Conformational Analysis. XX. The Stereochemistry of Reaction of Grignard Reagents with Ortho Esters. Synthesis of 1,3-Dioxanes with Axial Substituents at C-2

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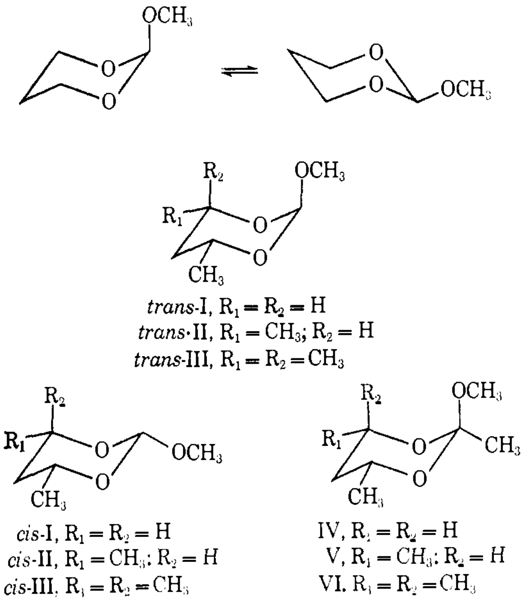
Abstract: The *cis* and *trans* isomers of 2-methoxy-4-methyl-1,3-dioxane, 2-methoxy-*r*-4,*cis*-6-dimethyl-1,3-dioxane, and 2-methoxy-4,4,6-trimethyl-1,3-dioxane (I–III) have been synthesized and their configuration is assigned on the basis of nmr data, dipole measurements, and, in the case of the 4,4,6-trimethyl compound, Overhauser effect studies. One stereoisomer each (the one with axial methoxyl) of 2-methoxy-2,4-dimethyl-, 2-methoxy-2,*r*-4,*cis*-6-trimethyl-, and 2-methoxy-2,4,4,6-tetramethyl-1,3-dioxane (IV–VI) has also been prepared. Reaction of the *trans* compounds (I–III, axial methoxyl) with methyl, ethyl, isopropyl, and variously *para*-substituted phenyl Grignard reagents proceeded smoothly at room temperature to give largely the corresponding 2-alkyl-1,3-dioxanes with *axial* 2-alkyl groups in purities generally in excess of 90% and yields ranging from 55 to 95%. The orthoacetates IV–VI reacted similarly. In contrast, the *cis* isomers (I–III, equatorial methoxyl) fail to react under corresponding conditions. Thus both the departing alkoxyl group and the incoming alkyl group prefer the axial position, presumably due to maximal orbital overlap with the unshared p electrons of the dioxane oxygens in the intermediate dioxocarbonium ion. The reaction proceeds with retention of configuration and provides an excellent method of synthesis of the very unstable 1,3-dioxanes with axial substituents (other than *t*-butyl) at the 2-position.

Although the reaction of ortho esters[3] with Grignard reagents[3,4] provides a well-known route to acetals and ketals and ultimately aldehydes and ketones, the stereochemistry of the reaction has never been studied, since ortho esters of the usual type $RC(OR')_3$ are devoid of the symmetry properties which would permit such an investigation. The recently reported synthesis of ring-substituted 2-methoxy-1,3-dioxanes[5]—which are readily obtained from variously substituted 1,3-diols and simple orthoformates or orthoacetates in the presence of acid catalysts—provided a handle for the stereochemical study.

Scheme I



trans-I, $R_1 = R_2 = H$
trans-II, $R_1 = CH_3$; $R_2 = H$
trans-III, $R_1 = R_2 = CH_3$

cis-I, $R_1 = R_2 = H$
cis-II, $R_1 = CH_3$; $R_2 = H$
cis-III, $R_1 = R_2 = CH_3$

IV, $R_1 = R_2 = H$
V, $R_1 = CH_3$; $R_2 = H$
VI, $R_1 = R_2 = CH_3$

Whereas 2-methoxy-1,3-dioxane itself exists as a mixture of axial and equatorial conformers in equilibrium (Scheme I), the introduction of alkyl groups in the 4- and/or 6-position leads to conformationally homogeneous (biased) ortho esters in which two of the alkoxy functions are locked in a relatively stable ring and the third, exocyclic one is either axial or equatorial, depending on the stereoisomer at hand. Thus in the *trans* isomers *trans*-I (*trans*-2-methoxy-4-methyl-1,3-dioxane), *trans*-II (*r*-2-methoxy-*trans*-4,*trans*-6-dimethyl-1,3-dioxane),[6] and *trans*-III (*trans*-2-methoxy-4,4,6-trimethyl-1,3-dioxane) the methoxy groups rest in the preferred[5] axial position whereas the majority of the alkyl groups are in the preferred equatorial position. In contrast, the corresponding *cis* isomers (*cis*-I, *cis*-II, and *cis*-III) have the methoxy groups and the majority of the alkyl groups equatorial. Fortunately, the diastereoisomeric orthoformates I, II, and III differ substantially in boiling point (*cf.* Table I)—presumably as a result of their large difference in dipole moment as predicted by the van Arkel dipole rule[7]—and were thus easily separated by fractional distillation. In the case of I and II, because of the anomeric effect[5b,8] the *trans* isomer (axial MeO)

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[1] Paper XIX: E. L. Eliel and E. C. Gilbert, *J. Amer. Chem. Soc.*, **91**, 5487 (1969).

[2] Preliminary communication: E. L. Eliel and F. Nader, *ibid.*, **91**, 536 (1969).

[3] H. W. Post, "The Chemistry of Aliphatic Ortho Esters," Reinhold Publishing Corp., New York, N. Y., 1943.

[4] *Cf.* M. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp 586–591.

