cedure used to prepare the title compounds containing, where indicated in Table III, the corresponding isomeric imines.

To a solution of 4 (1.08 g, 0.010 mol) in benzene (25 ml) was added N-methylethylenediamine (0.89 g, 0.012 mol). Fast, exothermic reaction occurred and the water formed was removed by azeotropic distillation with benzene. Vacuum distillation (0.1 mm) of the dark residual oil gave N-methylspiro[bicyclo[2.2.1]hept-2-ene-7,2'-imidazolidine] (1.2 g, 73%) as a colorless liquid. Both isomers were produced (Table I), the ratio being 1.4:1. Attempts to separate those isomers or any of the other isomeric mixtures of Table III were unsuccessful.

Approximate yields of mixtures of other imidazolidines and imines (Table III) by analogous treatment of 4 with N-alkylethylenediamines were: N-ethyl, 60%; N-isopropyl, 60%, N-tert-butyl, 20%; N-neopentyl, 10%. All mixtures showed the expected vinyl absorption in the pmr spectra (see Discussion). However, those spectra of all but the simplest systems were very complex in the high-field region. The N-isopropyl and N-tert-butyl systems (neat) absorbed strongly in the infrared, at 1720 and 1718 cm⁻¹, respectively. All of the samples were unstable in CCl₄, except for short periods, and all regenerated norbornen-7-one on treatment with water.

Equilibration of the imidazolidines (and imines) at 37°, in DMSO containing a trace of p-toluenesulfonic acid, was followed by pmr. Isomer ratios were determined by integration of the signals in the vinyl region.

Base-Catalyzed Transesterification of 7-Carbomethoxynorbornenes. A mixture of the isomeric esters (anti:syn = 1.38:1) was prepared by esterification of a mixture of the acids with diazomethane.[28] To 44 mg of the mixture in 0.4 ml of methanol-d_4 in an nmr tube at 35 ± 0.5° (probe temperature) was added sodium methoxide in methanol-d_4 (10 μl) from a solution containing 100 mg of NaO-CH₃/ml. Anisole (10 mg) was also injected into the tube, which was shaken and returned to the probe. The spectrum covering the range δ 3.5–3.8 was scanned at 2–3-min intervals for 80 min. Peak heights for anti- and syn-methoxyl groups, at δ 3.6 and 3.5, respectively, were expressed as fractions of the heights of the methoxy signal of anisole (δ 3.8). Logarithms of these fractions, plotted against time, were linear, first-order, plots over the fractions of reaction (anti, 43%; syn, 27%) that were followed. The slopes of these lines were in the ratio 1.8:1, the anti ester reacting more rapidly.

Acid-Catalyzed Transesterification. The above procedure was followed, except for the addition of fuming sulfuric acid (98 mg) instead of methoxide. Pseudo-first-order plots were straight, parallel lines for transesterification of the two esters. Reactions were followed to 31% of completion.

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Conformational Analysis. XXIX. 2-Substituted and 2,2-Disubstituted 1,3-Dioxanes. The Generalized and Reverse Anomeric Effects[1]

William F. Bailey[2a] and Ernest L. Eliel*[2b]

Contribution from the Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556, and the William Rand Kenan, Jr., Laboratories of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514. Received August 8, 1973

Abstract: In solvent carbon tetrachloride, the axial isomers of 2-ethynyl-cis-4,6-dimethyl-1,3-dioxane and 2-phenylethynyl-cis-4,6-dimethyl-1,3-dioxane predominate at equilibrium over their equatorial epimers. The preference is attenuated in the more polar solvent ether and reversed in the still more polar acetonitrile. 2-Phenyl- and 2-p-trifluoromethylphenyl-cis-4,6-dimethyl-1,3-dioxanes show a lesser solvent sensitivity in their axial–equatorial preference and, despite the very much larger dipole differences in the p-trifluoromethyl as compared with the unsubstituted phenyl compound, have very similar $\Delta G°$ values in any given solvent. These results show that the anomeric effect evident in the ethynyl and, to a much lesser extent, in the phenyl compounds is not entirely caused by dipole interaction but, at least in part, by double bond–no bond resonance or the quantum mechanical equivalent thereof, as originally proposed by Altona. The 2,4-dimethyl-2-chloromethyl- and -2-bromomethyl-1,3-dioxanes show little equatorial–axial preference and only a small and rather unusual solvent dependence in that the epimer of higher dipole moment is less favored in more polar solvents. The same solvent dependence is found in the equilibrium of the 2-carbethoxy-2,4-dimethyl-1,3-dioxanes which strongly favors the axial carbethoxy isomer. These results provide only tenuous evidence for the reverse anomeric effect of a C–X group postulated by Coxon.

The preference for the gauche conformation exhibited by gem-dihetero moieties of the type R–X–C–Y (X = O, N, S; Y = an atom having unshared electron pairs) has recently been termed the generalized anomeric effect.[3–5] This effect, observable in acyclic compounds (such as dimethoxymethane[6]), as well as within rings (as in N,N-dialkyl-1,3-diazanes[8]), is a generalized manifestation of the preference of axial over equatorial C-1 alkoxy groups (aglycones) in pyranose sugars which has long been known as the anomeric

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(3) E. L. Eliel, Angew. Chem., 84, 779 (1972); Angew. Chem., Int. Ed. Engl., 11, 739 (1972).

(4) R. U. Lemieux, Pure Appl. Chem., 25, 527 (1971).

(5) H. Booth and R. U. Lemieux, Can. J. Chem., 49, 777 (1971).

(6) T. Uchida, Y. Kurita, and M. Kubo, J. Polym. Sci., 19, 365 (1956); S. Mizushima, Y. Morino, and M. Kubo, Phys. Z., 38, 45 (1937); see also ref 3 and 7.
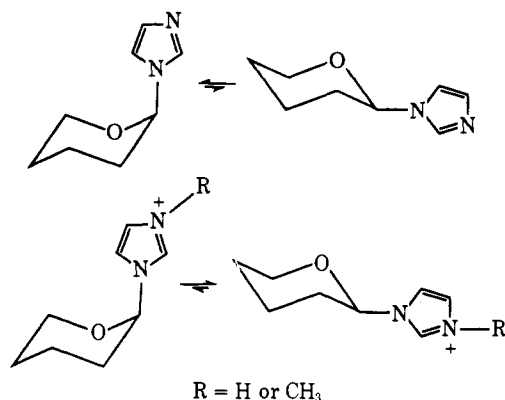
(7) R. U. Lemieux, "Molecular Rearrangements," P. de Mayo, Ed., Wiley-Interscience, New York, N. Y., 1964, p 709.

(8) R. O. Hutchins, L. D. Kopp, and E. L. Eliel, J. Amer. Chem. Soc., 90, 7174 (1968); see also ref 5.

effect.[9] The magnitude of the anomeric effect has been shown to be solvent dependent in most systems studied to date. For the tetrahydropyran ring system (glycosides,. 2-halo-, 2-alkoxy-, and 2-thioalkoxytetrahydropyrans, etc.), the proportion of axial isomer present at equilibrium is found to decrease with increasing solvent polarity,[10] and this solvent trend has generally been assumed to be indicative of the polar/electrostatic etiology of the effect advanced by a number of authors.[9,11,12] This subject has been extensively reviewed in recent articles.[7,13-16]

A much less studied but nonetheless interesting phenomenon is the excess preference for the equatorial position over what would be expected on steric grounds for an electropositive group, such as NR_3^+, attached to the C-2 position in tetrahydropyran systems which is postulated to arise from electrostatic repulsion between the bond from C-2 to the positively charged aglycone and the C-6 to oxygen bond.[17] Since this amounts to a reversal of the interactions considered by Lemieux and Chu to constitute the origin of the anomeric effect,[7,9] it was termed the "reverse anomeric effect"[17] and it has recently been exploited to synthetic advantage in the synthesis of α-glycosides.[18] A particularly convincing manifestation of the reverse anomeric effect is seen[4] in N-glycosylimidazoles where protonation or quaternization of the imidazole moiety changes its preferred conformation from axial to equatorial, as shown schematically in Scheme I. In 1966 Coxon sug-

gested[19] that substituents of the type CH$_2$-X, where X is an electronegative atom or group, might engender a reverse anomeric effect due to the induction of a small positive charge on the carbon atom by the electron withdrawing X group. Although this effect has been invoked to rationalize the higher than expected conformational energy of 2-carbomethoxytetrahydropyran,[20] it has never been demonstrated that a reverse anomeric effect is operative in systems possessing only partial positive charge at the atom attached to the anomeric carbon,[21] and no data are available on the role of solvent, if any, on the magnitude of this effect.

