high-resolution mass measurements, found 705.5098, $C_{16}H_6N_2{}^{79}Br_3{}^{81}Br_3$ requires 705.5106; found 707.5090, $C_{16}H_6N_2{}^{79}Br_2{}^{81}Br_4$ requires 707.5086.

1,1'-Diacetyl-2,2',5,5'-tetrabromo-3,3'-bi-1*H*-indole (7). A solution of 1 (30 mg) in an equivolume mixture of acetic anhydride and pyridine (3 mL) was allowed to stand at 20 °C for 7 days, after which a single crystal of **7** (29 mg) was obtained by decantation of excess liquid followed by washing with diethyl ether: ^{1}H NMR ($CDCl_3$) δ 8.11 (1 H, d, J = 9 Hz), 7.32 (1 H, dd, J = 9, 2 Hz), 7.17 (1 H, d, J = 2 Hz), 2.89 (3 H, s); mass spectrum, M^+ 628; $C_{20}H_{12}N_2O_2{}^{79}Br_4$ requires M^+ 628.

(+)-1-Acetyl-2,3',5,5'-tetrabromo-7'-methoxy-3,4'-bi-1*H*-indole (11) and (+)-1,1'-Diacetyl-2,3',5,5'-tetrabromo-7'-methoxy-3,4'-bi-1*H*-indole (12). A solution of **2** (120 mg) in an equivolume mixture of pyridine and acetic anhydride (10 mL) was allowed to stand at 20 °C for 2 days. Water (10 mL) was added to the mixture, which was stirred for 2 h and partitioned between chloroform (40 mL) and water (20 mL). The chloroform layer was washed successively with 1 M HCl (2 × 10 mL), 5% aqueous sodium carbonate (2 × 10 mL), and water (10 mL). HPLC (diisopropyl ether) of dried ($MgSO_4$) chloroform-soluble material gave **11** (51 mg), **12** (57 mg), and unreacted **2** (4 mg).

Monoacetate 11 crystallized from dichloromethane–hexane as colorless prisms: mp 109–111 °C, $[\alpha]^{20}_D$ +99° (c 1, $CHCl_3$); IR ν_{max} (KBr disk) 3425, 1710, 1560, 1435, 1360, 1280 cm^{-1}; UV λ_{max} (acetonitrile) 300 (ϵ 15 000), 280 (ϵ 21 000), 247 sh (ϵ 28 000), 227 (ϵ 61 000), 207 (ϵ 55 000) nm; ^{1}H NMR ($CDCl_3$) δ 8.76 (1 H, br s, D_2O exch), 8.26 (1 H, d, J = 9 Hz), 7.37 (1 H, dd, J = 9, 2 Hz), 7.16 (1 H, d, J = 3 Hz, becomes s on D_2O exch), 7.12 (1 H, d, J = 2 Hz), 6.98 (1 H, s), 3.96 (3 H, s), 2.90 (3 H, s); high-resolution mass measurements, found 617.7613, $C_{19}H_{12}N_2O_2{}^{79}Br_3{}^{81}Br$ requires 617.7609, found 619.7607, $C_{19}H_{12}N_2O^{79}Br_2{}^{81}Br_2$ requires 619.7589.

Diacetate 12 separated from dichloromethane–hexane as colorless prisms: mp 96–98 °C, $[\alpha]^{20}_D$ +71° (c 0.75, $CHCl_3$); IR ν_{max} (KBr disk) 1720, 1540, 1440, 1365, 1260, 1200, 1030 cm^{-1}; UV λ_{max} (acetonitrile) 307 (ϵ 15 000), 276 (ϵ 20 000), 243 (ϵ 39 000); ^{1}H NMR ($CDCl_3$) δ 8.22 (1 H, d, J = 9 Hz), 7.58 (1 H, s), 7.30 (1 H, dd, J = 9, 2 Hz), 7.18 (1 H, s), 7.10 (1 H, d, J = 2 Hz), 4.00 (3 H, s), 2.90 (3 H, s), 2.75 (3 H, s); high-resolution mass measurements, found 661.7717, $C_{21}H_{14}N_2O_3{}^{79}Br_2{}^{81}Br_2$ requires 661.7693, found 663.7660, $C_{21}H_{14}N_2O_3{}^{79}Br^{81}Br_3$ requires 663.7674.

Bromination of Indole and 5-Bromoindole. Solid pyridinium bromide perbromide (1.05 mol equiv) was added batchwise over 10 min to a stirred solution of the indole (150 mg) and sodium acetate (1 mol equiv) in methanol (20 mL) cooled in an ice bath. The mixture was concentrated to dryness below 20 °C in vacuo, the solid residue triturated with dichloromethane (20 mL), and the dichloromethane soluble material filtered through a bed of silica gel (Merck, Kieselgel H, 15 g) under vacuum. The silica gel was washed with dichloromethane (50 mL) and the combined dichloromethane filtrate taken to dryness below 20 °C. The resulting foam was used directly for ^{13}C NMR measurements, which, in each case, showed that the product was >95% of the required 3-bromoindole derivative.