[5] (a) M. C. Knoeber, Ph.D. Thesis, University of Notre Dame, Notre Dame, Ind., 1967; (b) E. L. Eliel and C. A. Giza, *J. Org. Chem.*, **33**, 3754 (1968).

[6] We are using the Beilstein system of nomenclature (see also IUPAC Bulletin 35, June 1969) for *cis–trans* isomers in rings with more than two substituents whose stereochemistry needs to be indicated. The lowest numbered substituent of specified stereochemistry (the 2-substituent where its stereochemistry is definitive, otherwise the 4-substituent) is used as the point of reference and is given the prefix *r*-. The stereochemistry of the remaining substituents is specified relative to the reference substituent as *c* (*cis*) or *t* (*trans*). (We have used *cis* and *trans* instead of *c* and *t* to achieve homogeneity of naming as between disubstituted and trisubstituted compounds.) We thank Dr. Kurt Loening, *Chemical Abstracts*, for a helpful discussion regarding this nomenclature.

[7] E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 217, 327.

[8] (a) R. U. Lemieux in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Division of John Wiley & Sons, Inc., New York, N. Y., 1967, p 709; (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A.

Table I. 2-Methoxy-1,3-dioxanes. Physical Properties and Chemical Shift Data[a]

Compd	Bp, °C (mm)	$n^{25}D$	μ[b]	ν_{H-2}	ν_{H-4}	ν_{MeO}	ν_{Me-4e}	ν_{Me-4a}
trans-I[5]	55–56 (18)	1.4158	1.96	308	*c*	194	66.2	
trans-II	57–58 (18)	1.4133	1.97	311	245.5[d]	195.5	66.2	
trans-III	58–59 (15)	1.4189	1.93	313	251	194	67, 66.5	82
trans-IV[i]	47–48 (15)	1.4182	1.79		*c*	192	66	
trans-V[i]	49–50 (15)		nd[e]		240.5[f]	191	65.4	
trans-VI[i]	54–55 (15)		nd[e]		245	190		79
cis-I[5]	69–70 (18)	1.4230	2.88	301	*c*	199	71.7	
cis-II	72–73 (18)	*g*	2.93	302	221.5[h]	200	72	
cis-III	72–73 (15)	1.4231	2.92	315	234	197	71, 74	76

[a] In Hz, at 60 MHz, in CCl_4 solution, downfield from TMS. [b] Dipole moment in benzene. [c] Complex signal. [d] J_{4a5e} = 3.8 Hz, J_{4a5a} = 10.4 Hz. [e] Not determined. [f] J_{4a5e} = 3.6 Hz, J_{4a5a} = 10.8 Hz. [g] Mp 38–39°, $n^{40}D$ 1.4140. [h] J_{4a5e} = 3.6 Hz, J_{4a5a} = 10.4 Hz. [i] The prefix *trans* refers to the relative stereochemistry of OMe-2 and the reference substituent Me-4.

predominates by a ratio of about 2:1 (the compounds are synthesized essentially under equilibrium conditions) and in the case of III where steric[9] and dipole effects oppose each other, the two isomers are obtained in about equal amounts.[10] In the preparation of the orthoacetates IV–VI, on the other hand, both steric and dipole effects strongly favor the stereoisomers shown, and since only a single compound was obtained in each of these three cases, it was assigned the *trans* configuration deemed[5b,9] to be the more stable one (axial OMe, equatorial Me).

Configurational Assignment

The physical properties listed in Table I suggest a configurational relation among the first six compounds, which have relatively low boiling points and refractive indices and a different relation among the last three compounds (of relatively high boiling points and refractive indices). In a previous paper,[5b] the low-boiling isomer of I was assigned the *trans* configuration on the basis of the chemical shift of its ortho ester proton (H-2) which resonates at higher field than that of the high-boiling (supposed *cis*) isomer; the assignment is in conformity with what is known about chemical shifts of H-2 protons in other 1,3-dioxanes.[9] It is now seen (Table I) that a similar difference in H-2 shifts exists in *trans*- and *cis*-II though not in *trans*- and *cis*-III where the *syn*-axial methyl group at C-4 not unexpectedly shifts the axial H-2 in the *cis* isomer downfield, so that it actually resonates at slightly lower field than that of *trans*-III. Additional distinctive features seen in the nmr spectra are concerned with the shifts of H-4a (where clearly seen), Me-4e, and MeO. Proton H-4a is shifted to lower field by the *syn*-axial methoxy group in the *trans* isomers, but the reciprocal effect on the methoxyl group is such that the axial methoxyl is upfield from the equatorial one. The equatorial Me-4 group is at lower field in those isomers having equatorial methoxyl than in those with axial methoxyl.

The dipole moments of the *trans* isomers in Table I are lower, by almost 1 D, than those of the *cis* isomers and thus provide not only an unassailable *correlation* of configuration, especially in conjunction with the nmr data, between the first six compounds in Table I on one hand and the last three on the other, but also strong presumptive evidence of the *actual* configuration. Calculations do indeed show that the *trans* isomers should have dipole moments about 1 D less than the *cis* epimers, but the configurational assignment is somewhat weakened by rather poor agreement between the calculated and observed values especially for the *trans* isomers.[11]

Fortunately, a completely convincing assignment of configuration was achieved in the case of *cis*- and *trans*-III through nuclear Overhauser effects.[12] In the case of *cis*-III, saturation of one of the singlet methyl signals led to an enhancement of the H-2 signal of 20%, whereas no corresponding enhancement (±2%) was achieved in *trans*-III by saturation of either singlet methyl. This result demonstrates without a doubt that H-2 in *cis*-III (but not in *trans*-III) is close to the axial Me-4 group and thus confirms the assigned configurations.