The dearth of knowledge concerning the role of the generalized anomeric effect on conformational equilibria in systems of the type R-O-C-Y wherein the Y group is an unsaturated substituent rather than a heteroatom possessing nonbonded electron pairs, along with the unanswered question as to the generality of the so called reverse anomeric effect, prompted this study. The 1,3-dioxane system was chosen for this investigation of equilibria involving polar and unsaturated substituents since a very convenient synthesis of axial isomers from readily available substituted 2-alkoxy-1,3-dioxanes and Grignard reagents has been devised[22] and since equilibration with either boron trifluoride etherate or an insoluble polystyrenesulfonic acid catalyst (Amberlyst-15) is facile.[23,24]

Results

We have investigated the cis-trans equilibria as a function of solvent in a number of anancomeric[25] 2-substituted cis-4,cis-6-dimethyl- and 2-substituted 2,4-dimethyl-1,3-dioxanes having unsaturated substituents and polar groups of the CH$_2$-X type (Scheme II).

Scheme I

R = H or CH$_3$

Scheme II

A   B

In all but one instance (Table I, footnote h) equilibration was effected by treating appropriate solutions (0.1-0.3 M) with beaded polystyrenesulfonic acid (Amberlyst-15) until equilibrium (approached from both sides) was reached. The results of the equilibrations are shown in Tables I (2-monosubstituted) and II (2,2-disubstituted 1,3-dioxanes).

Configurational Assignments

Eliel and Nader have shown[22] that r-2-methoxy-trans-4,trans-6-dimethyl-1,3-dioxane (Scheme II, A, R$_1$

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(10) (a) G. E. Booth and R. J. Ouellette, J. Org. Chem., 31, 544 (1966); (b) C. B. Anderson and D. T. Sepp, ibid., 32, 607 (1967); (c) E. L. Eliel and C. A. Giza, ibid., 33, 3754 (1968); (d) C. B. Anderson and D. T. Sepp, Tetrahedron, 24, 1707 (1968); (e) A. J. DeHoog, H. R. Buys, C. Altona, and E. Havinga, ibid., 25, 3365 (1969); (f) R. U. Lemieux, A. A. Pavia, J. C. Martin, and K. A. Watanabe, Can. J. Chem., 47, 4427 (1969); (g) cf. ref 7, 11-13, for further examples; (h) an exception to this general trend is found in certain 2-alkoxy-1,4-dioxanes; cf. ref 4 and 15.

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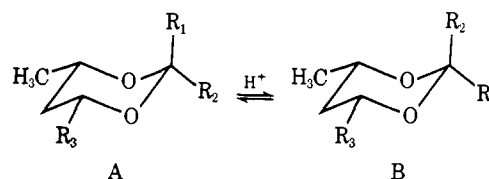(19) B. Coxon, Tetrahedron, 22, 2281 (1966).

(20) C. B. Anderson and D. T. Sepp, J. Org. Chem., 33, 3272 (1968).

(21) It has been suggested (ref 15, p 326) that the 1.62 kcal/mol equatorial preference of 2-carbomethoxytetrahydropyran, which exceeds the value in methyl cyclohexanecarboxylate (E. L. Eliel and M. C. Reese, J. Amer. Chem. Soc., 90, 1560 (1968)) by only 0.35 kcal/mol, may simply reflect the shorter syn-axial distance in the tetrahydropyran system.

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(23) E. L. Eliel and M. C. Knoeber, J. Amer. Chem. Soc., 90, 3444 (1968).

(24) F. W. Nader and E. L. Eliel, J. Amer. Chem. Soc., 92, 3050 (1970).

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Table I. Equilibria in 2-Substituted *cis*-4,*cis*-6-Dimethyl-1,3-dioxanes (Scheme II, R_2 = H, R_3 = CH_3)

Entry no. (compd)	R_1	Solvent $(\epsilon)^a$	K	$\Delta G°_{25}$,[b] kcal/mol	$\Delta G°$ for substituted Cyclohexane
1 (**1, 2**)	HC≡C—	CCl₄ (2.23)	0.70	+0.21 ± 0.02	−0.18,[d] −0.41[e]
2		Ether (4.22)	0.90	+0.06 ± 0.03	
3		CH₃CN (37.5)	4.92	−0.94 ± 0.03	
4 (**3, 4**)	C₆H₅C≡C—	CCl₄ (2.23)	0.60	+0.315 ± 0.03	
5		Ether (4.22)	1.00	0.00 ± 0.02	
6		CH₃CN (37.5)	2.77	−0.59 ± 0.01	
7 (**5, 6**)	C₆H₅	Hexane (1.90)	123.4	−2.86 ± 0.02	−3.0[f]
8		Benzene (2.27)	181.5	−3.08 ± 0.02	
9		Ether (4.22)	193.2	−3.12 ± 0.02[c]	
10		CH₃CN (37.5)	309.5	−3.40 ± 0.04	
11 (**7, 8**)	*p*-CF₃C₆H₄	Hexane (1.90)	182.2	−3.08 ± 0.02	
12		CCl₄ (2.23)	200.3	−3.14 ± 0.04	
13		Ether (4.22)	205.8	−3.16 ± 0.02[c]	
14		CH₃CN (37.5)	257.7	−3.29 ± 0.03	
15 (**9, 10**)	H₂C=CH	Ether (4.22)	⩽69.3	⩾−2.51 ± 0.07[h]	−1.35[g]
16 (**11, 12**)	CH₂Cl	Ether (4.22)	1168	−4.19 ± 0.06	

[a] Dielectric constants at 25°; *cf.* Landolt-Börnstein, "Zahlenwerte und Funktionen," Vol. II, 6th ed, Springer-Verlag, Berlin. Germany, 1959, p 613. [b] Errors are propagated standard deviations. [c] Taken from ref 24; all other values from this work. [d] Reference 28a. [e] Reference 28b. [f] Reference 30. [g] Reference 32. [h] This value is tentative. An initially "axial-rich" (**9**) mixture, containing **10** to **9** in a ratio of 7.8 to 1, reached a 63.9 to 1 ratio in 1 hr in the presence of boron trifluoride etherate. Since this was, within experimental error, the same ratio as that obtained upon similar treatment of a solution of pure equatorial isomer (**10**) for 2.5 hr, it was taken as the equilibrium ratio. However, in this particular instance, the ratio of **10** to **9** continued to increase for the initially axial-rich mixture whereas the ratio for the solution of equatorial isomer at first decreased to the presumed equilibrium value and then increased with time, probably due to decomposition of the axial compound. For related results see S. Kabuss, *Angew. Chem.*, **80**, 81 (1968); *Angew Chem., Int. Ed. Engl.*, **7**, 64 (1968).

Table II. Equilibria in 2,2-Disubstituted 2,4-Dimethyl-1,3-dioxanes (Scheme II, R_2 = CH_3, R_3 = H)

Entry no. (compd)	R_1	Solvent $(\epsilon)^a$	K	$\Delta G°_{25}$,[b] kcal/mol
17 (**13, 14**)	CH₂Cl	Cyclohexane (2.0)	1.015	−0.009 ± 0.004
18		Ether (4.22)	0.909	+0.058 ± 0.006
19		CH₃CN (37.5)	0.833	+0.108 ± 0.007
20		CH₃OH (32.6)	0.758	+0.17 ± 0.03
21 (**15, 16**)	CH₂Br	Cyclohexane (2.0)	0.826	+0.111 ± 0.004
22		Ether (4.22)	0.763	+0.159 ± 0.004
23		CH₃CN (37.5)	0.694	+0.22 ± 0.01
24 (**17, 18**)	CO₂C₂H₅	Cyclohexane (2.0)	0.0048	+3.16 ± 0.04
25		Ether (4.22)	0.0059	+3.0 ± 0.2
26		CH₂CN (37.5)	0.0013	+3.94 ± 0.06

[a] See footnote *a*, Table I. [b] Errors are propagated standard deviations.