Acetylation of 5-Methoxyindole and 7-Methoxyindole. *N*-Butyllithium (2 M in hexane, 3 mL) was added to a stirred solution of the methoxyindole (200 mg) in dry THF (10 mL) at −20 °C and the mixture allowed to stand for 5 min. Acetic anhydride (1 mL) was added dropwise and the mixture allowed to stand for 15 min and then poured onto ice (50 g). The mixture was extracted with pentane (40 mL), the pentane layer washed with water (2 × 20 mL), and the dried ($MgSO_4$) pentane solution concentrated. The acetylated indole was separated from ~5% starting material by HPLC (dichloromethane).

Acknowledgment. We thank Ray Lidgard for mass spectra and high-resolution mass measurements, Gerald Viset for technical assistance, David Edwards for writing the computer program for determining T_1 values, and the collectors already mentioned for supplying alga.

Registry No. 1, 81387-82-8; (+)-**2**, 81387-83-9; (+)-**3**, 81387-84-0; (+)-**4**, 81387-85-1; (−)-**5**, 81387-86-2; (+)-**6**, 81387-87-3; **7**, 81387-88-4; **8**, 1484-27-1; **9**, 10075-50-0; **10**, 81387-89-5; (+)-**11**, 81387-90-8; (+)-**12**, 81387-91-9; **13**, 1006-94-6; **14**, 58246-80-3; **15**, 3189-22-8; **16**, 81387-92-0.

Conformational Analysis. 42. Monosubstituted Tetrahydropyrans[1]

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Abstract: The conformational energies of 2-, 3-, and 4-methyl, 2-vinyl, 2-ethinyl, 2-ethyl, 2-carbomethoxy, and 2-hydroxymethyl substituents in tetrahydropyran have been determined (in kcal/mol): 2-Me, 2.86; 3-Me, 1.43; 4-Me, 1.95; 2-CH_2=CH, 2.27; 2-CH≡C, 0.34; 2-Et, 2.62; 2-CO_2Me, 1.38; 2-CH_2OH, 2.89. Some of these values differ appreciably from earlier reported ones, and the 2-CO_2Me value does not support the hypothesis of a reverse anomeric effect.

The tetrahydropyran (oxane, oxacyclohexane) ring system is of wide occurrence in nature, e.g., in the pyranose sugars, in polyether antibiotics, and in thromboxanes. However, conformational information in simple monosubstituted tetrahyodrpyrans is quite limited. The parent compound has been shown by microwave spectroscopy[2] to exist in the chair form, and while it was thought on the basis of the Lambert R value[3] that the chair was slightly flattened relative to cyclohexane, this is in fact probably not the case.[4] The inversion barrier in tetrahydropyran (10.3 kcal/mol[5]) is the same as that in cyclohexane. Existing conformational information has been reviewed in various places,[6-8] and the known conformational energies of various polar substituents in the 2-, 3-, and 4-positions of the tetrahydropyran ring in nonpolar solvents are summarized in Table I.[9] Of greatest interest

Scheme I

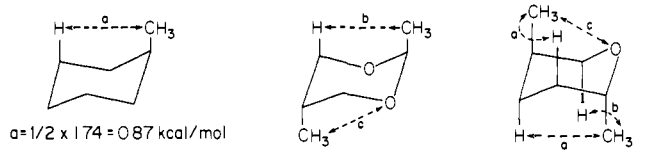

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Table I. Conformational Energies in Monosubstituted Tetrahydropyrans[a] (from Literature)[9]

substituent	2-Cl	2-Br	2-I	2-OCH_3		2-OEt		2-OCH_2CF_3	2-O-*n*Pr	2-O-*i*Pr	
$-\Delta G°$, kcal/mol	⩽−1.8	⩽−1.8	⩽−2.6	−0.73	−0.89	−0.67	−0.82	−0.83	−0.89	−0.64	−0.65
ref	10	10	11	12	13	12	13	12	13	12	13

substituent	2-O-*n*Bu	2-O-*t*Bu		2-$OC(Me)_2C{\equiv}CH$	2-OAc	2-SCH_3	2-S-*t*Bu	3-OAc	3-Cl
$-\Delta G°$, kcal/mol	−0.89	−0.5	−0.41	−0.54	−0.6	−0.35	−0.37	0.17	0.68
ref	13	12	13	12	15	12	12	14	16

substituent	3-Br		3-Me	3-CH_2OH	−CHO	3-CO_2CH_3	4-F	4-Cl	4-Br	4-I	4-OCH_3	4-OAc
$-\Delta G°$, kcal/mol	1.0	0.53[b]	1.44[b]	0.78[b]	0.0[b]	0.59[b]	−0.05[c]	0.31[c]	0.34[c]	0.44[c]	0.82[b]	0.80[d]
ref	16	1	1	1	1	1	17	17	17	17	1	18

[a] In CCl_4 unless otherwise specified. [b] In CD_2Cl_2. [c] In CS_2. [d] In $CDCl_3$.