Grignard Reactions

Study of the reaction of *trans*-I–III and IV–VI on one hand and *cis*-I–III on the other with various Grignard reagents revealed striking differences. The *trans* isomers (Table II) reacted very smoothly in ether at room temperature to give products in which the exocyclic alkoxy group was replaced by alkyl (eq 1). While the reaction of Grignard reagents with simple orthoformates usually requires forcing conditions (refluxing for several hours, replacement of ether by higher boiling solvents, or evaporation to near-dryness[3,4]) the reactions summarized in Table II proceeded rapidly and exothermically.

When the Grignard product mixture was decomposed with ice-cold aqueous ammonium chloride or potassium carbonate (to avoid, as far as possible, alteration of either product or recovered starting material by acid, to which acetals are, of course, very sensitive) the reaction product was found to be very largely the 2-axially substituted (*i.e. trans*-substituted) 2-alkyl- or 2-aryl-1,3-dioxane. Little if any displacement of the two ring oxygen atoms occurred; the corresponding cleavage products were not found in the reaction mixture. The diastereoisomeric purity of the 2-substituted dioxanes formed (determined by glpc analysis) was usually in ex-

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Morrison in "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1965, p 375; (c) S. J. Angyal, *Angew. Chem.*, **81**, 172 (1969); *Angew. Chem. Intern. Ed. Engl.*, **8**, 157 (1969).

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

(10) Equilibration results for compounds II and III will be discussed in a forthcoming publication: F. W. Nader and E. L. Eliel, *ibid.*, in press.

(11) The calculated dipole moment of the stable "Me-outside" rotamer of *trans*-II is *ca.* 1.54 D (the precise value depends, of course, on assumptions regarding the exact geometry and group dipole moments). The agreement for *cis*-II is slightly better: the symmetrical "Me-up" rotamer has μ = 2.49 D and the enantiomeric "Me-up" rotamers have μ = 3.25 D. The observed moment of 2.93 D would then correspond to 55% of the two latter conformations and 45% of the former (which appears too high a percentage).

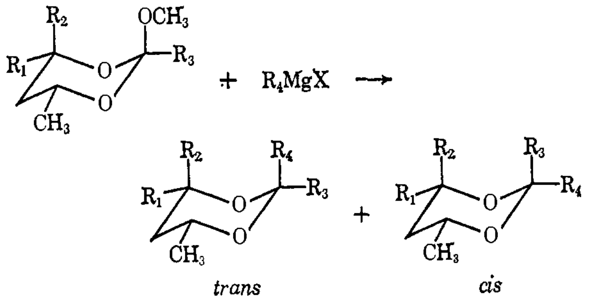
(12) F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **87**, 5250 (1965).

Table II. Reaction of *trans*-2-Methoxy-1,3-dioxanes with Various Grignard Reagents (eq 1)

2-Methoxy-1,3-dioxane	Purity,[a] %	Grignard reagent	Product	Purity,[b] %	Yield, %
trans-I	100	CH_3MgI	*trans*-VII	86	67
trans-I	95	Me_3CMgCl	4-Methyl-1,3-dioxane[c,d]		75
trans-II	100	CH_3MgI	*trans*-VIII	90	70
trans-II	100	C_2H_5MgI	*trans*-IX[e]	95	75
trans-II	89	$(CH_3)_2CHMgBr$	*trans*-X	90	63
trans-II	94	C_6H_5MgBr	*trans*-XI	95	95
trans-II	94	*p*-FC_6H_4MgBr	*trans*-XII	95	94
trans-II	94	*p*-BrC_6H_4MgBr	*trans*-XIII	95	55
trans-II	94	*p*-$CF_3C_6H_4MgBr$	*trans*-XIV	95	89
trans-III	100	CH_3MgI CH_3MgBr[f]	*trans*-XV	82	62
trans-III	95	C_6H_5MgBr	*trans*-XVI	73	72
trans-IV[g]	~100	C_2H_5MgI	XVII[d]	>95	55
trans-V[g]	~100	CD_3MgI	XVIII	>98	55

[a] Diastereoisomeric purity of starting material, remainder *cis* isomer. [b] Diastereoisomeric purity of reaction product. [c] No adduct isolated, only reduction occurs. [d] Product identified by nmr.[5,9] [e] *Ca.* 5% starting material recovered, composition 30% *trans* and 70% *cis* isomer. [f] Identical results were obtained with the two Grignard reagents. [g] See Table I, footnote *i*.

cess of 90% and in all cases exceeded 70% (see Table II);[13] in assessing the meaning of this finding it must be kept in mind that the 2-axially substituted 1,3-dioxanes are less stable than their equatorial epimers by about 4 kcal/mol[10,14] and that epimerization is relatively facile so that despite the mild reaction and work-up conditions the possibility of slight epimerization in the Grignard solution (containing $MgBr_2$) cannot be ruled out. However, even if 90% *trans* isomer does represent the true composition of the product, the kinetically controlled product composition differs from the thermodynamically controlled one by a ratio which corresponds to 5.3 kcal/mol[15] difference in free energy.