= OCH₃, R_2 = H, R_3 = CH₃) reacts with a Grignard reagent in a highly stereospecific manner with retention of configuration to give the corresponding 2-axially substituted 1,3-dioxane. The diastereoisomeric equatorial ortho ester fails to react under similar conditions.[22] Thus, the configurational assignments of axial phenylethynyl **3** (Scheme II, A, R_1 = C₆H₅C≡C, R_2 = H, R_3 = CH₃), axial phenyl[22] **5** (A, R_1 = C₆H₅, R_2 = H, R_3 = CH₃), axial *p*-trifluoromethylphenyl[22] **7** (A, R_1 = *p*-CF₃C₆H₅, R_2 = H, R_3 = CH₃), and axial vinyl **9** (A, R_1 = H₂C=CH, R_2 = H, R_3 = CH₃) follow directly from the method of synthesis since they were all prepared in greater than 90% diastereoisomeric purity from the appropriate Grignard reagents.

The assignment of configuration to the 2-phenylethynyl diastereoisomers **3** and **4** on the basis of the Grignard synthesis of axial **3** was independently established by catalytic hydrogenation of the equatorial isomer **4** to give a product (**21**) identical in all respects with the only isomer obtained by condensation of hydrocinnamaldehyde and *meso*-2,4-pentanediol. Since all the known conformational energies of alkyl groups at C-2 are 4 kcal/mol or more,[24] and since the condensation proceeds under conditions of thermodynamic control,[23] the hydrogenation product **21** was assigned the *r*-2-(2'-phenylethyl)-*cis*-4,*cis*-6-dimethyl configuration

(Scheme II, B, R_1 = C₆H₅CH₂CH₂, R_2 = H, R_3 = CH₃) and the configuration of precursor **4** follows from that assignment. Similarly, the configuration of the equatorial 2-ethynyl isomer **2** (Scheme II, B, R_1 = HC≡C, R_2 = H, R_3 = CH₃) follows from the assigned *r*-2-(1',2'-dibromoethyl)-*cis*-4,*cis*-6-dimethyl configuration of its precursor **22** (Scheme II, B, R_1 = BrCH₂CHBr, R_2 = H, R_3 = CH₃). These assignments were corroborated and the configurations of the remaining diastereoisomeric pairs were assigned, on the basis of pmr spectral data given in Table III. For 2-substituted 1,3-dioxanes, the equatorial proton at C-2 in an axially substituted compound invariably resonates at lower field than the axial proton in its epimer.[22-24] Furthermore, the C-2 equatorial proton is noticeably long-range coupled to the equatorial proton at C-5 ($J_{2e,5e}$ = 0.9 Hz).[26] As a consequence of this coupling, the signals for the proton at C-2 are broader in the axially substituted 1,3-dioxanes than in the corresponding equatorial isomers. Finally, in both the 2-substituted and 2,2-disubstituted series, the chemical shifts of the C-2 substituents are diagnostic of configuration. In every instance the signal for an alkyl group is found at lower field in that diastereoisomer in which the group is

(26) J. Gelan and M. Anteunis, *Bull. Soc. Chim. Belg.*, **77**, 423 (1968), and references therein.

Table III. Chemical Shift Data for 2-Substituted 1,3-Dioxanes[a]

R₁	R₂	R₃	A			B		
			Compd	δ(R₁)	δ(R₂)	Compd	δ(R₁)	δ(R₂)
HC≡C	H	CH₃	1	2.47	5.54	2	2.36	5.08
C₆H₅C≡C	H	CH₃	3	ca. 7.30	5.76	4	ca. 7.30	5.32
C₆H₅	H	CH₃	5	7.10–7.34[b]	6.00	6	7.14–7.46[b]	5.35
p-CF₃C₆H₄	H	CH₃	7	7.55	6.03	8	7.60	5.41
H₂C=CH	H	CH₃	9	5.15–6.20[b,c]	5.15–6.20[b,c]	10	4.77–6.05[b,c]	4.77–6.05[b,c]
CH₂Cl	H	CH₃	11	3.62	5.04	12	3.39	4.63
CH₂Cl	CH₃	H	13	3.86	1.34	14	3.35	1.475
CH₂Br	CH₃	H	15	3.575	1.39	16	3.22	1.51
CO₂CH₂CH₃ (1)(2)	CH₃	H	17	(1) 4.19 (2) 1.32	1.375	18	(1) 4.14 (2) 1.23	1.49
CH₂OH (1)(2)	CH₃	H	19	(1) c (2) 2.325	1.275	20	(1) 3.27 (2) 2.25	

[a] In ppm from internal TMS, CCl₄ solution. [b] Tightly coupled pattern. [c] Overlapping peaks.

axial.[22–24,27] The possibility that the strongly anisotropic carboethoxy group in the 2-carboethoxy-2-methyl compounds 17 and 18 might reverse the normally downfield signal of an axial methyl group was eliminated by independent reduction of 17 and 18 to the corresponding 2-hydroxymethyl-2-methyl compounds 19 and 20. The 2-carbomethoxy isomer with the higher field methyl resonance, 17 (Scheme II, A, R₁ = CO₂C₂H₅, R₂ = CH₃, R₃ = H), gave the 2-hydroxymethyl-2-methyl isomer with the higher field methyl resonance, 19 (Scheme II, A, R₁ = CH₂OH, R₂ = CH₃, R₃ = H), and the epimeric ester with the lower field methyl signal, 18, gave the epimeric alcohol with the lower field methyl signal, 20.

Equilibria in 2-Substituted cis-4,cis-6-Dimethyl-1,3-dioxanes

Conformational free energies, in various solvents, for 2-substituted cis-4,cis-6-dimethyl-1,3-dioxanes (Scheme II, R₂ = H, R₃ = CH₃) containing polar and/or electron-rich substituents are given in Table I. Also included in the table for comparison purposes are the corresponding values for analogously substituted cyclohexanes.

Inspection of the data reveals that the conformational free energies of the 2-ethynyl group (entries 1–3, Table I) and the 2-phenylethynyl group (entries 4–6, Table I) are strongly solvent dependent. In the nonpolar solvent carbon tetrachloride, both groups prefer the axial orientation (entries 1 and 4), whereas in the polar solvent acetonitrile, the conformational preference is reversed and the equatorial isomers predominate at equilibrium (entries 3 and 6). The stability of axial 2-ethynyl (+0.21 kcal/mol) and 2-phenylethynyl (+0.315 kcal/mol) in the low dielectric solvent carbon tetrachloride solution is all the more striking in light of the conformational preference of ethynyl for the equatorial position in cyclohexane,[28] where an axial substituent is less crowded than at C-2 in a 1,3-dioxane.[29] This axial stability in the dioxane, and the solvent behavior of the equilibria, demonstrate the operation of a substantial generalized anomeric effect for the 2-ethynyl and 2-phenylethynyl substituents. Thus the generalized anomeric effect is not simply limited to systems possessing hetero substituents having unshared electron pairs, a

finding which raises important questions concerning the nature and origin of generalized anomeric stability. We shall return to this point below.

The ΔG° values, in diethyl ether, for a number of para substituted 2-aryl-1,3-dioxanes, including 2-phenyl (entry 9) and 2-p-trifluoromethylphenyl (entry 13) as well as 2-p-bromophenyl and 2-p-fluorophenyl, have been reported to be identical within experimental error (3.15 ± 0.03 kcal/mol).[24] These values are appreciably lower than those of the 2-alkyl-1,3-dioxanes,[24] contrary to what is found for substituted cyclohexanes,[30] and are almost identical with the corresponding values in cyclohexane itself (3.0 kcal/mol).[30] These apparent anomalies have been noted previously[24] and will be discussed more fully in another context.[31] The significance of these results to the problem at hand lies in the fact that the para substituent apparently has no major effect on the conformational equilibria of a 2-aryl-1,3-dioxane in diethyl ether. Entries 8–10 and 12–14 (Table I) show that, within two standard deviations, the most polar of these groups, p-trifluoromethylphenyl, has the same conformational energy as phenyl in a given solvent of dielectric constant greater than 2.2. Furthermore, in hexane solution, where solvation effects are expected to be minimal, the equatorial preference of p-trifluoromethylphenyl (entry 11) is 0.22 kcal/mol greater than that of phenyl (entry 7), contrary to primitive expectations on the basis of simple dipolar considerations. Clearly, these results are incompatible with any treatment of the anomeric effect which ascribes the origin of that effect simply to dipole–dipole interactions.

