tetraphenylethane (TPE-*d*<sub>1</sub>), prepared by coupling of an equimolar mixture of benzhydryl chloride and benzhydryl chloride-*d*<sub>1</sub> with tin,<sup>22</sup> display an apparent vicinal HD coupling of less than 1 Hz in CDCl<sub>3</sub>, benzene-*d*<sub>6</sub>, toluene-*d*<sub>8</sub>, CCl<sub>4</sub>, and acetone-*d*<sub>6</sub>.<sup>23</sup> Application of eq 1 requires <sup>3</sup>J<sub>HH</sub> < 6.5 Hz, consistent only with a gauche conformation. We now describe the resolution of this paradox.

Rapid quadrupolar relaxation of a deuteron is theoretically capable<sup>24</sup> of effectively spin–spin decoupling the deuteron from a vicinal (or geminal) proton, thereby producing an anomalously small (in the absence of such relaxation) <sup>1</sup>H–<sup>2</sup>H coupling constant.<sup>25</sup> Thus, if molecular correlation is too slow (yielding short deuteron spin lattice relaxation times), <sup>1</sup>H–<sup>2</sup>H spin–spin coupling may be unobservable. In such a case, application of eq 1 and of the Karplus equations for conformational analysis is vitiated unless complete line shape analyses are undertaken.

The proton line shape, accounting for quadrupolar relaxation and natural (<sup>1</sup>H) line width, can be calculated from

$$I(\omega) = \text{re} \{ \mathbf{W} \cdot \mathbf{A}^{-1} \cdot \mathbf{1} \} \quad (2)$$

where *re* denotes “the real part of”, **W** is a row vector whose components are the probabilities of the lines of the multiplet (in this instance the row vector (1 1 1)), **A**<sup>–1</sup> is the inverse of the line shape matrix **A**, **1** is the column vector {1 1 1}, and  $\omega$  is the chemical shift from the center of the multiplet.<sup>24,26</sup> This equation has previously been employed for line-shape analyses of <sup>2</sup>H and <sup>14</sup>N coupled proton spectra.<sup>25,26</sup>

The <sup>2</sup>H spin-lattice relaxation times for TPE-*d*<sub>1</sub> in toluene are 0.091, 0.108, 0.160, and 0.191 s at 310, 330, 350, and 370 K, respectively. Proton spectra of the methine portion of TPE-*d*<sub>1</sub> were calculated with *T*<sub>2</sub>\* (“effective” transverse relaxation time) = 0.3 s,<sup>27</sup> and *J*<sub>HD</sub> = (11.3/6.514) = 1.74 Hz. Taking *T*<sub>1</sub> = 0.091 s, an apparent value of <sup>3</sup>J<sub>HD</sub> < 1 Hz is obtained, corresponding (eq 1) to <sup>3</sup>J<sub>HH</sub> < 6.5 Hz. With *T*<sub>1</sub> = 0.191 s, the corresponding values are 1.2 and 7.8 Hz, respectively. It is only when *T*<sub>1</sub> = 1 s (~600 K, estimated from the Arrhenius equation) that one obtains a value of <sup>3</sup>J<sub>HD</sub> = 1.68 Hz which corresponds to a realistic value of <sup>3</sup>J<sub>HH</sub> = 10.9 Hz.<sup>28</sup> It is thus evident that, at conventional temperatures, conformational assignments for TPE based on a first-order analysis of <sup>3</sup>J<sub>HD</sub> will lead to erroneous conclusions.<sup>29</sup>

We believe that the (deuterium) isotopic substitution method of obtaining spin–spin coupling constants for homotopic nuclei can continue to be a valuable aid in conformational analysis, provided that its limitations are realized. In general, efficient quadrupolar relaxation may be expected to affect significantly the “observed” value of <sup>2</sup>J<sub>HD</sub> and <sup>3</sup>J<sub>HD</sub> for rigid spherical molecules in normal organic solvents ( $\eta \sim 0.5$  cP) possessing radii > 3 Å for which correlation times are > 10<sup>–11</sup> s at ambient temperatures.<sup>30</sup>

**Acknowledgment.** We thank the National Science Foundation (CHE74-18161) and the National Institutes of Health

(1-R01-GM22788-01) for support of this work, and Mr. D. R. Nordlund for technical assistance. We are especially indebted to Dr. K. U. Ingold for communicating the results in ref 1 and 2 prior to publication and for pointing out the need to verify the TPE structure calculated in ref 5.

