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Conformational Analysis of 4-Aryl-2,2,6,6-tetramethylheptane-3,5-diones. Dipole Moment Determinations and Molecular Mechanics Calculations

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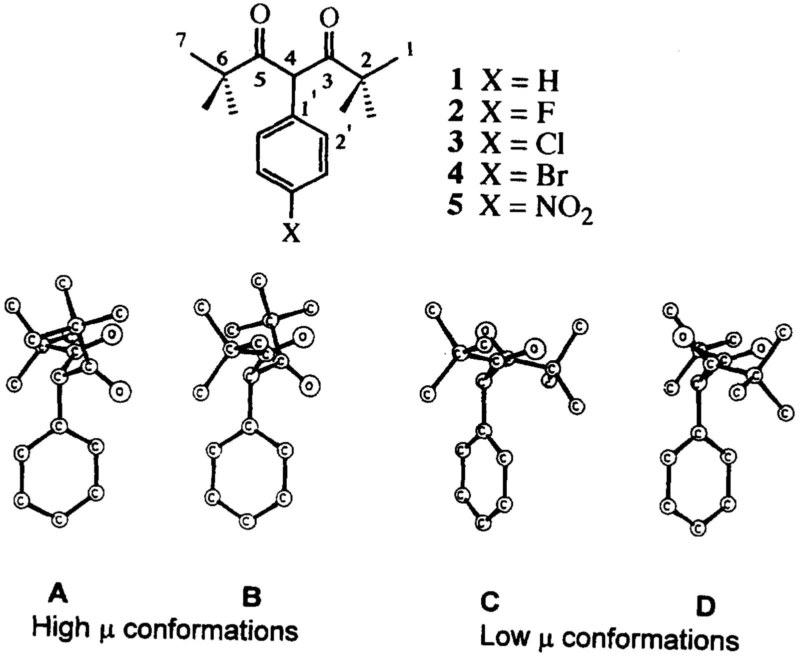
Abstract: The dipole moments of the title diketones have been measured and compared with the values calculated by MM2. Both sets of values are in good agreement. The diketones exist (74-94%) in pairs of enantiomeric conformations with angles between both carbonyl dipoles in the range 62-66°.

INTRODUCTION. The conformational complexity of open-chain compounds makes their conformational analysis difficult. Extensive use of NMR techniques, mainly correlation of coupling constants with dihedral angles, has given rise to important advances in the conformational knowledge of cyclic and acyclic molecules. But other solutions have to be sought for compounds that are not amenable to NMR studies. Molecular mechanics has opened new avenues in the conformational analysis of a broad variety of molecules,[1] although it is always desirable to compare the computational results with experimental data whenever possible.

The dipole moment is a molecular property which changes with the molecular geometry. The agreement between calculated and measured dipole moments for simple model molecules is one of the tests for any molecular mechanics program.[1] Therefore, the calculation of the bulk dipole moment and the successful comparison of this data with the experimental one (MM-DM method) is a perfectly valid system for conformational analysis of more complex molecules. However, one requisite should be fulfilled: the molecule to be studied must bear no less than two independent dipoles, each with a well defined intrinsic orientation (*e.g.* carbonyl group, nitro group, carbon-halogen bond). If the molecule fulfils this unexceptional condition the problem is limited to finding out the relative orientation of the independent dipoles, which will afford valuable information on the populated conformations. This powerful MM-DM methodology has not been extensively used by organic chemists, probably due to the non routine access to dipole moment instrumentation.

Molecules featuring a carbonyl group and a second dipole are particularly suitable to the MM-DM approach. Examples of its application are the conformational analyses of haloketones[2a,b] and of methylthio and methylsulfonylketones.[2c] Non enolic β-diketones are also amenable to be studied by this method. Thus, Allinger reported a comparison between the measured dipole moment and the value calculated by molecular mechanics for 3,3-dimethylpentane-2,4-dione.[3] The first generation of his nowadays widely popular force field was used, and the agreement between both values was not satisfactory enough. More recently we used the MM2 force field with better results in a conformational analysis of several fully dicarbonylic β-diketones. The agreement between calculated and experimental dipole moments was very good in general and sometimes excellent.[4] Therefore, the MM-DM method has emerged as an useful tool in conformational analysis.

On the other hand, some of us have developed a general method for arylation of β-diketones which has allowed the preparation of a vast array of α-aryl-β-diketones.[5] 4-Aryl-2,2,6,6-tetramethylheptane-3,5-diones, **1-5** (Figure 1) are particularly interesting since they are fully diketonic, as evidenced by HMR spectra in $CDCl_3$ and in C_6D_6, and they have three independent dipoles of well defined orientations.