The ΔG° value given for a 2-vinyl group (entry 15) represents a minimum value (see footnote h, Table I) and any conclusions from the fact that it is larger than the reported conformational free energy of the vinyl group in the cyclohexane system[32] would be highly speculative, especially since the cyclohexane value was obtained indirectly from a pmr study of the hydroxyl resonance in 1-vinylcyclohexanol and 4-tert-butyl models by assuming additivity of ΔG° values of the geminal substituents,[32] an assumption which has been shown to be of doubtful validity.[33]

(27) K. Pihlaja and P. Ayras, Acta Chem. Scand., 24, 531 (1970), and references therein.
(28) (a) R. J. Ouellette, J. Amer. Chem. Soc., 86, 3089 (1964); (b) F. R. Jensen, C. H. Bushweller, and B. H. Beck, ibid., 91, 344 (1969).
(29) Cf. E. L. Eliel, Accounts Chem. Res., 3, 1 (1970).

(30) J. A. Hirsch in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967.
(31) E. L. Eliel, J. R. Powers, and W. F. Bailey, manuscript in preparation.
(32) R. J. Ouellette, K. Liptak, and G. E. Booth, J. Org. Chem., 31, 546 (1966).
(33) E. L. Eliel and R. M. Enanoza, J. Amer. Chem. Soc., 94, 8072 (1972).

The conformational free energy of a 2-chloromethyl group (Table I, entry 16) is the same, with the limits of experimental error, as that of 2-methyl (3.98 ± 0.9 kcal/mol).[24] Since this result suggests that the $\Delta G°$ values of CH_2-X groups will be very similar to that of CH_3, the "counterpoise" technique (wherein a substituent is pitted against CH_3) was employed to evaluate subtle differences in conformational preference of bulky substituents as a function of solvent. The equilibration results for 2,2-disubstituted 2,4-dimethyl-1,3-dioxanes (Scheme II, R_1 = CH_2Cl (13, 14), CH_2Br (15, 16), and $CO_2C_2H_5$ (17, 18), R_2 = CH_3, R_3 = H) are given in Table II and will be discussed below in connection with the reverse anomeric effect.[34]

Discussion. Gross dipole moment differences between diastereoisomers[35] will affect the solvent dependence of the equilibria in a predictable way. Since the electron-rich C-2 substituents act as polar electron-attracting groups relative to an sp^3 hybridized carbon, the equatorial isomers possess larger dipole moments than their axial epimers.[36] Qualitatively, the isomer of higher dipole moment is expected to be more stable in polar media[37] and this is indeed the trend found for the solvent-dependent equilibria listed in Table I. A more quantitative treatment of solvent effects, as given by Abraham,[38] includes quadrupole and higher order terms. In any event, the vapor phase energy difference between two conformational isomers is approached as the dielectric constant of the medium approaches unity so that in solvents of low dielectric constant intramolecular factors (steric, electrostatic, dipolar, etc., vide infra) dominate conformational equilibria.

In view of the rather low bond dipole of an ethynyl group (0.72–0.84 D),[34] it is difficult to ascribe the axial stability, in the low-dielectric solvent carbon tetrachloride, of the 2-ethynyl group (Table I, entry 1) and the 2-phenylethynyl group (Table I, entry 4) to dipolar or electrostatic interactions alone. Moreover, it has already been noted, on the basis of the equilibrium results for 2-phenyl and para-substituted 2-phenyl groups, that dipole-dipole interactions cannot be the sole factor governing generalized anomeric stability in nonpolar

solvents, since the equilibria are independent of the nature of the para substituent. The problem then becomes one of explaining the stability of the gauche conformation preferentially adopted by a moiety R-X-C-Y, where X is an atom having unshared electron pairs and Y is a ligand more electronegative than sp^3 hybridized carbon, without recourse to dipole-dipole interactions.

Recently, a number of authors have suggested that Altona's conception of the anomeric effect,[39] which involves donation of electrons from a lone pair orbital situated on X into the antibonding C-Y orbital, plays a significant role in determining anomeric stability.[40–42] Bond length measurements[39] and nqr studies[43] on halogenated 1,4-dioxanes as well as the results of an ab initio study of conformation and bond lengths in carbohydrate systems[40] are compatible with this interpretation. We feel that our results support this interpretation and allow for extension of the electron delocalization concept to the generalized anomeric effect. Such extension in terms of the valence bond description of double bond-no bond resonance, R—X—C—Y → R—X+=C- Y, as introduced by Brockway[44] and discussed by Pauling,[45] has the advantage of pictorial clarity. Resonance structures of this type describe the effect of double bond character of the C-X bond induced by the partial ionic character of the C-Y bond[45] formed by the same carbon. If one treats the nonbonded electrons as directed ligands and requires that double bond-no bond resonance occur only when the pair is located antiperiplanar to the C-Y bond, the gauche preference of a R-X-C-Y moiety is easily visualized (Scheme III) since no such stabilization is possible in the anti conformation.

Scheme III
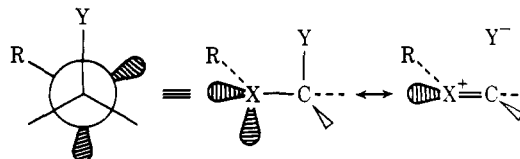
This representation implies a distinction between the electron donor (X) and the electron acceptor (Y). In valence bond terminology, the bond which possesses greatest ionic character will act as acceptor when both atoms, X and Y, have nonbonded electron pairs located antiperiplanar to the other atom, Y or X. Furthermore, the more ionic the C-Y bond the greater should be the anomeric stability, other factors (such as steric and medium effects) being equal. This is precisely the trend which has been observed[16] for anomeric stability.[46]

(34) In a 2,2-disubstituted 1,3-dioxane, a single methyl group at C-4 serves as a holding group. This group, in either diastereomer, must hold the equatorial conformation or else be forced into a highly crowded (and therefore little populated) syn-axial position with either one or the other substituent at C-2. Since 1,3-butanediol is much more readily available (for the synthesis of 4-methyl-1,3-dioxanes) than meso-2,4-pentanediol (for the synthesis of cis-4,6-dimethyl substituted dioxanes), we opted for the single 4-methyl holding group, especially since control experiments had shown[31] that equilibria in the 4-methyl and cis-4,6-dimethyl substituted systems are very similar.

(35) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman, San Francisco, Calif., 1963.

(36) The magnitude of this difference will, of course, depend on the nature of the C-2 substituent. The measured[24] 1.8 D difference in dipole moment between the p-trifluoromethylphenyl isomers 7 and 8 is large, as one might expect from consideration of the large dipole moment of trifluoromethylbenzene (2.6–2.8 D).[33] Both the 0.43 D dipole moment of toluene[33] and the 0.38–0.65 D dipole moment of cumene[33] indicate that there is only a small difference in dipole moment between the phenyl isomers 5 and 6. The reported dipole moments of propyne (0.72–0.77 D)[33] and phenylacetylene (0.72–0.84 D)[33] indicate that the dipole moment difference between the acetylenic diastereoisomers is somewhat larger than the difference for phenyl but smaller than the difference for p-trifluoromethylphenyl.

(37) (a) N. Sheppard, Advan. Spectrosc., 1, 288 (1959); (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley-Interscience, New York, N. Y., 1965.

(38) For leading references see (a) R. J. Abraham, H. D. Banks, E. L. Eliel, O. Hofer, and M. K. Kaloustian, J. Amer. Chem. Soc., 94, 1913 (1972), and (b) R. J. Abraham and M. A. Cooper, J. Chem. Soc. B, 202 (1967).

(39) (a) C. Altona, Ph.D. Thesis, University of Leiden, 1964, p 117; (b) C. Romers, C. Altona, H. R. Buys, and E. Havinga in "Topics in Stereochemistry," Vol. 4, N. L. Allinger and E. L. Eliel, Ed., Wiley-Interscience, New York, N. Y., 1969, pp 73–77.

(40) G. A. Jeffrey, J. A. Pople, and L. Radom, Carbohyd. Res., 20, 440 (1972).

(41) S. David, O. Eisenstein, W. J. Hehre, L. Salem, and R. Hoffmann, J. Amer. Chem. Soc., 95, 3806 (1973).

(42) G. Baddeley, Tetrahedron Lett., 1645 (1973).

(43) (a) E. A. C. Lucken, J. Chem. Soc., 2954 (1959); (b) P. Linscheid and E. A. C. Lucken, Chem. Commun., 425 (1970); see also J. F. A. Williams, Trans. Faraday Soc., 57, 2089 (1961); Tetrahedron, 18, 1477 (1962).

