explains satisfactorily the observed positional reactivity orders, provided that allowance is made for the differences in the steric factors.

It further appears that the substituent effect satisfactorily predicts the reactivity order of positions for which the L's of the parent arene are the same, provided that the steric effects are the same.

Acknowledgment. I gratefully acknowledge my collaborators Mmes. A. Koeberg-Telder and Z. R. H. Schaasberg-Nienhuis and Messrs. T. A. Kortekaas, K. Laali, H. J. A. Lambrechts, K. Lammertsma, and P. de Wit for stimulating me in writing this paper by their very skillful contributions to the field of arenesulfonic acid sulfonation.

Carbon-13 Nuclear Magnetic Resonance Chemical Shifts and the Twist Conformations of 1,3-Dioxanes. Geminal Substitution at the 4-Position: A Guaranty for the Chair Form?[1a]

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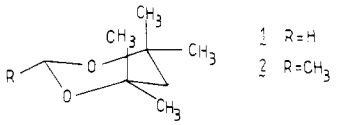
In contrast to earlier reports, the ^{13}C NMR chemical shifts for a set of 2,2,4,4-tetramethyl-substituted 1,3-dioxanes together with the derived substituent effects show that a pseudoaxial substituent in the 2,5- or 1,4-twist form is so greatly disfavored that these derivatives rather exist in the 2,4-diaxially substituted chair form. Those derivatives with syn-axial methyl groups at the 2- and 4-positions but without a geminal substitution at both of them seem, however, to greatly prefer either a 2,5- or 1,4-twist form. In the shift increment parametrization the new δ-syn-axial 2a,4a ($\alpha_a\gamma_a$) increments have large positive values at C(2) and C(4) which almost cancel out the negative γ_a effects. Their influences at C(5) and C(6) are small, however.

On the basis of the ^{13}C NMR chemical shifts[1b] and the ^1H vicinal coupling constants[2] it has been concluded that 2,4-syn-diaxially methyl-substituted 1,3-dioxane rings always escape into twist conformations. On assumption of the additivity of conformational energies, the above postulate also found some support in thermochemical studies,[3] e.g., in that of 2,2,4,4,6-pentamethyl-1,3-dioxane.[3c] On the other hand, Burkert's molecular mechanics calculations[4a] speak for the conclusion that all 2,2,4,4-tetramethyl-substituted 1,3-dioxanes greatly prefer the chair conformation.

In a recent paper[5] we reported the ^{13}C NMR spectra of methyl-substituted 1,3-dioxanes and used the data for 1,3-dioxane itself and 44 methyl derivatives known to exist in chair conformations to calculate the values of different substituent effects on the ^{13}C chemical shifts of the ring carbon atoms. In the same context[5] it was pointed out that 4,4,6,6-tetramethyl-substituted 1,3-dioxanes with the possible exception of the *cis*-2,4,4,5,6,6-hexamethyl derivative exist predominantly in the chair conformation. This observation is also in agreement with the enthalpies of formation[3d,h] of **1** and **2**. As to the conformation-holding influence of the geminal substitution at position 4 (and/or



at position 2), some controversy between Burkert's calculations[4a] and our ^{13}C NMR results[5] still exists. In order to get a consistent insight into the chair–twist equilibria of 1,3-dioxanes with all the available data,[1-6] we prepared *trans*-2,4,4,6-tetramethyl- (**3**) and *trans*-2,2,4,5,5,6-hexamethyl-1,3-dioxane (**6**) and a set of 2,2,4,4-tetramethyl-substituted 1,3-dioxanes (**7**, **10–12**), and their ^{13}C NMR spectra were recorded. The ^{13}C chemical shifts of **4**, **5**, **8**, and **9** were available from our earlier work.[5] The aim of the present study is to establish with the necessary shift data to what extent the simultaneous geminal substitution at C(2) and C(4) is a guaranty for the chair form and to establish how strong a conformation-holding group is a single geminal substituent in the case of 2,4-syn-diaxially methyl-substituted 1,3-dioxanes.