1 X = H
2 X = F
3 X = Cl
4 X = Br
5 X = NO_2

A B
High μ conformations

C D
Low μ conformations

Figure 1

RESULTS. The MM2(91)[6] version of Allinger's force field was used through this work. Phenyl rings were treated either mechanically[7] or as a delocalized π system but no significant differences in the calculated dipole moments were observed when using both different approaches. One torsional energy surface was calculated for each studied compound by driving both CH-CO bonds from -180° to +180° at 15° intervals. The one-bond drive rotation of the CH-Aryl bond was carried out on each of the previously obtained energy minima. The populations were calculated by Boltzman's distribution neglecting the entropy contribution since entropy differences between conformations possessing the same symmetry number are negligible. This applies to our calculated conformations and in such situations the major contributions to entropy arise from groups of atoms.[8]

Table 1 contains the geometries, energies, geometrical parameters and percentages for the most populated conformations as determined by the program MM2(91)[6] for compounds **1-5**. The calculations show the predominant existence of one pair of enantiomeric conformations A and B (See figure) for all compounds, where the carbonyl groups define a pseudodihedral angle of about 63°. These pairs of conformations cover more than 94% of the total population for all compounds **1-5** and the conformational preferences are

Table 1. Geometries and Populations of the four most Populated Conformations of Compounds **1-5** Calculated by MM2(91) with Mechanical Tretament of the Benzene Rings ($\varepsilon = 2.02$).

Compound	1				2				3			
Conformation	A	B	C	D	A	B	C	D	A	B	C	D
Relative ΔH_f (Kcal/mol)	0.0	0.0	2.0	2.0	0.0	0.0	2.2	2.2	0.0	0.0	2.1	2.1
Population (%)	47.2	47.1	1.6	1.6	47.7	47.7	1.2	1.2	47.7	47.6	1.3	1.3
ω° (C2-C3-C4-C1')	-144.9	-76.2	54.0	-91.0	-145.7	-76.5	54.0	-91.1	-145.7	-76.4	54.1	-91.1
ω°(C6-C5-C4-C1')	76.0	144.6	88.1	-53.1	76.3	145.1	88.2	- 53.2	76.2	145.1	88.1	-53.1
ω°(C2'-C1'-C4-H)	-21.1	-158.1	128.4	-126.2	-20.3	-158.0	128.3	-126.2	-20.2	-158.0	128.4	-126.1
ω°(O=C3....C5=O)	-62.6	62.2	114.8	-116.2	-62.5	62.1	115.1	-116.5	-63.0	62.5	115.1	-116.5
Calcd. Dipole Moment	4.96	4.97	2.94	2.87	5.36	5.36	1.91	1.88	5.40	5.40	1.86	1.84
Calculated averaged μ	**4.85**				**5.24**				**5.28**			

Compound	4				5			
Conformation	A	B	C	D	A	B	C	D
Relative ΔH_f (Kcal/mol)	0.0	0.0	2.1	2.1	0.0	0.0	2.4	2.4
Population (%)	47.6	47.6	1.3	1.3	48.5	48.0	0.9	0.9
ω° (C2-C3-C4-C1')	-145.9	-76.3	53.9	-91.1	-147.8	-76.2	73.3	-132.6
ω°(C6-C5-C4-C1')	76.1	145.2	88.3	-53.1	76.0	145.6	134.1	-72.6
ω°(C2'-C1'-C4-H)	-20.5	-158.1	128.2	-126.3	-20.2	-157.8	90.6	-91.9
ω°(O=C3....C5=O)	-63.2	62.7	115.1	-116.5	-65.9	64.4	167.9	-166.1
Calcd. Dipole Moment	5.39	5.39	1.87	1.85	6.76	6.78	4.08	4.02
Calculated averaged μ	**5.27**				**6.68**			

independent from the electronic nature of the phenyl substituent that range from σ_p 0.00 to +0.78. Table 2 contains the calculated and the experimental dipole moments. Figure 2 shows the dependence of the dielectric constant on solute concentration for products **1-5**. Good linearity is observed in all the cases. The values of $(\delta\varepsilon/\delta w_2)^o$, $(\delta n/\delta w_2)^o$, and $(\delta v/\delta w_2)^o$, (ε = dielectric constant, n = refractive index, v = specific volume, w_2 = solute weight fraction) determined as the slope of the corresponding plots by least-square fitting, are summarized in Table 3. Those results allowed the computation of the dipole moments by Guggenheim-Smith and Halverstadt-Kumler methods. The values are in the last two columns of Table 3. Differences in the values obtained from both methods are below the experimental error. The calculated dipole moments are systematically higher by *ca.* 0.5 D. This is not attributable to force field inadequacies when treating the aromatic ring since the experimental dipole moments of the corresponding monosubstituted benzenes[9] were correctly reproduced using the same force field. The calculated dipole moments are very sensitive to small changes of the populated conformations. Thus, an artificial decrease of 10% in the population of each the most stable enantiomeric conformers (from 47% to 37%), when introduced in the calculations, results in a reduction of the averaged calculated dipole moment down to values near the experimental.