(44) L. O. Brockway, J. Phys. Chem., 41, 185 (1937).

(45) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, pp 314–315.

The axial preference of the C-2 acetylenic groups in nonpolar solvent (entry 1 and entry 4, Table I) may now be attributed to generalized anomeric stabilization of the axial isomers mainly by conformationally controlled double bond–no bond resonance[47] arising from the partial ionic character of the sp–sp^3 bond (Scheme IV).

Scheme IV
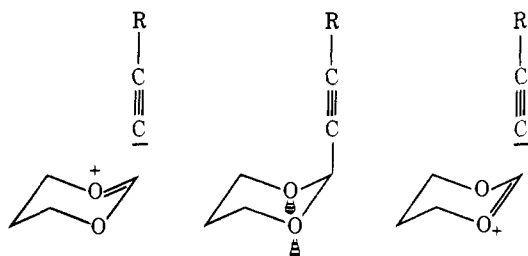
In general, such stabilization should decrease as the solvent polarity increases, since solvation of the non-bonded electrons will enhance the energy difference between a lone pair orbital and an antibonding orbital,[48] thereby decreasing the effective overlap. In polar solvents, medium effects dominate the equilibria.[38] The above conclusions are consistent with the finding that both propargyl alcohol[49] and hydroxyacetonitrile[50] exist almost exclusively in the HOCH$_2$C≡X gauche conformation in the gas phase.

Double bond–no bond resonance of this type would not be expected to contribute as significantly to the axial stability of 2-phenyl-1,3-dioxane since the sp^2–sp^3 bond is much less ionic than the sp–sp^3 bond. In any event, the fact that the ^{13}C shieldings of the methyl carbon of para substituted toluenes are essentially independent of the nature of the para substituent,[51] which indicates that the para substituent does not affect the charge density at this carbon, suggests that there should be no difference between 2-phenyl- and 2-para-substituted-phenyl-1,3-dioxanes in terms of double bond–no bond resonance stabilization since the σ* orbital is not affected. With this in mind, the fact that the equatorial preference in hexane solution of a 2-p-trifluoromethylphenyl substituent is 0.2 kcal/mol greater than that of a 2-phenyl substituent in this nonpolar solvent suggests that the strongly electron withdrawing p-CF$_3$ group induces a reverse anomeric effect in 2-p-trifluoromethylphenyl-1,3-dioxane. This comes about

because the phenyl ring is at the positive end of the F$_3$C–C$_6$H$_4$ dipole, and the positive charge next to the ring C$^+$–O moiety compensates for the overall enhanced dipole moment of F$_3$C–C$_6$H$_4$ relative to C$_6$H$_5$ (see below). In any case, the dipole of the CF$_3$ group is probably too far away from the dioxane ring dipole to engender a sizeable attraction (in the axial orientation) or repulsion (in the equatorial orientation).

In contrast, the equatorial preference of the imidazolium moiety (Scheme I) is probably predicated largely on dipolar factors, since a double bond–no bond canonic structure, similar to that shown in Scheme IV (but with imidazole instead of acetylide ion), would predict preferential stability of the axial imidazolidinium substituent, contrary to what is found experimentally.

Equilibria in 2-Substituted 2,4-Dimethyl-1,3-dioxanes

Inspection of the equilibration data for the geminally substituted compounds (Scheme II, A ⇌ B, R$_2$ = CH$_3$, R$_3$ = H) listed in Table II indicates that (1) the $\Delta G°$ values for the methyl–chloromethyl compounds (entries 17–20) and the methyl–bromomethyl compounds (entries 21–23) are small, (2) axial carboethoxy is strongly favored relative to axial methyl in all solvents[52] (entries 24–26), and (3) the preference of the C-2 substituent (CH$_2$Cl, CH$_2$Br, and CO$_2$C$_2$H$_5$) for the axial position increases as the dielectric constant of the medium increases. Before discussing these results it is instructive to consider the dipole situation in these compounds.

Dipole moments determined in cyclohexane solution for the 2-carboethoxy-2-methyl compounds **17** and **18** and the 2-chloromethyl-2-methyl compounds **13** and **14** are given in Scheme V. The dipole moments of the 2-

Scheme V. Dipole Moments

17
$\mu = 2.32 \pm 0.03$ D^a

13
$\mu = 2.69 \pm 0.02$ D^b

18
$\mu = 2.42 \pm 0.06$ D^a

14
$\mu = 3.16 \pm 0.01$ D^b
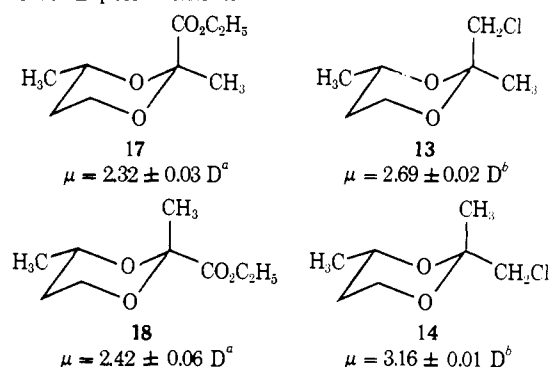
bromomethyl-2-methyl isomers **15** and **16** should be very similar to those of the 2-chloromethyl-2-methyl analogs since the C–Br and C–Cl bond moments are almost identical.[53]

The axial 2-carboethoxy isomer **17** has a slightly lower dipole moment than its epimer **18** in cyclohexane. Unfortunately, the preferred rotameric arrangement of the CO$_2$C$_2$H$_5$ group in these isomers cannot be evaluated from the measured dipole moments beyond stating that they are consistent with conformations in which the ester function (assumed to be in the s-trans conformation in cyclohexane solution) has C=O eclipsed with a

(46) We realize that the two unshared electron pairs of oxygen are not, in fact, equienergetic and that it may be better to consider one pair occupying an s, the other a p orbital; e.g., D. A. Sweigart, *J. Chem. Educ.*, **50**, 322 (1973), and references there cited; for the somewhat more complex case of 1,3-dioxane (interaction of two oxygens), see D. A. Sweigart and D. W. Turner, *J. Amer. Chem. Soc.*, **94**, 5599 (1972). However, for the purpose of resonance representation one may employ equivalent localized (hybrid) orbitals; alternatively, one may replace the anticoplanar (to the C–Y bond) hybrid orbital in Scheme III by p orbitals which would be parallel to the C–Y bond and thus in a position to overlap with it.

(47) This pictorial representation is entirely analogous to the "superjacent orbital control" interpretation of Salem and coworkers; cf. ref 41.

(48) The hypsochromic shift of the n → σ* transitions with increasing solvent polarity is well documented. See, for example, K. Kimura and S. Nagakura, *Spectrochim. Acta*, **17**, 166 (1961).

(49) (a) E. Hirota, *J. Mol. Spectrosc.*, **26**, 335 (1968); (b) K. Bolton, N. L. Owen, and J. Sheridan, *Nature (London)*, **217**, 164 (1968); (c) cf. ref 50b.

(50) (a) G. Cazzoli, D. G. Lister, and A. M. Mirri, *J. Chem. Soc., Faraday Trans. 2*, 569 (1973); (b) G. L. Bendazzoli, F. Bernardi, and P. Palmieri, *ibid.*, 579 (1973).

(51) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N. Y., 1972, p 202.

(52) Accordingly, the pmr spectrum in CCl$_4$ of 2-carboethoxy-2-methyl-1,3-dioxane (23) shows little, if any, conformational averaging: δ 1.35 (t, J = 7.5 Hz, 3 H), 1.38 (s, 3 H), 4.22 (q, J = 7.5 Hz, 2 H); compare pmr of 17, Table III.

(53) J. W. Smith, "Electric Dipole Moments," Butterworths, London, 1955, p 92.

ring C—O bond when axial and eclipsed with either a ring C—O or the C(2)—CH₃ bond when equatorial.