Experimental Section

Compound **3** was prepared with the method of Eliel and Nader.[7] Compounds **6**, **7**, and **10–12** were prepared conventionally from 2,2-dimethoxypropane and a suitable diol.[1b,2,8]

The ^{13}C spectra were recorded on a JEOL FX-60 FT NMR spectrometer operating at 15.03 MHz with 8K data points. Samples were prepared in 10-mm-o.d. tubes as 10% v/v solutions in $CDCl_3$ with 2% Me_4Si as a reference. The deuterium of the solvent provided the lock signal, and the probe temperature was kept at 298 ± 1 K. The ^{13}C chemical shifts of compounds **7–12** are collected in Table I, those of compounds **4–6** in Table II and

(1) (a) This report is also part 2 in "^{13}C Chemical Shifts: Sensitive Detectors in Structure Determination" (for part 1 see ref 5) and part 5 in "^{13}C NMR Studies of Saturated Heterocycles" (for part 4 see ref 5). (b) Kellie, G. M.; Riddell, F. G. *J. Chem. Soc. B.* **1971**, 1030.

(2) Pihlaja, K.; Kellie, G. M.; Riddell, F. G. *J. Chem. Soc. B*, **1972**, 252.

(3) (a) Pihlaja, K.; Luoma, S. *Acta Chem. Scand.* **1968**, *22*, 2401. (b) Clay, R. M.; Kellie, G. M.; Riddell, F. G. *J. Am. Chem. Soc.* **1973**, *95*, 4632. (c) Pihlaja, K.; Steele, W. V. 7th Experimental Thermodynamics Conference, University of Bristol, April 1976, Paper A 34. (d) Pihlaja, K.; Kivimäki, M.; Vainiotalo, P. 9th Experimental Thermodynamics Conference, University College, London, April 1980, Paper B 40. (e) Pihlaja, K.; Jalonen, J. *Org. Mass Spectrom.* **1971**, *5*, 1363. (f) Vainiotalo, P. Ph.Lic. Thesis, University of Turku, Turku, Finland, 1980. (g) Pihlaja, K.; Heikkilä, J. *Acta Chem. Scand.* **1967**, *21*, 2430. (h) Pihlaja, K.; Vainiotalo, P., to be submitted for publication.

(4) (a) Burkert, U. *Tetrahedron* **1979**, *35*, 691. (b) Pihlaja, K.; Vainiotalo, P. to be submitted for publication in *J. Chem. Eng. Data*. See also: Pihlaja, K. *Acta Chem. Scand.* **1971**, *25*, 451.

(5) Pihlaja, K.; Nurmi, T. *Isr. J. Chem.* **1980**, *20*, 160.

(6) (a) Pihlaja, K. *Kem.—Kemi* **1974**, *1*, 492 and references therein. (b) Pihlaja, K.; Äyräs, P. *Acta Chem. Scand.* **1970**, *24*, 204, 531. (c) Anteunis, M. J. O.; Tavernier, D.; Borremans, F. *Heterocycles* **1976**, *4*, 293 and references therein.

(7) Eliel, E. L.; Nader, F. W. *J. Am. Chem. Soc.* **1970**, *92*, 584.

(8) Pihlaja, K. *Turun Yliopiston Julk., Sar. A1* **1967**, *No. 114*.

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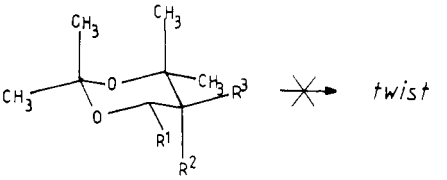
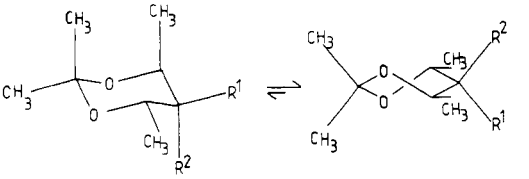
Table I. Observed and Calculated ^{13}C Chemical Shifts for the 2,2,4,4-Tetramethyl-Substituted Derivatives