In summary, the most populated conformers of diketones **1-5** are A and B to an extent of 74-94 %.

Table 2.- Calculated and experimental (in cyclohexane, $\varepsilon = 2.02$) dipole moments (Debye units) for **1-5**

Product	Calculated						Experimental[a]
	Mechanical treatment of aryl rings [7]			Delocalyzed π electrons system [7]			
	$\varepsilon = 1.50$	$\boldsymbol{\varepsilon = 2.02}$	$\varepsilon = 2.28$	$\varepsilon = 1.50$	$\varepsilon = 2.02$	$\varepsilon = 2.28$	$\boldsymbol{\varepsilon = 2.0159}$
1	4.73	**4.85**	4.87	4.70	4.83	4.87	**4.17-4.19**
2	5.14	**5.24**	5.27	5.11	5.22	5.25	**4.61-4.64**
3	5.18	**5.28**	5.31	5.14	5.26	5.29	**4.67-4.70**
4	5.17	**5.27**	5.30	5.13	5.25	5.28	**4.68-4.70**
5	6.61	**6.68**	6.70	6.57	6.64	6.66	**6.21-6.23**[b]

[a] Guggenheim-Smith[10] and Halverstadt-Kumler[11] methods. See Table 3; [b] In dioxane ($\varepsilon = 2.209$).

Table 3. Values of $(\delta\varepsilon/\delta w_2)^o$, $(\delta n/\delta w_2)^o$, and $(\delta v/\delta w_2)^o$ and dipole moments determined by Guggenheim-Smith, $\mu^{G\text{-}S}$, and Halverstadt-Kumler, $\mu^{H\text{-}K}$, methods for **1-5**, in cyclohexane ($\varepsilon_{Ch} = 2.0159$) at 25°

Product	$(\delta\varepsilon/\delta w_2)^o$	$(\delta n/\delta w_2)^o$	$(\delta v/\delta w_2)^o$ (cm^3 x g^{-1})	$\mu^{G\text{-}S}$	$\mu^{H\text{-}K}$
1	5.882	0.050	-0.2570	4.19	4.17
2	6.676	0.040	-0.2907	4.64	4.61
3	6.523	0.056	-0.3230	4.70	4.67
4	5.712	0.060	-0.4452	4.70	4.68
5	15.954	0.095	-0.0518	6.21[a]	6.23[a]

[a] In dioxane ($\varepsilon_{Dx} = 2.209$)

CONCLUSION. These data together with our previous results[4] lead us to conclude that the conformational preferences of β-diketones R^1-CO-CR^3R^4-CO-R^2 depend on the nature of radicals R^1 and R^2 rather than on the nature of the substituents at Cα. For bulky R^1 and R^2 (*tert*-butyl) the minimization of energy in the predominant conformations (high dipole moment conformations of types A and B, Figure 1) is achieved in spite of the strong dipolar repulsion produced between both carbonyl groups. 4-(1-Adamantyl)-2,2,6,6-tetramethylheptane-3,5-dione behaves the same.[4b] On the contrary, for $R^1 = R^2$ = Me, low dipole moment conformations (types C and D in Figure 1) predominate.[4b]