In contrast, it proved possible to calculate the dipole moments given in Scheme VI for each staggered con-

Scheme VI. Calculated Dipole Moments

$\mu = 1.1$ D $\mu = 2.9$ D

$\mu = 3.9$ D $\mu = 2.9$ D
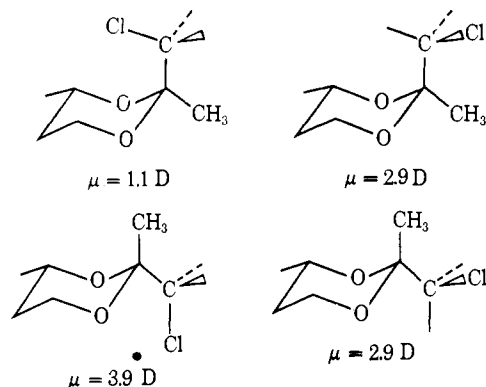
former of the diastereoisomeric 2-chloromethyl-2-methyl compounds.[54] If one disregards the low dipole moment "halogen inside" conformation of axial CH₂Cl on steric grounds, the calculated dipole moment of 2.9 D is in reasonable agreement with the experimental value (2.7 D). It is tempting to attribute the higher dipole moment of the equatorial CH₂Cl isomer to a contribution from the high dipole moment "halogen down" conformation. This rotamer, which places chlorine gauche to two oxygen atoms, is beset with the same repulsive enthalpic interaction as axial 5-chloro-1,3-dioxane (1.5 kcal/mol in cyclohexane).[38a] The magnitude of this interaction decreases linearly as the $E_T(30)$ value of the solvent increases.[55] Clearly, this rotamer will contribute only insofar as entropic stabilization, resulting from an increase in entropy of mixing, compensates for any enthalpic loss. Thus, its populations, and therefore the overall dipole moment of the equatorial CH₂Cl isomer, will increase as the solvent polarity increases. As there are only two enantiomeric conformations for the axial CH₂Cl group likely on steric grounds, its rotameric populations and dipole moment will be solvent independent.

Discussion. The increased axial preference of the C-2 substituents (CH₂Cl, CH₂Br, and CO₂C₂H₅) with increasing dielectric constant of the medium is somewhat startling in that, contrary to the solvent dependency found for most systems having polar substituents adjacent to ring heteroatoms,[9] the isomer of lower dipole moment is apparently stabilized, relative to its epimer, with increasing solvent polarity. It is difficult to rationalize this behavior in any straightforward manner. Solvation effects will influence the rotameric distribution of the equatorial CH₂X isomers as well as the relative proportion of s-cis ester contributing to the conformations of the CO₂C₂H₅ group. These changes, in turn, affect the solvent dependence of the diastereoisomer equilibria. Furthermore, the small differences in dipole moment between the dia-

stereoisomers, as reflected in the 0.1 D difference between **17** and **18** and the 0.5 D difference between **13** and **14** in cyclohexane solution, suggest that quadrupole terms[38] may well be the determining factor in the solvent dependence of these equilibria.

The high $\Delta G°$ values for the 2-carboethoxy-2-methyl equilibria (entries 24-26) may be viewed as resulting from either a destabilization of the equatorial CO₂C₂H₅ group or a stabilization of the axial. Neither of these approaches appear to us to be completely satisfactory, and since additivity of conformational energies is not to be expected in this instance[31,33] (the CO₂C₂H₅ group possesses neither C_{3n} nor $C_{∞v}$ symmetry), no firm conclusion may be drawn until the $\Delta G°$ value of the 2-carboethoxy group itself is known.[56]

The consistently higher proportion of axial CH₂Br compared to CH₂Cl at equilibrium in a given solvent (entries 17-19 and 21-23) is understandable in terms of the reverse anomeric effect which Coxon has suggested[19] may be operative in these systems because of the induction of a small positive charge at the carbon atom of the CH₂X group by the electron withdrawing X substituent. Electrostatic (or dipolar) repulsion between the CH₂X carbon and the C-4 and C-6 positions of the 1,3-dioxane ring, which is pictorially represented below,
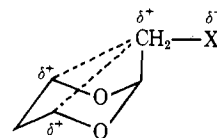
would be greater for axial CH₂Cl than axial CH₂Br since, formally, the charge on the CH₂Cl carbon must be greater than the charge on the CH₂Br carbon in order for the shorter C-Cl bond to have the same bond moment as the longer C-Br bond.[53] As one might expect this intramolecular interaction is most pronounced in (nonpolar) cyclohexane solution wherein the CH₂Cl substituent demonstrates a small, but real (−0.009 ± 0.004 kcal/mol), preference for the equatorial position (compare entries 17 and 21). In solvents of higher dielectric constant the difference in $\Delta G°$ between the 2-bromomethyl-2-methyl and 2-chloromethyl-2-methyl equilibria decreases.

In conclusion, it would appear that a small reverse anomeric effect is operative in the 2-halomethyl-2-methyl equilibria. However, the effect is of relatively minor importance in determining conformational equilibria, and the solvent dependence of the equilibrations is complex, presumably depending on quadrupole as well as dipole terms.[38]

Experimental Section

Melting points were determined on a Sargent "Mel-Temp" variable temperature heating block. Boiling points are uncorrected. Nmr spectra were recorded on Varian A-60A, Varian XL-100, or JEOLCO C60HL instruments; pertinent data are summarized in Table III. Additional nmr data are given in Table VII in the microfilm.[57] Infrared spectra were recorded on either a Perkin-Elmer 257 or 457 grating infrared spectrometer. Preparative glc was effected with Varian Aerograph Series 1520 and 2700 preparative chromatographs equipped with 0.25 in. aluminum columns.

(54) Based on the 1,3-dioxane ring geometry determined by A. J. de Kok and C. Romers, *Recl. Trav. Chim. Pays-Bas*, **89**, 313 (1970), assuming a C-C-Cl bond angle of 111° and a CH₃-C-C-Cl torsional angle of 58° and taking the C-O moment of 1.315 D from the observed 2.14 D dipole moment of 1,3-dioxane in cyclohexane solution[35] and a C-Cl moment of 1.93 D from the dipole moment of 1-chloro-2,2-dimethylpropane.[34]

(55) E. L. Eliel and O. Hofer, *J. Amer. Chem. Soc.*, **95**, 8041 (1973).

(56) The preparation of simple 2-carboethoxy-1,3-dioxanes has been delayed by synthetic difficulties.

(57) See paragraph at end of paper regarding supplementary material.

Microanalyses were performed by either Midwest Microlab, Inc., or Galbraith Laboratories, Inc.

The preparation of the 2-phenyl- (**5** and **6**) and 2-*p*-trifluoromethylphenyl- (**7** and **8**) -*cis*-4,*cis*-6-dimethyl-1,3-dioxanes has been described elsewhere.[22]

meso-**2,4-Pentanediol**. A solution of 60 ml of acetylacetone (58.2 g, 0.582 mol) in 80 ml of absolute ethanol containing 10 ml of triethylamine was hydrogenated over *ca.* 5 g of W-2 Raney nickel at an initial pressure of 1300 psi at 100°. Total hydrogen uptake ceased after 1.5 hr. The catalyst was removed by filtration and washed well with absolute ethanol, and the solution was concentrated at reduced pressure (*ca.* 20 mm). The viscous residue was distilled to give 58.8 g (97%) of mixed *meso*- and *dl*-diols: bp 52–52.5° (0.5 mm); $n^{20}D$ 1.4320 (lit.[54] bp 73° (3 mm), $n^{20}D$ 1.4327). Pure *meso*-2,4-pentanediol (62% of the reaction mixture) was isolated as described by Pritchard and Volmer.[58]

r-**2-Ethynyl-*cis*-4,*cis*-6-dimethyl-1,3-dioxane** (**2**). Equimolar quantities of 2,3-dibromopropanal[59] and *meso*-2,4-pentanediol were condensed in the presence of a catalytic amount of *p*-toluenesulfonic acid in methylene chloride solvent using a "heavy-solvent" Dean-Stark trap for collection of water. After the theoretical amount of water was collected the mixture was cooled to room temperature and stirred for 45 min with 1 g of anhydrous potassium carbonate to neutralize the catalyst. The mixture was filtered, the solid residue washed well with methylene chloride, and the solvent removed at reduced pressure (*ca.* 20 mm) to afford 58 g (94.5%) of crude *r*-2-(1′,2′-dibromoethyl)-*cis*-4,*cis*-6-dimethyl-1,3-dioxane (**22**) which was used in subsequent reactions. Distillation gave **22** in low recovery (due to thermal decomposition): bp 76–80° (0.25 mm), $n^{20}D$ 1.4984; ir (neat) 1375 (m), 1174 (vs), 1120 (vs), 1120 (vs), 1040 (s), 1028 (s) cm⁻¹; nmr (CCl₄), δ 1.0–1.6 (m, 2 H), 1.23 (d, *J* = 6.2 H, 6 H), 3.55–4.13 (m, 5 H), 4.74 (d, *J* = 2.7 Hz, 1 H).