				chemical shift, δ								
				C-2		C-4		C-5		C-6		
no.	R^1	R^2	R^3	obsd	calcd	obsd	calcd	obsd	calcd	obsd	calcd	obsd C-methyls (position)
7	H	H	H	97.91	98.09	70.50	70.56	35.57	35.58	56.89	57.09	28.18 (2,2), 30.42 (4,4)
8[a]	CH_3	H	H	98.35	98.26	70.90	71.05	43.37	43.24	61.76	61.83	24.93 (2a), 32.04 (2e), 27.98 (4a), 33.38 (4e), 22.21 (6e)
9	H	H	CH_3	97.99	97.75	74.60	74.83	37.89	37.86	62.90	62.79	25.30 (2a), 30.82 (2e), 23.19 (4a), 30.62 (4e), 12.59 (5e)
10	CH_3	H	CH_3	97.70	97.92	74.52	74.47	44.95	44.91	66.96	66.98	24.85 (2a), 32.16 (2e), 23.39 (4a), 31.06 (4e), 19.94 (6e), 12.18 (5e)
11	CH_3	CH_3	H	98.87	98.82	74.23	74.11	39.47	39.45	64.04	63.96	25.01 (2a), 31.76 (2e), 28.67 (4a), 29.56 (4e), 19.25 (6e), 7.59 (5a)
12	H	CH_3	CH_3	98.01	97.99	76.83	76.57	34.56	34.76	68.26	68.16	28.02 (2,2), 25.86 (4,4), 21.60 (5,5)
av difference, ppm				±0.13		±0.15		±0.07		±0.10		

[a] The assignment of 2a- and 4a-methyls is opposite the tentative one in ref 5.

Table II. Observed and Calculated ^{13}C Chemical Shifts for 2,2-*trans*-4,6-Tetramethyl-Substituted Derivatives[a]



			chemical shift, δ								
			C-2		C-4		C-5		C-6		
no.	R^1	R^2	obsd	calcd	obsd	calcd	obsd	calcd	obsd	calcd	obsd C-methyls (position)
4	H	H	100.02	96.72	62.70	64.52	41.54	36.34	62.70	64.52	25.18 (2,2), 21.72 (4/6)
5	CH_3	H	100.26	96.39	70.62	73.11	42.27	38.62	64.93	65.70	25.22 (2), 24.20 (2'), 20.34 (4), 16.57 (6), 11.57 (5)
6	CH_3	CH_3	100.50	96.88	71.63	73.02	39.19	34.97	71.63	73.02	24.24 (2,2), 19.49 (5,5), 14.82 (4,6)
av difference, ppm			±2.91		±1.90		±4.36		±1.33		

[a] The parameters shown in Tables IV-VI for the chair forms have been used to obtain the calculated values. [b] Calculated for the 5-equatorial chair form only. The deviation for the 5-axial form is even greater.

that of compound **3** in Table III.

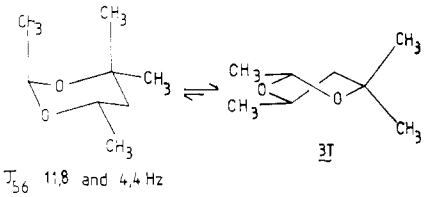
Results and Discussion

If compounds **7–12** exist exclusively in chair conformations as concluded by Burkert from the molecular mechanics calculations,[4a] their ^{13}C chemical shifts should give constant values for the new δ-syn-axial 2a,4a or 2a,6a substituent effects at C(2), C(4/6), and C(5), respectively, when compared with the calculated shift values based on the substituent effects derived earlier[5] for the derivatives in the chair form. First we proved manually that this is indeed the case, and then the data for **7–12** were included in the linear regression analysis of the shift data reported earlier.[5] The values of the revised shift parameters together with those of the new δ-syn-axial parameters are shown in Tables IV–VI. The revised values deviate but little from the original ones:[5] by 0.00–0.05 ppm in 52 cases, by 0.06–0.15 ppm in 7 cases, and by 0.16–0.24 ppm in 4 cases only, which also shows that the new compounds fit into the correlation with the chair forms very well. Hence we can now conclude in agreement with Burkert's calculations[4a] but in contrast to our own preliminary suggestion[5] that 2,2,4,4-tetramethyl-substituted 1,3-dioxanes exist, in the light of the ^{13}C chemical shift data, exclusively in deformed chair forms. This is also in accordance with our thermochemical data[3c-h] and X-ray results discussed later.[9] The vicinal J_{5H6H} coupling constants determined earlier for **8** (10.9 and 2.5 Hz), **9** (10.3 and 4.9 Hz), **10** (9.7 Hz), and **11** (2.4 Hz) and stated to be in favor of the 1,4-twist form fit the deformed chair forms equally well with an equatorial methyl at position 6.

Let us next apply the chair parameters (Tables IV–VI) to the 2,2,*trans*-4,6-tetramethyl-substituted derivatives

(9) Kellie, G. M.; Murray-Rust, P.; Riddell, F. G. *J. Chem. Soc., Perkin Trans. 2* **1972**, 2384.