(1)

VII–XVIII

$R_3 = H$

VII, $R_1 = R_2 = H$; $R_4 = CH_3$

VIII, $R_1 = CH_3$; $R_2 = H$; $R_4 = CH_3$

IX, $R_1 = CH_3$; $R_2 = H$; $R_4 = C_2H_5$

X, $R_1 = CH_3$; $R_2 = H$; $R_4 = CH(CH_3)_2$

XI, $R_1 = CH_3$; $R_2 = H$; $R_4 = C_6H_5$

XII, $R_1 = CH_3$; $R_2 = H$; $R_4 = p\text{-}FC_6H_4$

XIII, $R_1 = CH_3$; $R_2 = H$; $R_4 = p\text{-}BrC_6H_4$

XIV, $R_1 = CH_3$; $R_2 = H$; $R_4 = p\text{-}CF_3C_6H_4$

XV, $R_1 = R_2 = R_4 = CH_3$

XVI, $R_1 = R_2 = CH_3$; $R_4 = C_6H_5$

XIX, $R_1 = R_2 = H$; $R_4 = C_6H_5$

$R_3 = CH_3$

XVII, $R_1, R_2 = H$; $R_4 = C_2H_5$

XVIII, $R_1 = CH_3$; $R_2 = H$; $R_4 = CD_3$

Nmr chemical shift parameters for the products are summarized in Table III.

Table III. Chemical Shifts[a] in *cis*- and *trans*-2-Substituted 1,3-Dioxanes[b]

Compd	ν_{H-2}	ν_{H-4a}
trans-VII	294	*Ca.* 236
cis-VII	273	*Ca.* 225
trans-VIII	310[c]	237
cis-VIII	273[d]	215
trans-IX	290	235.5
cis-IX	262	216.4
trans-X	255.5[e]	233
cis-X	249[f]	216
trans-XI	360	227.5
cis-XI	321.5	226.2
trans-XII	371.8	234
cis-XII	321	227.5
trans-XIII	357.8	225
cis-XIII	320.8	228.4
trans-XIV	362	226
cis-XIV	324.7	229
trans-XV	304	238
cis-XV	286	235
trans-XVI	351	247
cis-XVI	336	235
trans-XIX	352	*Ca.* 240
cis-XIX	322	*Ca.* 235

[a] In Hz at 60 MHz, in CCl_4 solution, downfield from TMS. [b] There are no substantial differences in shift patterns of axial and equatorial 2-aryl substituents. [c] Me-2a at 80 Hz. [d] Me-2e at 72 Hz. [e] $C\mathit{H}(CH_3)_2$-2a at 137 Hz. [f] $(CH_3)_2C\mathit{H}$-2e at 100 Hz.

trans-2,4-Dimethyl-1,3-dioxane (*trans*-VII) and *r*-2,-*trans*-4,*trans*-6-trimethyl-1,3-dioxane (*trans*-VIII) had been previously characterized[9] and their configuration assigned on the basis of chemical shift arguments pertinent to the Me-2 group and the H-2 proton. A similar configurational assignment may be made to the remaining dioxanes listed in Table III on grounds that the axial H-2 for the *cis* isomers (synthesized from appropriate aldehydes and *meso*-2,4-pentanediol in the presence of a mineral acid catalyst[6]) resonates at higher field than the equatorial H-2 for the *trans* isomers. Perhaps more convincing is the finding that *all* the isomers obtained in the Grignard synthesis and assigned the *trans* (axial) configuration were converted readily, by treatment with acid, into their (more stable) epimers which may thus be assigned the equatorial or *cis* configuration. (The *trans*-2-alkyl compounds are actually partially converted into their *cis* epimers upon standing in carbon tetra-

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(13) While the reaction was found to be independent of the Grignard reagent, *t*-butylmagnesium chloride did not yield any 2-alkyl-1,3-dioxane. In several experiments under various conditions the only product found was the reduction product (see Table II).

(14) K. Pihlaja and S. Luoma, *Acta Chem. Scand.*, 22, 2401 (1968).

(15) Namely 4 kcal for the excess stability of the *cis* isomer and 1.3 kcal for the 9:1 preference of the *trans* isomer in the Grignard product.

chloride solution, probably due to adventitious acid. The solutions may be stabilized by the addition of a drop of pyridine.)

In contrast to the *trans*-substituted 2-methoxydioxanes (axial methoxyl), the *cis*-substituted epimers of I and II (equatorial methoxyl) proved to be completely unreactive toward Grignard reagents in ether at room temperature (Table IV).

Table IV. Reactions of *cis*-2-Methoxy-1,3-dioxanes with CH_3MgI

Compd	Purity,[a] %	Recovered starting material, %	Purity,[b] %	Reaction[c] product (%)	Yield, %
cis-I	94	87	89	*trans*-VII (87)	6
cis-II	100	80	*d*	*e*	0
cis-III[f]	97	*Ca.* 70[g]	74	*trans*-XV (80)	20
Mixed I	31	*d*	82	*trans*-VII (88)	51
Mixed I[h]	*Ca.* 35	*d*	*d*	*trans*-XIX (78)	58

[a] Of starting material: *cis* isomer, remainder *trans*. [b] Of recovered starting material. [c] Diastereoisomeric purity in parentheses. [d] Not determined. [e] None detected by glpc. [f] Using CH_3MgBr the same result was obtained. [g] During work-up complete decomposition occurred in the distillation. [h] Reaction with C_6H_5MgBr.

Partially epimerized starting material (epimerization evidently occurs in the work-up, or else reaction of the epimerized ortho ester with the Grignard reagent would have occurred) was recovered in high yield. Only with *cis*-III a small amount of product (of the same composition as that obtained from *trans*-III) resulted; this may have been due to epimerization of *cis*-III in the ether solution by $MgBr_2$ prior to reaction or (less likely) to reaction *via* a skew-boat shaped transition state (*vide infra*) which, in the case of III, may be more ready to attain because of the steric compression of the axial methyl substituent engendered in the chair. Mixtures of *cis*- and *trans*-I were also treated with methylmagnesium iodide and phenylmagnesium bromide (Table IV); in this case it is clear from the results that the recovered starting material is mainly the *cis* component and that the reaction product is obtained largely if not exclusively from the *trans* component. These results show that in an actual preparation of the otherwise inaccessible 2-axially substituted 1,3-dioxanes, it may not be necessary to separate the stereoisomeric 2-methoxy-1,3-dioxane precursors at all, as long as the starting material is reasonably rich in the axially substituted epimer.