**Supplementary Material Available:** details of the TPE crystal structure refinement, including a discussion of the twofold disorder, and final atomic parameters with standard deviations (6 pages). Ordering information is given on any current masthead page.

## References and Notes

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- The gauche preference in tetraalkylethanes has been attributed to distortion of the tertiary carbons due to steric repulsion between gem-alkyl groups.<sup>1,2,4</sup>
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- "Confirmations should count only if they are the results of risky predictions; that is to say, if, unenlightened by the theory in question, we should have expected an event which was incompatible with the theory—an event which would have refuted the theory" (K. R. Popper, "Conjectures and Refutations", Basic Books, New York, N.Y., 1962, p 36). For "theory" substitute "calculation". See also J. A. Berson, *Acc. Chem. Res.*, **1**, 152 (1968).
- Force field calculations are generally less reliable in their predictions of relative conformer energies than of structural features. For example, the ground state of 1,2-diphenylpropane is experimentally anti, whereas a gauche conformer is calculated (EFF) to be more stable by 1.2 kcal/mol (J. Jacobus, *Tetrahedron Lett.*, 2927 (1976)). Caution is therefore indicated in the interpretation of calculated energy differences smaller than ~2 kcal/mol.
- For additional details, cf. paragraph at the end of this paper regarding supplementary material.
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- An equimolar mixture of Ph<sub>2</sub><sup>12</sup>CO and Ph<sub>2</sub><sup>13</sup>CO (89.5% enriched) was reduced (LiAlH<sub>4</sub>) to the carbinol, which was converted (HCl) to benzhydryl chloride. Coupling (Sn, toluene) gave TPE, mp 214–215 °C. The expected isotopic composition was confirmed by mass spectrometry. The <sup>1</sup>H NMR spectrum shows lines corresponding to all three isotopic species; the spectrum of the <sup>13</sup>C<sup>13</sup>C species is consistent with that of the <sup>12</sup>C<sup>13</sup>C species (cf. text).
- M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Am. Chem. Soc.*, **85**, 2870 (1963). See also, F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, N.Y., 1969, p 355 ff; L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, New York, N.Y., 1969, Chapter 4-2.
- The normal central C–C bond length in TPE indicates the absence of significant through-bond coupling of the  $\pi$  systems.<sup>15,16</sup> It may therefore be concluded that electronic factors need not be considered in the conformational analysis of TPE and similar unclamped polyarylethanes.<sup>15</sup> We suggest that the flattish nature of the aryl rings in such molecules greatly reduces the geminal repulsions and adverse inter-end interactions<sup>15</sup> present in tetraalkylethanes, in large part because the ability of the geminal aryl rings to stack obviates the necessity for the spreading of the C<sub>aryl</sub>–C<sub>ethylene</sub>–C<sub>aryl</sub> angle.<sup>3</sup> This analysis is supported by the EFF data for TPE.
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- Values of <sup>1</sup>J<sub>CH</sub> for PhCH<sub>3</sub>, Ph<sub>2</sub>CH<sub>2</sub>, and Ph<sub>3</sub>CH are 126, 127, and 132 Hz, respectively; cf. J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, p 339. The present value of <sup>1</sup>J<sub>CH</sub> was confirmed by proton-coupled <sup>13</sup>C NMR.
- These spectra are however of poor quality due to the low solubility of TPE in CDCl<sub>3</sub> and the weak intensity of <sup>13</sup>C satellites.
- Indirect evidence that TPE has the anti conformation in solution derives from dipole moment and spectroscopic studies on tetraarylethanes (S. P. Chen and H. H. Huang, *J. Chem. Soc., Perkin Trans. 2*, 1301 (1972)).
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- A. Carrington and A. D. McLachlan, "Introduction to Magnetic Resonance", Harper and Row, New York, N.Y., 1967: (a) p 2; (b) p 210 ff; (c) p 188 ff.
- The expected isotopic composition (statistical ratio of 1:2:1 for TPE-*d*<sub>0</sub>:TPE-*d*<sub>1</sub>:TPE-*d*<sub>2</sub>) was confirmed by mass spectrometry.
- The methine proton resonance of TPE-*d*<sub>1</sub>, by first-order analysis, should comprise a 1:1:1 triplet. However, the resonance line in the solvents mentioned is unresolved,  $w_{1/2} < 2$  Hz. Dr. K. U. Ingold (private commu-