Table III. Observed and Calculated ^{13}C Chemical Shifts for *trans*-2,4,4,6-Tetramethyl-1,3-dioxane (3)[a]



3T

J_{56} 11.8 and 4.4 Hz

	C-2	C-4	C-5	C-6	obsd methyls (position)
δ(obsd)	88.81	71.92	41.58	65.38	21.68 (2),[b] 21.77 (6)[b]
δ(calcd)	94.30	69.74	43.90	60.90	28.91 (4), 27.74 (4)
diff, ppm	5.49	2.18	1.49	4.48	

[a] The parameters shown in Tables IV–VI for the chair forms have been used to obtain the calculated values. [b] Tentative assignment only.

Table IV. Parameters for Shifts at C(2) in the Chair Form

position of source of substituent effect	parameter	value,[b] ppm	no. of occurrences
2e	α_e	5.06 ± 0.05	32
4e (or 6e)	γ_e	−0.43 ± 0.03	63
5e	δ_e	−0.33 ± 0.05	24
2a	α_a	−0.97 ± 0.18	13
4a (or 6a)	γ_a	−7.12 ± 0.07	26
5a	δ_a	0	21
2,2	G_a	−0.52 ± 0.16	12
4,4 (or 6,6)	G_γ	1.37 ± 0.08	20
5,5	G_δ	0.21 ± 0.08	9
4e,5a (or 5a,6e)	$\gamma_e\delta_a$	0.28 ± 0.03	23
2a,4e (or 2a,6e)	$\alpha_a\gamma_e$	0.60 ± 0.06	18
2e,4a (or 2e,6a)	$\alpha_e\gamma_a$	−0.58 ± 0.07	16
4a,6a	$\gamma_a{}^4\gamma_a{}^6$	0.96 ± 0.14	2
4,4,5,5 (or 5,5,6,6)	$\gamma_a\gamma_e\delta_a\delta_e$	−0.26 ± 0.11	3
2a,4a (or 2a,6a)[a]	$\alpha_a\gamma_a$	6.39 ± 0.10	6

[a] The new δ-syn-axial shift effect. [b] rms, 0.134 ppm; average difference, ±0.09 ppm; range, 16.65 ppm. The ^{13}C chemical shifts of 1,3-dioxane itself are 94.29, 66.92, and 26.56 ppm for C(2), C(4/6), and C(5), respectively.

(4–6, Table II). If they would favor the chair form, their ^{13}C chemical shifts could also be estimated very accurately. This is not, however, possible, but in all cases the calculated values deviate 1–5 ppm from the experimental results (Table II). This observation does not necessarily prove that these derivatives escape exclusively in the 2,5-twist forms, but at least it lends strong support to the predominance of this ring conformation in these compounds in contrast to the conclusion of Burkert[4a] about nearly equal contributions of the chair and twist forms of **4** and **5**. Furthermore, it is possible to pinpoint some questionable if not mistaken arguments in favor of the chair form in Burkert's paper. First he uses *cis*-2,2,4,6-tetramethyl-1,3-dioxane as the model in determining the *A* values for the Karplus equation ($J = A\cos^2\phi + C$) which he then in turn applies to the estimation of the vicinal HH coupling constants. He should have used 2,2,4,4,6-pentamethyl-1,3-dioxane as the model at least for the 2,4-syn-axial chair form since the Karplus *A* values may vary from a system to another.[10] This model system leads us to the equation

$$J = 12.3\cos^2\phi - 1.3$$

which for the average value of the vicinal coupling constants in the 2,5-twist form of the *trans*-2,2,4,6-Me_4 derivative (**4**; see ref 4a) gives a value of 7.6 Hz, in excellent agreement with the experimental finding of 7.5 Hz.[2] Similarly, we believe that also **5** and **6** exist predominantly in the 2,5-twist conformations which in the case of **5** also find some support from the values of the vicinal coupling

(10) Pihlaja, K.; Nurmi, T.; Pasanen, P. *Acta Chem. Scand., Ser. B* **1977**, *B31*, 895.