Reaction Mechanism

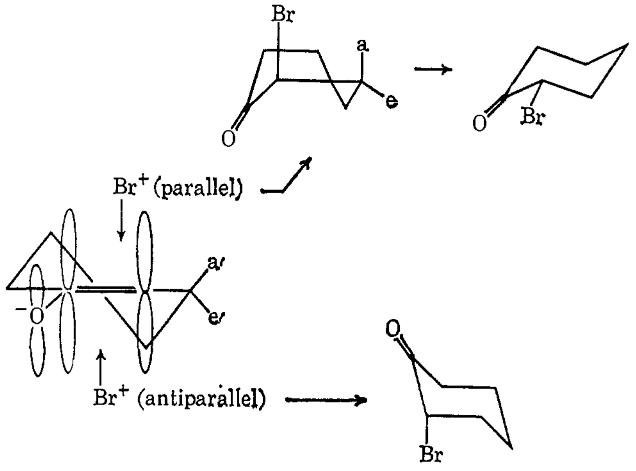
The results presented indicate that axially substituted 2-methoxy-1,3-dioxanes react smoothly with Grignard reagents with retention of configuration to give axially substituted 2-alkyldioxanes. Equatorially substituted 2-methoxy-1,3-dioxanes are essentially inert under these conditions. The minor deviations from these statements which have been observed may or may not be real; they could be explained by small amounts of epimerization occurring during work-up and, in some cases, during the Grignard reaction itself. Attempts to replace the Grignard reagents by alkyllithiums failed completely; no reaction occurred.

The results are best explained on a conformational basis. Generally speaking, two types of effects have been distinguished[16] in reactions of six-membered rings—stereoelectronic effects and steric effects. Stereoelectronic effects imply an optimal spatial arrangement of the electrons or electron pairs involved in a reaction; for example, the antiperiplanar arrangement of the bonds which are broken in an E2 elimination reaction. When this arrangement cannot be attained without undue distortion of the molecule, the reaction may fail or may become extremely slow. Steric effects refer to a crowding of reactants or substituents in either the ground state or the transition state and sometimes also to other unfavorable interactions, such as angle deformation or torsional strain, which may be incurred in either of these states. If the interaction is greater in the transition state than in the ground state, the reaction is slowed down (as compared to a model reaction in which there are no steric factors) whereas steric interactions in the ground state which are relieved in the transition state lead to steric acceleration.

Extensive studies, especially by Barton,[17,18] Corey,[19] and Djerassi,[20] have shown that in reactions involving transition from π-electron systems to σ-electron systems—for example, ionic addition to olefins[17,18] or bromination or protonation of enolate ions[19,20]—the incoming group or groups will approach in the plane of the π electrons, *i.e.*, generally axially. A corresponding stereoelectronic constraint is found in the reverse reactions, elimination and enolate formation; here again the axial group or groups are abstracted preferentially.

The stereoelectronic restraints in addition reactions normally ensure that the incoming group or groups occupy the axial position (Scheme II, "antiparallel addition"[21]). However, it has been pointed out[20,21] that steric factors may impede addition along the direction of the axes of the π electrons in such a way as to produce an axially substituted chair. If that happens, as for example in the bromination of enolates derived from 3-ketosteroids in which antiparallel attack is impeded

Scheme II



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(16) Reference 8b: (a) p 81; (b) p 92; (c) p 307.

(17) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4284 (1954); D. H. R. Barton, *Experientia, Suppl.*, II, 121 (1955).

(18) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).

(19) E. J. Corey, *Experientia*, **9**, 329 (1953).

(20) R. Villotti, H. J. Ringold, and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 5693 (1960).

(21) J. Valls and E. Toromanoff, *Bull. Soc. Chim. Fr.*, 758 (1961).

Table V. Yields and Properties of 2-Methoxy-1,3-dioxanes

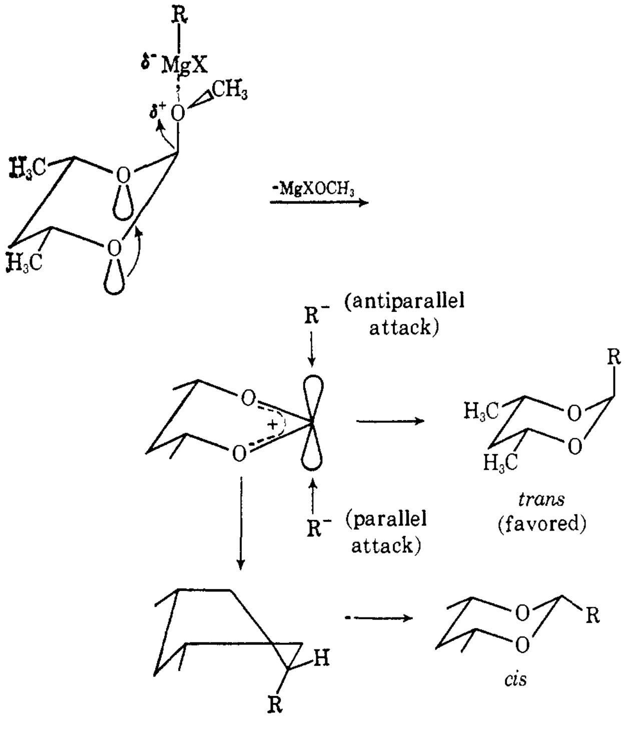
2-Methoxy-1,3-dioxane	Formula	Yield,[a] %	Bp, °C (mm)	Analysis Calcd C	Analysis Calcd H	Analysis Found C	Analysis Found H
4-Me[5]	*trans*-I	65	55–56 (18)				
	cis-I		69–70 (18)				
r-4,*cis*-6-di-Me	*trans*-II	80	57–58 (18)	57.53	9.59	57.24	9.60
	cis-II		72–73 (18)[b]	57.53	9.59	57.66	9.43
4,4,6-tri-Me	*trans*-III	61	58–59 (15)	60.02	10.00	59.86	9.96
	cis-III		72–73 (15)	60.02	10.00	59.57	10.10
cis-2,*r*-4-di-Me	IV (*trans*)[c]	65	47–48 (15)	57.53	9.59	57.31	9.59
cis-2,*r*-4-di-Me	V (*trans*)[c]	61	49–50 (15)	60.02	10.00	59.64	9.76