Dibromide **22** was dehydrobrominated by a modification of a procedure described by Sheehan and Robinson.[50] Crude **22** (0.10 mol) was added dropwise with stirring to a solution of 16.83 g (0.30 mol) of potassium hydroxide in 100 ml of absolute ethanol allowing the temperature to rise to 60°. The solution was stirred an additional 0.5 hr, then cooled to 10° (ice–salt bath). Potassium bromide was removed by filtration and washed well with 20 ml of absolute ethanol. The combined filtrate and washings were refluxed 2.5 hr, cooled to room temperature, poured into 700 ml of water, and extracted with three 100-ml portions of chloroform. The extracts were washed twice with 10-ml portions of water, dried (MgSO₄), and concentrated at reduced pressure to give 28.4 g of solid product (94% crude yield). Two recrystallizations from hexane afforded **2**, mp 88–89°, in 54% overall yield based on 2,3-dibromopropanal. An analytical sample was prepared by sublimation: mp 88.5–89°; ir (CCl₄), 3310 (vs), 2140 (m), 1372 (s), 1132 (vs), 1172 (s), 1120 (vs), 1090 (s), 1025 (vs), 901 (s), 863 (s) cm⁻¹.

The mother liquor concentrate from the crystallizations was chromatographed on a 20-ft, 20% QF-1 on Chromosorb W (45–60 mesh) column at 150° to give additional **2** and a long-retention-time bromine-containing olefin identified as *r*-2-(1′bromovinyl)-*cis*-4,*cis*-6-dimethyl-1,3-dioxane (Scheme II, B, R_1 = $H_2C=CBr$, R_2 = H, R_3 = CH₃) on the basis of its spectral properties: ir (neat), 1630 (m), 1381 (m), 1174 (s), 1171 (vs), 1062 (s), 1030 (vs), 902 (m), 851 (m) cm⁻¹; nmr (CCl₄) δ 1.1–1.5 (m, 2 H), 1.22 (d, *J* = 6.0 Hz, 6 H), *ca.* 3.77 (m, 2 H), 4.82 (s, 1 H), 5.58 (m, 1 H), 6.07 (m, 1 H). *Anal.* Calcd for C₈H₁₃BrO₂: C, 43.46; H, 5.93; Br, 36.14. Found: C, 43.84; H, 5.97; Br, 36.03.

r-**2-Ethynyl-*trans*-4,*trans*-6-dimethyl-1,3-dioxane** (**1**). Two grams of equatorial ethynyl isomer **2**, dissolved in 6 ml of carbon tetrachloride to which 500 mg of Amberlyst-15 was added, was sealed in an ampoule under nitrogen and left for 5 days at room temperature. Analytical glc[57] indicated the presence of two isomers in a 1:1 ratio. The solution was decanted from the catalyst, neutralized by shaking with anhydrous potassium carbonate, and concentrated. Preparative glc of the concentrate on a 20-ft, 20% QF-1 on Chromosorb W (45–60 mesh) column at 106° afforded a 35% recovery (17.5% yield) of shorter retention time isomer **1**: ir (neat) 3270 (m. broad), 2110 (m), 1330 (m), 1120 (vs), 1072 (vs), 1026 (vs), 952 (s) cm⁻¹.

r-**2-Phenylethynyl-*trans*-4,*trans*-6-dimethyl-1,3-dioxane** (**3**). Phenylethynylmagnesium bromide (0.04 mol) in 40 ml of anhydrous THF was prepared under nitrogen by the method of Kroeger and

Nieuwland.[61] Chromatographically pure *r*-2-methoxy-*trans*-4,-*trans*-6-dimethyl-1,3-dioxane[22] (5.85 g, 0.04 mol) in 5 ml of THF was added at once with stirring. The mixture was then refluxed for 12 hr under nitrogen. In an attempt to avoid epimerization of the product dioxane by prolonged reflux, the mixture was worked up as described by Eliel and Nader[22] before completion of the reaction (as indicated by the presence of unreacted Grignard reagent[62]) and fractionated to give epimerized methoxydioxane precursor and 2.13 g (25%) of **3**, bp 161–165° (20 mm), in 90% isomeric purity by glc.[57] The distillate was further purified by preparative glc on a 20-ft, 25% QF-1 on Chromosorb A (60–80 mesh) column at 193° to give analytically pure **3**: $n^{20}D$ 1.5358; ir (neat) 2230 (w), 1486 (m), 1441 (m), 1382 (s), 1171 (s), 1118 (vs), 1069 (vs), 1021 (vs), 968 (m), 759 (s), 691 (s) cm⁻¹.

r-**2-Phenylethynyl-*cis*-4,*cis*-6-dimethyl-1,3-dioxane** (**4**). Transacetalization of 5.00 g (0.0224 mol) of phenylpropargylaldehyde diethyl acetal[63] with 2.54 g of (0.0224 mol) *meso*-2,4-pentanediol was effected in 22 ml of cyclohexane containing a catalytic amount of *p*-toluenesulfonic acid by removal of the cyclohexane–ethanol azeotrope through a short Vigreux column until the still-head temperature reached 80°. At this point heating was stopped and the mixture cooled to room temperature and stirred with 1 g of anhydrous potassium carbonate to neutralize the catalyst. The suspension was filtered, the solid washed well with cyclohexane, and the solvent removed at reduced pressure (*ca.* 20 mm) to afford a mixture containing 88% **4** and 12% **3**, as indicated by analytical glc.[57] Fractional crystallization from hexane gave **4**, mp 74–75°, in 52.5% yield. Sublimation afforded an analytical sample, mp 74.5–75°. The mother liquor from the crystallizations was concentrated and chromatographed on a 20-ft, 25% QF-1 on Chromosorb A (60–80 mesh) column at 193° to give shorter retention time **3** in 8% overall yield and an additional quantity of **4**: ir (CCl₄) 2258 (m), 2238 (m), 1488 (s), 1441 (s), 1400 (vs), 1375 (vs), 1350 (vs), 1155 (vs), 1018 (vs), 965 (s), 950 (s), 909 (s) cm⁻¹.

r-**2-Vinyl-*trans*-4,*trans*-6-dimethyl-1,3-dioxane** (**9**). A mixture of 12.86 g of *r*-2-methoxy-*cis*-4,*cis*-6- and *trans*-4,*trans*-6-dimethyl-1,3-dioxane (80%, 0.0704 mol of trans-4,trans-6 isomer) was added all at once to vinylmagnesium bromide[64] (0.076 mol) in anhydrous tetrahydrofuran under nitrogen. The mixture was refluxed for 25 hr under nitrogen[65] before work-up.[22] Fractionaction of the residue afforded an equilibrium mixture[24] of methoxydioxane precursor and 40% **9**, bp 156–160°, in 94% diastereoisomeric purity (by glc).[57] An analytical sample was obtained by repeatedly rechromatographing the product on a 20-ft, 25% QF-1 on Chromosorb A (60–80 mesh) column at 85°: ir (neat) 1442 (m), 1382 (s), 1178 (vs), 1130 (vs), 1099 (m), 1068 (s), 1005 (s), 986 (s), 928 (s), 795 (w) cm⁻¹.

r-**2-Vinyl-*cis*-4,*cis*-6-dimethyl-1,3-dioxane** (**10**). Transacetalization of 15.50 g (0.111 mol) of acrolein diethyl acetal with 11.55 g (0.111 mol) of *meso*-2,4-pentanediol in 20 ml of cyclohexane was effected as described above for **4**. Distillation afforded 10.54 g (67%) of glc pure[57] **10**: bp 153–154°; $n^{20}D$ 1.4335; ir (neat) 1430 (m), 1380 (s), 1345 (m), 1183 (vs), 1120 (vs), 1075 (s), 1055 (s), 1014 (vs), 990 (vs), 932 (m), 900 (m), 848 (m), 709 (w) cm⁻¹.

r-**2-Chloromethyl-*cis*-4,*cis*-6-** (**12**) and -*trans*-4,*trans*-6- (**11**) dimethyl-1,3-dioxane. A procedure similar to that described by Rondestvedt[66] for the preparation of the unbiased compound was employed. Transacetalization of 12.46 g (0.10 mol) of chloroacetaldehyde dimethyl acetal with 10.41 g (0.10 mol) of *meso*-2,4-pentanediol without solvent[66] gave 14.3 g (87%) of product: bp 70–75° (20 mm). Analysis by analytical glc[57] indicated that the product mixture contained 92.4% cis-4,cis-6 isomer **12** and 7.6% trans-4,trans-6 isomer **11**.[67] The epimers were separated and purified by preparative glc on a 6-ft, 20% FFAP on Chromosorb A (60–80 mesh) column at 155°: ir spectra of the cis-4,cis-6 isomer

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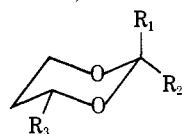(66) C. S. Rondestvedt, *J. Org. Chem.*, 26, 2247 (1961).
(67) The formation of so large an amount of the unstable (trans-trans) epimer is unusual.[23] Probably, because of the sluggish epimerization of **11** (see below), it is formed in a partially kinetically controlled process.