Table V. Parameters for Shifts at C(4/6) in the Chair Form

position of source of substituent effect	parameter	value,[a] ppm	no. of occurrences
2e	$\gamma_e{}^2$	−0.15 ± 0.05	45
4e	α_e	5.76 ± 0.08	51
5e	β_e	6.34 ± 0.08	35
6e	$\gamma_e{}^6$	−0.38 ± 0.09	51
2a	$\gamma_a{}^2$	−7.79 ± 0.22	14
4a	α_a	0.95 ± 0.19	24
5a	β_a	4.93 ± 0.12	30
6a	$\gamma_a{}^6$	−4.74 ± 0.19	24
2,2	$G_\gamma{}^2$	1.08 ± 0.20	13
4,4	G_α	−2.71 ± 0.18	17
5,5	G_β	−0.81 ± 0.11	12
6,6	$G_\gamma{}^6$	1.17 ± 0.18	17
2e,4a	$\gamma_e{}^2\alpha_a$	0.38 ± 0.12	15
2a,4e	$\gamma_a{}^2\alpha_e$	−0.87 ± 0.12	11
2a,6e	$\gamma_a{}^2\gamma_e{}^6$	0.24 ± 0.12	11
4a,6e	$\alpha_a\gamma_e{}^6$	0.31 ± 0.13	16
4e,6a	$\alpha_e\gamma_a{}^6$	−0.47 ± 0.14	16
4e,6e	$\alpha_e\gamma_e{}^6$	0.32 ± 0.16	21
4a,6a	$\alpha_a\gamma_a{}^6$	3.44 ± 0.19	2
4e,5a	$\alpha_e\beta_a$	−2.43 ± 0.15	18
5a,6e	$\beta_a\gamma_e{}^6$	2.01 ± 0.14	18
4a,5e	$\alpha_a\beta_e$	−1.48 ± 0.20	12
5e,6a	$\beta_e\gamma_a{}^6$	−1.12 ± 0.19	12
5e,6e	$\beta_e\gamma_e{}^6$	−0.30 ± 0.13	21
2a,4a[b]	$\gamma_a{}^2\alpha_a$	6.99 ± 0.14	6
2a,6a[b]	$\gamma_a{}^2\gamma_a{}^6$	0.74 ± 0.12	6
4e,5e,6e	$\alpha_e\beta_e\gamma_e{}^6$	−0.55 ± 0.12	6
4e,5a,6e	$\alpha_e\beta_a\gamma_e{}^6$	−0.70 ± 0.18	9
4e,5a,6a	$\alpha_e\beta_a\gamma_a{}^6$	−0.58 ± 0.17	6
4e,4a,5e	$\alpha_e\alpha_a\beta_e$	−0.59 ± 0.24	8
5e,6e,6a	$\beta_e\gamma_e{}^6\gamma_a{}^6$	0.79 ± 0.23	8
4e,4a,5a	$\alpha_e\alpha_a\beta_a$	−0.75 ± 0.17	6
5a,6e,6a	$\beta_a\gamma_e{}^6\gamma_a{}^6$	−1.09 ± 0.22	6
4,4,5,5	$\alpha_e\alpha_a\beta_e\beta_a$	0.80 ± 0.23	3
5,5,6,6	$\beta_e\beta_a\gamma_e{}^6\gamma_a{}^6$	0.33 ± 0.24	3

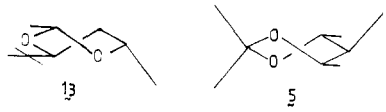
[a] rms, 0.162 ppm; average difference; ±0.10 ppm; range, 24.57 ppm. [b] The new δ-syn-axial shift effects.

Table VI. Parameters for Shifts at C(5) in the Chair Form

position of source of substituent effect	parameter	value,[a] ppm	no. of occurrences
2e	δ_e	−0.92 ± 0.03	32
4e (or 6e)	β_e	7.10 ± 0.04	63
5e	α_e	3.59 ± 0.06	24
2a	δ_a	−1.06 ± 0.13	13
4a (or 6a)	β_a	3.84 ± 0.06	26
5a	α_a	3.30 ± 0.08	21
2,2	G_δ	1.06 ± 0.11	12
4,4 (or 6,6)	G_β	−0.74 ± 0.06	20
5,5	G_α	−2.60 ± 0.11	9
2a,4e (or 2a,6e)	$\delta_a\beta_e$	0.20 ± 0.04	18
2a,4a (or 2a,6a)[b]	$\delta_a\beta_a$	−0.44 ± 0.07	6
4e,5e (or 5e,6e)	$\beta_e\alpha_e$	−0.61 ± 0.05	24
4e,5a (or 5a,6e)	$\beta_e\alpha_a$	−3.27 ± 0.05	23
4a,5e (or 5e,6a)	$\beta_a\alpha_e$	−0.70 ± 0.06	13
4e,6e	$\beta_e{}^4\beta_e{}^6$	0.37 ± 0.06	21
4a,6a	$\beta_a{}^4\beta_a{}^6$	−1.02 ± 0.11	2
4e,5,5 (or 5,5,6e)	$\beta_e\alpha_e\alpha_a$	−0.53 ± 0.08	6
4e,5a,6a (or 4a,5a,6e)	$\beta_e{}^4\alpha_a\beta_a{}^6$	−0.55 ± 0.06	6