[a] Overall, *cis–trans* mixture. [b] Mp 38–39°. [c] See Table I, footnote *i*.

by the *syn*-axial methyl group at C-10, attachment to the opposite π lobes ("parallel attack,"[21] see Scheme II) may occur. This type of attack still involves approach of the reagent in the direction of the π electrons (favorable stereoelectronic factor) but it leads to a twist boat-shaped transition state (unfavorable steric factor). (The product may, of course, revert to the chair form later.) As already mentioned, parallel attack is thus sterically disfavored to the point where it normally does not occur at all; only in cases where antiparallel attack is also strongly disfavored by steric factors of other types does parallel attack normally come to the fore.

The application of these concepts to the Grignard-orthoformate reaction is now straightforward. As shown in Scheme III the stereolectronic factor in this case requires departure of the alkoxy group (probably catalyzed by MgX_2 or RMgX, in view of the inertness of RLi) along the axis of the π electrons in the developing dioxocarbonium ion. This type of departure is facile for the axial alkoxy group but in the case of an equatorial alkoxy group would require a boat-shaped transition state, since in the chair form the axis of the $C-OCH_3$ bond which breaks cannot be properly aligned for overlap with the p electrons of the ring oxygens. Since the twist boat form in 1,3-dioxanes is disfavored, *vis-à-vis* the chair, by nearly 6 kcal/mol,[14] the inertness of the equatorially substituted 2-alkoxy-1,3-dioxanes is readily explained.

Scheme III



Similar arguments apply to the direction of addition of the alkyl groups of the Grignard reagents to the dioxocarbonium ion intermediates. The preferred addition (antiparallel) will be from the top side (Scheme III) so as to produce the axially substituted 2-alkyldioxane in the chair form. Addition from the bottom side (parallel) would have to proceed *via* a boat-shaped transition state which is disfavored by the instability of the dioxane skew boat.[14] This mode of addition, followed by ring inversion, would give rise to an equatorially substituted 2-alkyldioxane; it is thus clear why this product is not formed in major amount.

For the general case of the Grignard-orthoformate reaction the present result implies a two-stage reaction: first formation of a dioxocarbonium ion catalyzed by RMgX or MgX_2 and then reaction of the ion with the nucleophilic alkyl group of the Grignard reagent. Stereoelectronic and steric factors are important in both stages. In the dioxane series, as shown in Table II, the reaction provides ready access to the very unstable and otherwise inaccessible isomers in which the 2-substituent is axial. The conformational behavior of these compounds may thus be studied readily and will form the subject of a forthcoming paper.[10]

Experimental Section

General Procedure for Synthesis of 2-Methoxy-1,3-dioxanes. This procedure represents a modification of that developed earlier by Knoeber[5a] which was reported previously.[5b] In a 250-ml round-bottomed flask equipped with a magnetic stirrer, condenser for downward distillation, and heating mantle are placed 0.2–0.3 mol (21.2–31.8 g) of trimethyl orthoformate, the equivalent amount of the 1,3-diol,[22] 40–60 ml of cyclohexane, and a catalytic amount of *p*-toluenesulfonic acid. The mixture is heated with stirring and the azeotrope of cyclohexane and methanol formed is distilled until the overhead temperature reaches 80°. At this point heating is stopped and the mixture is cooled to room temperature and stirred for 1–2 hr with 1–2 g of anhydrous potassium carbonate until the acid is neutralized. The suspension is filtered, the solid washed twice with ether, and the combined product and ether are subjected to distillation first at atmospheric then at reduced pressure through a short Vigreux column, to obtain the product which boils over a 12–15° range.

Separation of the isomers was effected by distillation through a 3-ft spinning band column at a reflux ratio in excess of 5:1 at water aspirator pressure. The distillate is collected (and stored) over

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[22] Butane-1,3-diol and 2-methylpentane-2,4-diol were obtained from Aldrich Chemical Co. *meso*-2,4-Pentanediol was prepared following the procedure given by J. G. Pritchard and R. L. Vollmer, *J. Org. Chem.*, **28**, 1545 (1963).