Table IV. Properties and Preparative Data of 2,2-Disubstituted 1,3-Dioxanes

Compd no.	R_1	R_2	R_3	Yield, %[a]	Column[b] (temp, °C)	Prop, %[c]	Bp,[d] °C	Calcd C	Calcd H	Found C	Found H
13	CH_2Cl	CH_3	CH_3	78	A (102)	38	73–75	51.07	7.98	51.27	8.06
14	CH_3	CH_2Cl	CH_3	78	A (102)	62	(12 mm)			51.20	7.92
15	CH_2Br	CH_3	CH_3	68	B (130)	51	99–106 (2.8 mm)	40.21	6.27	40.44	6.35
16	CH_3	CH_2Br	CH_3	68	B (130)	49	mp 23.5–24.5			40.40	6.30
17	$CO_2C_2H_5$	CH_3	CH_3	30	C (135)	36	65–70	57.43	8.62[e]	57.50	8.35[f]
18	CH_3	$CO_2C_2H_5$	CH_3	30	C (135)	64	(1.2 mm)			57.67	8.53[g]
19	CH_2OH	CH_3	CH_3	60	D (105)	25	70–80	57.51	9.65	57.54	9.56
20	CH_3	CH_2OH	CH_3	60	D (105)	75	(3.8 mm)			57.74	9.74
23	$CO_2C_2H_5$	CH_3	H	ca. 40			90 (5 mm)	55.16	8.10	55.00	8.23

[a] Combined yield of diastereoisomers. [b] A, 20-ft, 25% QF-1 on Chromosorb A (60–80 mesh); B, 20-ft, 20% QF-1 on Chromosorb W (45–60 mesh); C, 10-ft, 10% FFAP on Chromosorb W (60–80 mesh); D, same as C but 20% FFAP. [c] Proportion of diastereoisomers, reported as per cent of cis–trans mixture. [d] Boiling point of mixture. [e] Br calcd: 38.22. [f] Br found: 38.14. [g] Br found: 38.30.

(12) (neat) 1375 (s), 1332 (s), 1172 (vs), 1156 (s), 1121 (vs), 1030 (vs), 989 (m), 922 (m), 902 (m), 885 (m), 755 (m) cm⁻¹; in spectra of the trans-4,trans-6 isomer (11) (neat) 1440 (s), 1382 (s), 1208 (s), 1171 (s), 1122 (vs), 1079 (vs), 1030 (vs), 891 (m), 801 (m), 755 (m), 699 (m) cm⁻¹.

r-2-(2'-Phenylethyl)-cis-4,cis-6-dimethyl-1,3-dioxane (21). (a) Condensation of 6.71 g (0.05 mol) of hydrocinnamaldehyde and 5.20 g (0.05 mol) of meso-2,4-pentanediol in 20 ml of benzene containing a catalytic amount of p-toluenesulfonic acid monohydrate by the general method of Salmi,[68] as modified by Eliel and Knoeber,[23] gave 6.0 g (55%) of glc pure[57] 21: bp 86° (0.05 mm); n²⁰D 1.4980. (b) The same product (as evidenced by ir and nmr spectrum) was obtained in quantitative yield by catalytic hydrogenation of 1.0 g of r-2-phenylethynyl-cis-4,cis-6-dimethyl-1,3-dioxane (4) in 40 ml of ethyl acetate over 500 mg of 5% palladium on carbon at an initial pressure of 32 psi at room temperature: ir (neat) 1600 (m). 1493 (m), 1375 (s), 1172 (vs), 1125 (vs), 1035 (vs), 750 (m), 701 (s) cm⁻¹; nmr (CCl₄) δ 1.0–1.5 (m, 2 H), 1.13 (d, J = 6.2 Hz, 6 H), ca. 2.67 (m, 2 H), ca. 3.53 (m, 2 H), 4.40 (t, J = 5.0 Hz, 1 H), 7.11 (s, 5 H).

2,2-Disubstituted-1,3-dioxanes. This procedure represents a modification of that developed earlier by Knoeber.[23] Equimolar amounts of carbonyl compound and 1,3-butanediol in benzene (60 ml for a 0.1-mol run), and a catalytic quantity of p-toluenesulfonic acid monohydrate, were placed in a round-bottom flask of appropriate size fitted with a magnetic stirrer and a reflux condenser with a Dean-Stark trap. The reaction mixture was refluxed until the theoretical amount of water had collected in the trap, then cooled to room temperature, and 1 g of anhydrous potassium carbonate was added to neutralize the catalyst. Stirring was continued for 40 min. The mixture was then filtered, the solid residue washed with a 50-ml portion of benzene, and the benzene removed by flash evaporation. The residue was distilled and the diastereoisomers were separated by preparative gas chromatography. The isomers having an equatorial 2-methyl group had the shorter retention time. Yields and properties of products are listed in Table IV.

The 2-hydroxymethyl-2,4-dimethyl-1,3-dioxanes 19 and 20 were also prepared independently by lithium aluminum hydride reduction of the esters 17 and 18.

Equilibrations. For each pair of diastereoisomeric 1,3-dioxanes equilibrium was approached from the cis-rich and trans-rich sides. In general 0.1–0.3 M solutions were equilibrated over Amberlyst-15 (10–15 beads) in sealed ampoules under a nitrogen atmosphere at 25°. Periodically ampoules were opened and the solutions neutralized by shaking with powdered anhydrous potassium carbonate and analyzed by glc on either an F & M Chromatograph, Model 810, equipped with a thermal conductivity detector maintained at 295°, or a Hewlett Packard chromatograph, Model 5750B, equipped with a thermal conductivity detector maintained at 250° (injector block maintained at 220° on both instruments). Stainless steel columns (i.d. ¹/₈ in. or ¹/₁₆ in.) were used. Helium inlet pressure was maintained at 50 psi. When the same area ratios

were obtained from the initially cis-rich and trans-rich samples, it was deemed that equilibrium had been attained. Area ratios for the equilibrium mixtures were taken as the average of 6–10 determinations from each side. The corrected equilibrium constant for a system was calculated from the area ratio of that system and response ratios for the isomers which were determined at the same time and under the same conditions as the equilibrium mixture analyses. The analytical glc data and response ratios are collected in Table V.[57] All reported errors (Tables I and II) are propagated standard deviations.

In the case of the 2-vinyldioxane equilibrium, Amberlyst-15 catalysis led to decomposition at a rate comparable to the rate at which equilibrium was attained. Since the decomposition product (less than 2%) had a retention time very similar to that of the minor isomer, the analysis was suspect. When boron trifluoride etherate (1 drop per milliliter of solution) was employed as catalyst, equilibrium was attained before decomposition began.

Dipole Moments. Dielectric measurements were made using a Wissenschaftlich-Technische Werkstätten Dipolmeter DM 01 (measuring frequency 2 MHz) equipped with a DFL 2/D measuring cell thermostated at either 20.0 or 25.0°. Dielectric constants of solutions of pure compounds in cyclohexane were determined as described[69] and dipole moments were calculated by the method of Higasi.[70] Data obtained in these measurements are given in Table VI.[57] The reported errors in Scheme IV are propagated standard deviations.

Supplementary Material Available. Analytical glc data, data obtained in the measurement of dipole moments and elemental analyses, and nmr data additional to those in Table III will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24×reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-1798.

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