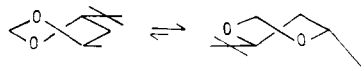
[a] rms, 0.092 ppm; average difference ±0.05 ppm; range, 20.67 ppm. [b] The new δ-syn-axial shift effect.

constants on the methyl side of **13** (7.5 and 6.4 Hz as compared with 7.8 and 5.3 Hz in **5**) which inevitably attains the 1,4-twist conformation.[11]



13 **5**

Using a revised set of group increments for the estimation of enthalpies of formation of saturated organic oxygen compounds,[4b] we obtain for the hypothetically strain-free chair form of 2,2,*trans*-4,6-tetramethyl-1,3-dioxane (**4**) $-\Delta H_f°(g) = 511.4$ kJ mol^{-1}. Experimentally[3g-h] we have found $-\Delta H_f°(g) = 482.7 \pm 2.4$ kJ mol^{-1}. The difference, 29.7 kJ mol^{-1}, is actually equal to the chair–2,5-twist enthalpy difference, $\Delta H_{CT}(2,5)$, since the NMR evidence given above showed that **4** attains predominantly the 2,5-twist conformation. Accordingly, the estimate for $\Delta H_{CT}(2,5)$ is even slightly less than the figure, 32.9 kJ mol^{-1}, we quoted earlier.[3a,e,f,6a] Second, Burkert[4a] explains that Anteunis[12] et al. have measured a chair–twist enthalpy difference of 25.7 kJ mol^{-1} for the 2,5-twist form of *trans*-4-*tert*-butyl-6-methyl-1,3-dioxane (**14**), but in ac-



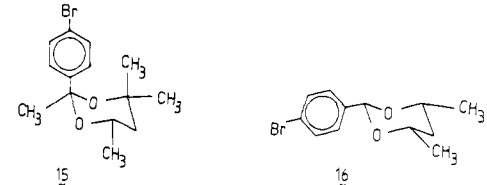
14b **14a**

cordance with his own suggestions about the preference of the 1,4-twist form, this compound also preferably attains the 1,4-twist conformation (**14a**), and the proportion of (**14b**) is only about 15%. In this context it should be mentioned that Anteunis et al.[6c] actually stated that it is the 2,5-twist and not the 1,4-twist form which is thermochemically more stable in contrast to our results[2,3a,e,6a,14] and Burkert's calculations.[4a] This is, of course, forgivable since in the case of compounds like **13** and **14** it is possible to find both a 2,5- and a 1,4-twist form without pseudoaxial substitution. From the above results we can estimate a value (25.0 kJ mol^{-1}) for the chair–1,4-twist enthalpy difference, $\Delta H_{CT}(1,4)$. Thus the experimental difference of $\Delta H_{CT}(2,5) - \Delta H_{CT}(1,4) = 29.7 - 25.0 = 4.7$ kJ mol^{-1} is rather close to the difference (24.8 − 16.4 = 8.4 kJ mol^{-1}) calculated by Burkert.[4a] There is, however, a ca. 5–9 kJ mol^{-1} difference in his calculations and in the experimental finding which can be mainly due to the extra interactions of the pseudoequatorial and isoclinal substituents in the twist forms.