Table VI. Properties of Axially Substituted 2-Alkyl- and 2-Aryl-1,3-dioxanes

Compound	Formula	Bp, °C (mm)	Analysis: Calcd C	Calcd H	Found C	Found H
trans-2,4-di-Me	*trans*-VII	128–129 (745)	62.07	10.35	62.25	10.49
r-2,*trans*-4,*trans*-6-tri-Me	*trans*-VIII	135–136 (745)	64.61	10.77	64.76	10.90
r-2-Et-*trans*-4,*trans*-6-di-Me	*trans*-IX	152–153 (745)	66.67	11.11	66.54	11.20
r-2-*i*-Pr-*trans*-4,*trans*-6-di-Me	*trans*-X	51–52 (15)	68.35	11.39	68.31	11.44
r-2-C_6H_5-*trans*-4,*trans*-6-di-Me	*trans*-XI	57–58 (0.1)[a]	75.00	8.33	74.85	8.29
r-2-(*p*-FC_6H_4)-*trans*-4,*trans*-6-di-Me	*trans*-XII	68–69 (0.2)[b]	68.77	7.14	68.33	7.09
r-2-(*p*-BrC_6H_4)-*trans*-4,*trans*-6-di-Me	*trans*-XIII	91–93 (0.1)[c]	53.14	5.53	53.16	4.93
r-2-(*p*-$CF_3C_6H_4$)-*trans*-4,*trans*-6-di-Me	*trans*-XIV	83–85 (0.1)[d]	60.00	5.77	60.13	5.95
trans-2,4,4,6-tetra-Me	*trans*-XV	51 (30)	66.67	11.11	66.18	11.04
trans-2-C_6H_5-4-Me	*trans*-XIX	73 (0.2)	74.16	7.86	73.69	7.86

[a] Mp 41–43°. [b] Mp 38–39°. [c] Mp 57–59°. [d] Mp 36–37°.

Table VII. Properties of Equatorially Substituted 2-Alkyl- and 2-Aryl-1,3-dioxanes

1,3-Dioxane	Formula	Bp, °C (mm)	Analysis: Calcd C	Calcd H	Found C	Found H	Yield, %
cis-2,4-di-Me	*cis*-IV	128–129 (745)	62.07	10.35	62.18	10.71	*a*
r-2,*cis*-4,*cis*-6-tri-Me	*cis*-VIII	55–56 (40)	64.61	10.77	64.33	10.77	*b*
r-2-Et-*cis*-4,*cis*-6-di-Me	*cis*-IX	40–41 (15)	66.67	11.11	66.32	11.24	70
r-2-*i*-Pr-*cis*-4,*cis*-6-di-Me	*cis*-X	56–57 (18)	68.35	11.39	68.16	11.41	84
r-2-C_6H_5-*cis*-4,*cis*-6-di-Me	*cis*-XI	64–65 (0.3)	75.00	8.33	74.78	8.49	65
r-2-(*p*-FC_6H_4)-*cis*-4,*cis*-6-di-Me	*cis*-XII	56 (0.05)	68.57	7.14	68.38	7.13	*c*
r-2-(*p*-BrC_6H_4)-*cis*-4,*cis*-6-di-Me	*cis*-XIII	*d*	53.14	5.53	53.20	5.81	60
r-2-(*p*-$CF_3C_6H_4$)-*cis*-4,*cis*-6-di-Me	*cis*-XIV	64–65 (0.01)[e]	60.00	5.77	59.97	5.93	68
cis-2,4,4,6-tetra-Me	*cis*-XV	131–133 (745)	66.67	11.11	66.42	11.22	*f*
cis-2-C_6H_5-4-Me	*cis*-XIX	72 (0.2)	74.16	7.86	74.05	7.92	85

[a] Prepared by $LiAlH_4$ reduction of I, forthcoming publication. [b] Prepared by $LiAlH_4$ reduction of II. [c] Prepared by epimerization of *trans*-XII. [d] Mp 97–98°. [e] Mp 38–39°, prepared from *p*-$CF_3C_6H_4CH(OEt)_2$, available from *p*-$CF_3C_6H_4MgBr$ and triethyl orthoformate, and *meso*-pentane-2,4-diol. [f] Prepared by $LiAlH_4$ reduction of III.

anhydrous potassium carbonate to avoid epimerization by adventitious acid. The *trans* (axial) isomer has the lower boiling point. The isomers are readily obtained in 94–98% purity. Details of the preparations and properties of the products are shown in Table V.

Reaction of Grignard Reagents with 1,3-Dioxanes. General Procedure. In a dry 100-ml three-necked round-bottomed flask equipped with a reflux condenser with drying tube, magnetic stirrer, and gas inlet tube, 0.035 mol of the desired Grignard reagent is prepared in the usual manner[4] in 20 ml of anhydrous ether under a nitrogen atmosphere.[23] The 2-methoxy-1,3-dioxane (0.030 mol) dissolved in 10 ml of ether is added dropwise with stirring. The reaction is quite exothermic and if the addition is too rapid external cooling with water must be resorted to. After completion of the addition the mixture is stirred 1 hr at room temperature at which stage the color of the Grignard reagent has faded and an oily precipitate is formed. Ice-cold concentrated aqueous ammonium chloride or potassium carbonate (3.5 ml) is added very slowly with stirring.[24] The white solid precipitate is filtered with slight suction and washed 4 times with 50-ml portions of warm ether. To the combined ether filtrate is added a small amount of anhydrous potassium carbonate (to prevent epimerization by adventitious acid) and concentration by rotary evaporation is followed by distillation at the appropriate pressure to yield the product which is collected over a small amount of anhydrous K_2CO_3. Yields and purity of products are shown in Table II and properties in Table VI. Glpc analysis of 2-alkyl-1,3-dioxanes was carried out on a 20-ft 6% TCEP (tricyanoethoxypropane) on firebrick column. The *trans* isomers have the higher retention time. Preparative purification, where desired, was effected on a 30-ft 6% TCEP on Chromosorb G column. The 2-aryl compounds were analyzed on a 10-ft 20% Carbowax on Chromosorb W column; here the *trans* isomers had the shorter retention time.

Table VIII. Data Obtained in Measurement of Dipole Moments

Compd	R_{20}	R_M	d^{25}	μ
trans-I	114.87	33.78	0.9813	1.96
trans-II	117.44	37.91	0.9678	1.97
trans-III	118.59	42.21	0.9586	1.93
IV-(*trans*)[a]	102.94	37.54	0.9818	1.79
cis-I	203.3	32.93	1.0219	2.88
cis-II	213.25	37.45	0.9876	2.93
cis-III	218.16	43.70	0.9426	2.92

[a] See Table I, footnote *l*.