- nication) has obtained a similar value for TPE- $d_1$  in  $\text{CDCl}_3$ .
- (24) A. Abragam, "The Principles of Nuclear Magnetism", Clarendon Press, Oxford, 1961, p 504.
- (25) See, for example, C. Brevard, J. P. Kintzinger, and J. M. Lehn, *Chem. Commun.*, 1193 (1969); C. Brevard and J. M. Lehn, *J. Am. Chem. Soc.*, **92**, 4987 (1970).
- (26) J. P. Kintzinger, J. M. Lehn, and R. L. Williams, *Mol. Phys.*, **17**, 135 (1969).
- (27)  $T_1$  for the methine resonance ( $^1\text{H}$ ) of TPE is  $\sim 0.7$  s. The value of  $T_2^*$  employed in the line-shape calculations is based on the width at half height (1.0 Hz) of this resonance.
- (28) For another analysis of a spin coupled to a relaxing nucleus, cf. J. A. Pople, *Mol. Phys.*, **1**, 168 (1958), and ref 21b.
- (29) The TPE used in the present study contains  $\sim 25\%$  TPE- $d_0$ , and the  $d_0$  line effectively "hides" the spectrum of the  $d_1$  species. Analyses based on width at half height therefore measure essentially only the line width of the  $d_0$  species. It is significant, however, that over the temperature range 310–370 K (toluene- $d_6$ ) the methine proton resonance of this sample does not perceptibly broaden ( $W_{1/2h} \sim 1.6$  Hz;  $W_{\text{baseline}} \sim 5$  Hz), nor does the  $^2\text{H}$  coupling become apparent.
- (30) Estimated from the Debye–Einstein equation (ref 21c).

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Received April 25, 1977

### Rapid Access to Analogues of Phalloidin by Replacing Alanine-1 in the Natural Toxin by Other Amino Acids<sup>1</sup>

Sir:

In extensive studies of structure–activity correlations of the phallotoxins from the toxic mushroom *Amanita phalloides*,<sup>2</sup> the amino acid in position 1 (alanine) of phalloidin (**1a**) has

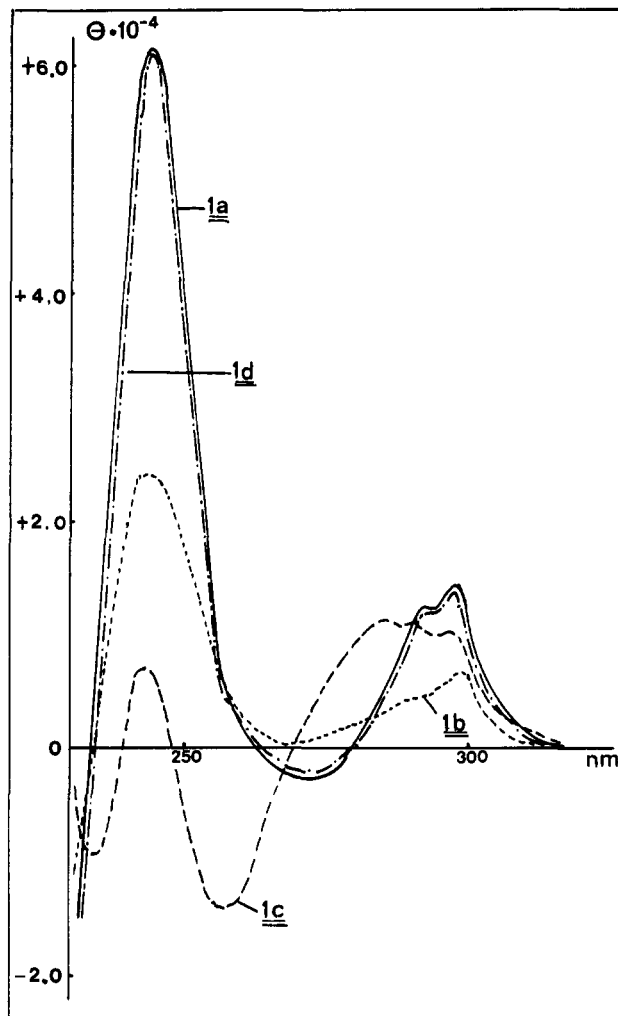


Figure 1. CD spectra of phalloidin **1a** and its analogues **1b**, **1c**, and **1d** measured in water solution.

#### Scheme I