In Table III we have collected the experimental and calculated ^{13}C chemical shifts of *trans*-2,4,4,6-tetramethyl-1,3-dioxane (**3**). The values of the vicinal J_{5H6H} coupling constants show that this molecule must be a chair with an axial methyl at the 2-position or the 1,4-twist form where the geminal methyl groups are isoclinal (see Table III). In this case the values calculated for the 2,4-syn-axial chair conformation differ again from the observed ones by about 2–6 ppm. Hence we conclude again in full agreement with Burkert's calculations[4a] and with our own earlier reports[2,5] that **3** exists predominantly in the 1,4-twist conformation (**3T**). Taking into account the experimental chair–1,4-twist enthalpy difference (25.0 kJ mol^{-1}) and the conformational energy (12.2 kJ mol^{-1}) of the 4-axial methyl group[3a,6c] in the *cis*-2,4,4,6-tetramethyl derivative, one sees that the trans isomer (**3T**) should be only about 12 kJ mol^{-1} thermochemically less stable than the cis isomer, in excellent agreement with Burkert's calculated value (12.9 kJ mol^{-1}) but in contrast to a lower limit estimate[13] of $\Delta G°$ at 22.8 kJ mol^{-1} and a microcalorimetric determination[3b] of $\Delta H°$ at 24.1 kJ mol^{-1}. It would be interest to study this equilibration again since the excess entropy of the twist conformation[14] should make **3T** even more attractive in terms of the Gibbs energy difference ($-\Delta G°_{trans-cis} < 12$ kJ mol^{-1}).

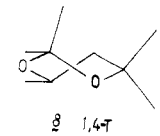
Concluding Remarks

(i) 2,2,4,4-Tetramethyl- (or tetraalkyl) substituted 1,3-dioxanes greatly prefer a deformed chair form. This could have already been concluded earlier from the difference in the crystal structure data of *r*-2-(*p*-bromophenyl)-2,4,4,*t*-6-tetramethyl-1,3-dioxane (**15**) and *r*-2-(*p*-bromophenyl)-*c*-4,*c*-6-dimethyl-1,3-dioxane (**16**)[9] which both attain the chair form.



15 **16**

For instance, the torsion angles in the O–C–O part of **15** are about 20° smaller than those in **16**. The ring flattening and also the widening of the bond angles is reflected in the distance between the 2,4-diaxial groups. In **15** this distance is 314 pm whereas in an "ideal" chair form it is about 80 pm shorter.[15] Accordingly, the 2,4-digeminally substituted 1,3-dioxane ring can through deformation minimize the steric compression due to the 2a,4a-substitution to such a level that even the 1,4-twist form,[2] which then inevitably has a pseudoaxial methyl group at position 2, cannot compete with the chair conformation. Hendrickson[16] calculated that in the cyclohexane ring the interaction due to a pseudoaxial methyl group in the twist form is at least 1.5 times that of an axial methyl group in the chair form. Accordingly, we can estimate that the total interaction energy for the 1,4-twist form of **8** would be $25.0 + 1.5 \times 16.8$[3a,6a,14] ≈ 50 kJ mol^{-1}



8 1,4-T

(for a 2,5-twist form the total interaction energy would be almost the same: $29.7 + 1.5 \times 12.2 \approx 48$ kJ mol^{-1}). If we now compare this value with the experimental value of the total strain (30.4 kJ mol^{-1}), the difference between the experimental,[3c,h] −520.9 ± 3.2 kJ mol^{-1}, and calculated[4b] (for the hypothetically strainfree chair form again), −551.3 kJ mol^{-1}, enthalpies of formation, it is easy to understand that **8** and the other 2,2,4,4-tetramethyl-substituted compounds greatly prefer the deformed chair conformation. In the light of the above discussion we also hope to delete the next to the last paragraph before the conclusions section in our preceding paper[5] since it was based on an erroneous calculation.

(ii) When there is no pseudoaxial substituent in the twist form, the 2,4-syn-axially substituted derivatives attain a

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2,5- or 1,4-twist form, depending on the location of the geminal substitution in position 2 or 4, respectively. The chair–twist enthalpy difference for the 1,4-twist form appears to be ca. 5 kJ mol^{-1} smaller than that for the 2,5-twist form. Two small discrepancies between our present results and Burkert's molecular mechanics calculations still remain. First we conclude that compounds **4–6** exist predominantly if not exclusively in the 2,5-twist form whereas according to Burkert's calculations the chair form has an appreciable contribution. Second, the question about the influence of the substitution on the chair–twist enthalpy difference cannot be exactly answered. This is not, however, crucial since the experimental results[3,4b,12] apply very well to those cases where the twist form really has an important role whereas Burkert's calculations[4a] deal with the unsubstituted ring.