The *cis* isomers shown in Table VII were prepared from appropriate aldehydes and 1,3-diols by the procedure of Salmi.[25]

Dielectric Measurements. Dipole moments were determined by measuring dielectric constants and densities of three solutions (weight fractions ranging from 0.04 to 0.007) at 25 ± 0.1° in benzene (ϵ 2.273, d^{25} 0.8738) as described[26] with an oscillator similar to that described by Estok.[27] The total polarization P_{20} was measured by the method of Halverstadt and Kumler;[28] the dipole moment was then calculated from the equation $\mu = 0.22(P_{20} - R_M)^{1/2}$. Results are shown in Table VIII.

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[23] The *p*-BrC_6H_4MgBr was prepared following procedure of R. Quelet, *Bull. Soc. Chim. Fr.*, **41**, 933 (1927).

[24] *Cf.* L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 418.

[25] E. J. Salmi, *Chem. Ber.*, **71B**, 1803 (1938).

[26] C. Curran, P. A. McCusker, and H. S. Makowski, *J. Amer. Chem. Soc.*, **79**, 5188 (1957).

[27] G. K. Estok, *J. Chem. Educ.*, **39**, 478 (1962).

[28] I. F. Halverstadt and W. D. Kumler, *J. Amer. Chem. Soc.*, **64**, 2988 (1942).

California at Los Angeles) for the determinations of the nuclear Overhauser effects and to Dr. R. O. Hutchins and Sr. M. Knoeber for several stimulating discussions. The A-60A nmr instruments used in this investigation were acquired under National Science Foundation equipment Grant GP-6875.

Ground States of σ-Bonded Molecules. IX.[1] The MINDO/2 Method[2]

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Abstract: A computer program has been written for automatically optimizing the parameters in MO treatments. Using this, and using parametric functions for the core resonance integrals and core–core repulsions similar to those used in the PNDO approximation, we have been able to develop a version (MINDO/2) of the MINDO method which gives good estimates of bond lengths, heats of formation, and force constants simultaneously for a wide variety of hydrocarbons, thus satisfying the minimum requirements for a procedure to be used convincingly for calculating potential surfaces. Potential surfaces are calculated for the torsional isomerization of ethylene and cumulenes, for hydrogen abstraction reactions of methyl, and for the dimerization of ethylene. The results are encouraging. The method also gives good estimates of first ionization potentials.

The present theory of organic chemistry is very largely based on simple qualitative versions of MO theory; there is, however, a growing need for some more quantitative approach which would allow the mechanisms and rates of chemical reactions to be predicted. If an approach of this kind is to be of practical value to organic chemists in their study of reactions, on a basis analogous, say, to kinetic studies or nmr spectroscopy, it must be generally applicable, and the calculations involved in it must be feasible for quite large systems without unreasonable expense.

In order to predict chemical reactivity and reaction mechanisms, we must be able to calculate complete potential surfaces for assemblies of atoms as a function of their coordinates in space. The minima in the corresponding many-dimensional potential surface for a given assembly correspond to possible stable species, and the cols separating them to transition states for their interconversion. If our predictions are to be reliable, the potential surface must be calculated with an accuracy of the order of ± 1 kcal/mol.

Such accuracy cannot of course be attained by direct or approximate integration of the Schrödinger equation, except for the very simplest systems. In the case even of simple organic molecules, the energies given by the best methods at present available are in error by chemically speaking huge amounts. If therefore the results of such calculations are to be usefully correlated with chemical phenomena, the correlations can be established only on an empirical basis.

It would of course be entirely possible for the errors to be the same for a given assembly of atoms regardless of their geometry; this could apply to exact SCF calculations if the correlation energy were constant. In that case heats of formation would be correctly predicted and the errors in the absolute energies would be chemically unimportant. This unfortunately is not the case. The most reliable SCF calculations for diatomic molecules lead to heats of atomization that can be in error by ±100% and similar huge errors appear in the results of more approximate calculations for polyatomic molecules. Even errors of this kind might be tolerable in certain connections if the errors in the calculated heats of atomization were the same for different sets of molecules formed from the same set of atoms; in this case one could at least predict heats of reaction. Even here, however, the errors are not constant.[4] This kind of approach cannot therefore be applied with any assurance to chemical problems. It would be necessary first to carry out very extensive calculations for a wide variety of molecules and try to devise empirical corrections to the calculated heats of formation to bring them into line with experiment;[5] even if an approach of this kind were feasible, it would be of very little practical value to organic chemists because the computations for molecules of even quite moderate size would take too much time and so cost too much.

An alternative procedure is to try to improve the practical results of quantum mechanical calculations by treating some of the integrals appearing in them as parameters. This type of approach has of course often been used in chemistry in cases when exact mathematical solutions of chemical problems were not available (*e.g.*, the theory of strong electrolytes) and the HMO method represents an early application of this kind to quantum theory.

Insofar as quantum chemistry claims to be a branch of chemistry, its sole criterion must be its usefulness to chemists. Which of these two equally empirical approaches is the better must be decided on this basis. The main requirements are that the procedure should

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(1) Part VIII: N. Bodor and Michael J. S. Dewar, *Tetrahedron*, in press.

(2) This work was supported by the Air Force Office of Scientific Research through Grant No. AF-AFOSR-1050-67.

(3) Robert A. Welch Postdoctoral Fellow.

(4) L. C. Snyder, *J. Chem. Phys.*, **46**, 3602 (1967).

(5) An approach of this kind has been applied to the CNDO/2 method by K. B. Wiberg, *J. Amer. Chem. Soc.*, **90**, 59 (1968).