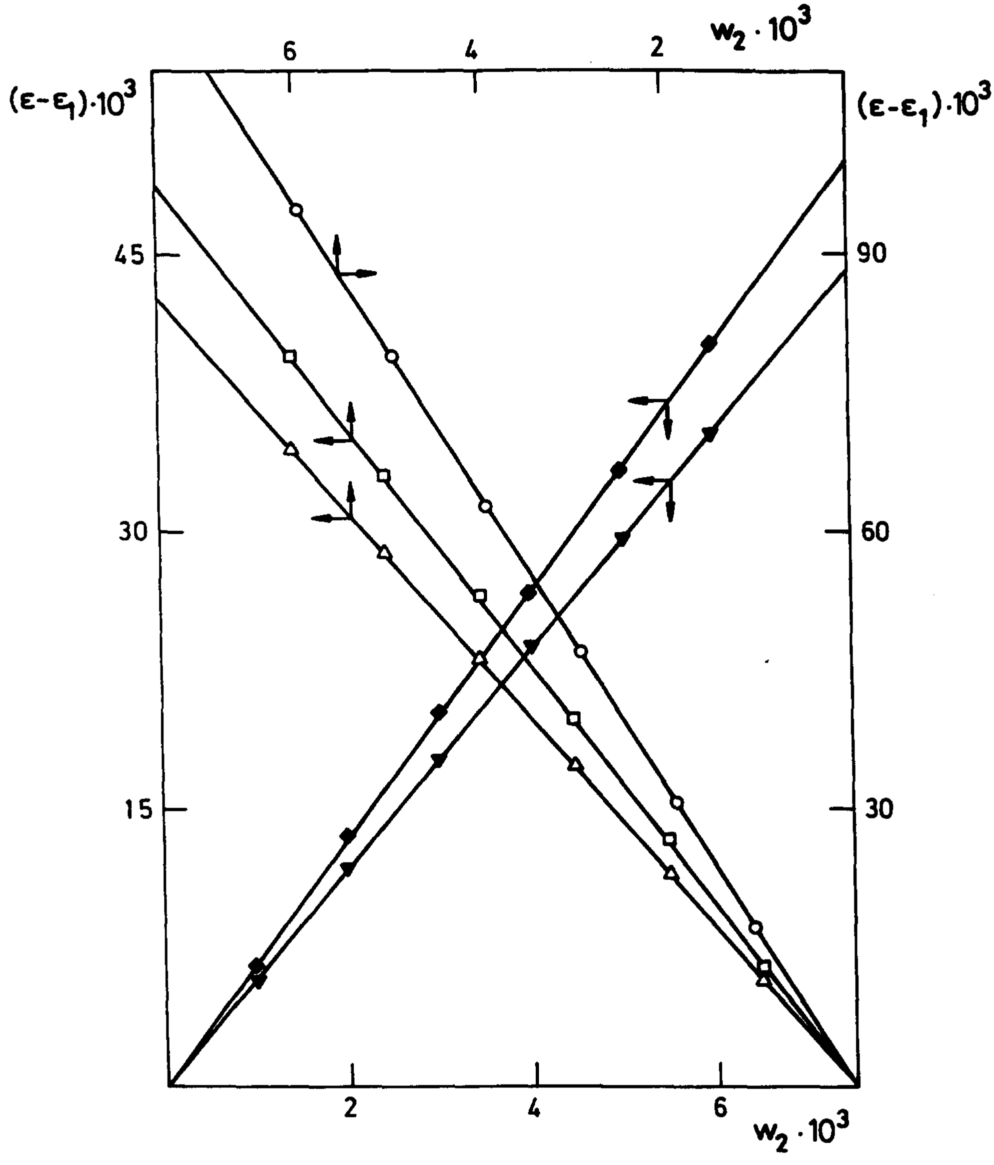


Figure 2. Dependence of dielectric constant, ε, on weight fraction of solute, w_2, for products: **1** (▼), **2** (◆), **3** (□), and **4** (Δ), in cyclohexane, and for **5** (O), in dioxane, at 25°C

EXPERIMENTAL. Compounds **1-5** were prepared as previously described[5] and showed no enol forms in their HMR spectra neither in $CDCl_3$ nor in C_6D_6.

Dipole Moments. The dielectric measurements were performed on a WTW Model DK 06 Multidekameter, at a frequency of 2.0 MHz. The cell used was made of silvered Pyrex glass and was calibrated at the working temperature, $25.0 \pm 0.02°$ using liquids of well known dielectric constants (benzene, toluene and cyclohexane). The concentration range of the solutions was $1 \times 10^{-3} < w_2 < 6 \times 10^{-3}$ (w_2 = solute weight fraction). The same solutions were used for dielectric constants, refractometry, and densimetry measurements. The differences between the refractive indices of solutions and pure solvents were measured at 546 nm in a Brice Phoenix 2000V differential refractometer, calibrated with aqueous solutions of KCl at 25.0°. For specific volume determinations an Anton Paar DMA 55 digital densimeter was used, with distilled water and air as calibrating substances. The temperature in the measuring cell was regulated to $25.00 \pm 0.01°$. The solvents used for calibrating the dielectric cell and for all the measurements (dielectric constant, specific volume and refractive index) were from Carlo Erba RPE and were dried before use over Merck 4A molecular sieves. Guggenheim-Smith[10] and Halverstadt-Kumler[11] extrapolations were used for the dipole moment determinations. The contribution of the atomic polarization was considered to be 5% of the electronic polarization in the Halverstadt-Kumler method. In the Guggenheim-Smith method the usual assumption about this magnitude was adopted, i.e. atomic polarizations of solute and solvent are in the same ratio than their molar volumes.

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