(iii) Last but not least we emphasize the importance of different experimental approaches like thermochemistry,[3a,c,d,f–h,4b] mass spectrometry,[3e] ^{1}H and ^{13}C NMR spectroscopy,[2,5,6,11,12] X-ray results,[9] and succesful molecular mechanics calculations[4a] in defining the detailed molecular structures.

Registry No. 3, 21589-58-2; 4, 20268-00-2; 5, 28231-59-6; 6, 36376-78-0; 7, 56444-60-1; 8, 32560-29-5; 9, 35776-46-6; 10, 35776-45-5; 11, 35776-44-4; 12, 83115-78-0.

Ester Enolates from α-Acetoxy Esters. Synthesis of Aryl Malonic and α-Aryl Alkanoic Esters from Aryl Nucleophiles and α-Keto Esters

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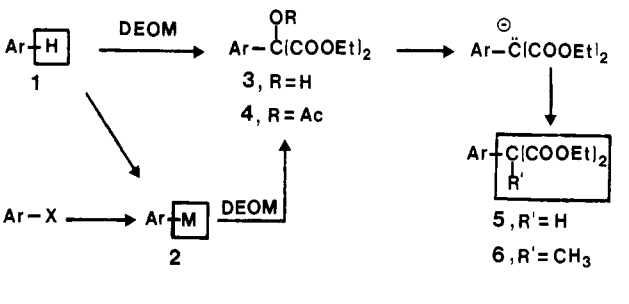
Ester enolates are generated by reductive α-deacetoxylation of α-acetoxy-α-arylmalonic esters or α-acetoxy-α-arylalkanoic esters with lithium in liquid ammonia or sodium α-(dimethylamino)naphthalenide in hexamethylphosphoramide–benzene. Since the requisite α-acetoxy esters are available from aryl nucleophiles, the reductions provide effective new synthetic routes to arylmalonic esters and α-arylalkanoic esters. For example, 2-(*p*-isobutylphenyl)propionic acid (ibuprofen, a commercially important nonsteroidal antiinflammatory agent) is obtained in 73% yield overall from isobutylbenzene. Arenes, aryllithiums, or arylmagnesium halides react with α-keto esters, e.g., diethyl oxomalonate, ethyl pyruvate, methyl phenylglyoxalate, or alkyl glyoxylates, to afford α-hydroxy esters. These are acetylated with acetic anhydride–triethylamine and *p*-(dimethylamino)pyridine as a catalyst. Reductive α-deoxygenation then allows replacement of the acetoxy group by hydrogen or an alkyl group.

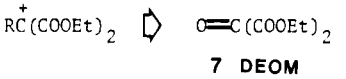
Arylmalonic acid esters are important rudimentary synthons inter alia for preparation of medicinally valuable nonsteroidal antiinflammatory agents and barbiturates.[1] Arylation of malonic ester carbanions is of limited utility since electrophilic arylating agents are not generally available. We now report widely applicable new synthetic methodology which exploits diethyl oxomalonate (DEOM) as a malononium equivalent for construction of diethyl arylmalonates **5** or **6** from aryl nucleophiles **1** or **2** (Scheme I). The conversion depends on our recent discovery of effective methods for reductive deoxygenation and reductive alkylation of α-acetoxymalonates **4**.[2] We also report analogous syntheses of α-arylalkanoic esters from α-oxoalkanoic esters.

Construction of arylmalonic esters from aryl *electrophiles* and malonate carbanions is sometimes achievable via benzyne intermediates.[3] However, this approach is unattractive for preparing ring-substituted arylmalonates because it produces positional isomers. Thus, electrophilic attack occurs nonselectively at both carbons of the formal C≡C bond. Regiospecific replacement of the aryl nucleofuge by a malonate nucleophile does occur, by an addition–elimination sequence, if ortho or para electron-withdrawing substituents such as nitro or acyl groups are present.[4-6] Aryl bromo substituents situated ortho to a carboxylate group exhibit a unique susceptibility in the presence of copper(I) salts toward substitution by malonate carbanions.[7] Copper(I) salts promote a more general replacement of aryl iodo substituents by malonate carbanions, especially in hexamethylphosphoric triamide solutions.[8]

Scheme I



In view of the wide availability of aromatic *nucleophiles*, it is remarkable that no synthetic method is known which exploits these synthons in reactions with a carbon electrophile to produce diethyl arylmalonates. This gap in synthetic methodology prompted us to explore the possibility that diethyl oxomalonate (DEOM, **7**) can serve a malononium ion equivalent.



7 DEOM

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