Table II. Equilibrium Parameters for Substituted Tetrahydropyrans 1–14 in CD_2Cl_2[a]

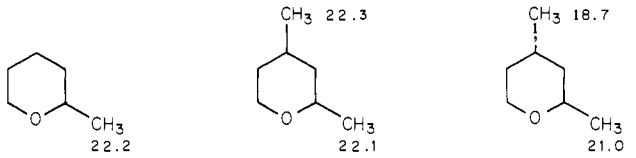
compd	substituents	temp, K	K	$-\Delta G°$, kcal/mol
1	3-Me	173 ± 6	65.7 ± 1.5	1.44 ± 0.04
2	*cis*-2,3-di-Me	173 ± 6	>80	>1.5
3	*trans*-2,4-di-Me[a]	173 ± 6	13.12 ± 0.8	0.89 ± 0.04
4	*cis*-2,5-di-Me	183 ± 3	86.0 ± 1.1	1.62 ± 0.03
5	*cis*-3,4-di-Me[a]	173 ± 6	9.00 ± 0.68	0.76 ± 0.04
6	*trans*-2-CO_2Me-4-Me	163 ± 3	5.63 ± 0.35	0.56 ± 0.03
7	*cis*-2-CO_2Me-5-Me	163 ± 7	1.15 ± 0.04	0.05 ± 0.02
8	2-C≡CH	183 ± 5	2.52 ± 0.18	0.34 ± 0.03
9	*cis*-2-C≡CH-5-Me	173 ± 6	23.4 ± 1.0	1.08 ± 0.04
10	*trans*-2-CH=CH_2-4-Me	173 ± 3	2.51 ± 0.16	0.32 ± 0.03
11	*cis*-2-CH=CH_2-5-Me	173 ± 3	11.53 ± 0.46	0.84 ± 0.02
12	*trans*-2-CH=CH_2-6-Me	163 ± 3	3.61 ± 0.25	0.42 ± 0.03
13	*trans*-2-CH_2OH-6-Me	163 ± 3	1.07 ± 0.05	0.03 ± 0.01
14	*trans*-2-Et-6-Me	163 ± 3	2.10 ± 0.2	0.24 ± 0.03

[a] Measurements for compounds 3 and 5 were performed in $(CD_3)_2CO/Cl_2C{=}CHCl$ (35:65) solutions, for compound 13 in 50% CD_2Cl_2/30% CD_3COCD_3/20% $Cl_2C{=}CHCl$.

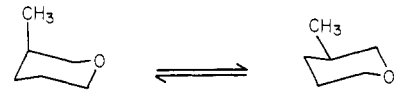
in the past has been the fact that electron-withdrawing substituents (such as halogen, RO, RS) at the 2-position prefer the axial position, as a result of the well-known anomeric effect.[19] Little information is available, however, regarding nonpolar substituents for comparison purposes except for a paper on the conformational energies of the 2-, 3- and 4-methyl groups and the 2-carbomethoxy group in tetrahydropyran that was published a number of years ago.[20]

As shown in Scheme I, the conformational energy of methyl in methylcyclohexane is 1.74 kcal/mol,[21] and corresponding values for methyl in the 2-, 4-, and 5-positions of 1,3-dioxane are 4.0, 2.8, and 0.8 kcal/mol, respectively.[22] By a rather primitive method of compilation, one may then estimate that, in tetrahydropyran, $-\Delta G°_{2\text{-Me}}$ is one-half the Me-2 value in 1,3-dioxane, or 2.0 kcal/mol plus one-half the cyclohexane value or 0.87 kcal/mol for a total of 2.87 kcal/mol. (Alternatively it could be simply taken as equal to the Me-4 value of 2.8 kcal/mol.) Similarly, $-\Delta G°_{3\text{-Me}}$ should be one-half the Me-5 value in 1,3-dioxane (0.4 kcal/mol) plus one-half the cyclohexane value (0.87 kcal/mol) or 1.27 kcal/mol. Finally $-\Delta G°_{4\text{-Me}}$ in tetrahydropyran should be equal to the cyclohexane value of 1.74 kcal/mol. The reported[20] values are 1.70, 1.27, and 1.70 kcal/mol, respectively, for Me-2, Me-3, and Me-4. While the Me-3 and Me-4 values are in agreement with prediction, the value for Me-2 appears substantially too small. In this connection, recent ^{13}C NMR data for

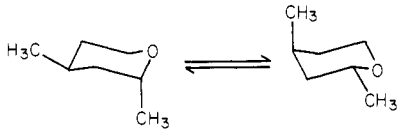
Scheme II



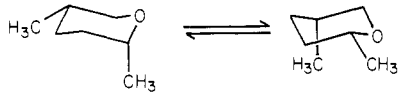
Scheme III



1, $-\Delta G°$ = 1.44 kcal/mol



3, $-\Delta G°$ = 0.89 kcal/mol



4, $-\Delta G°$ = 1.62 kcal/mol

2-methyl- and *cis*- and *trans*-2,4-dimethyltetrahydropyrans[23] are also of interest. The salient chemical shift data[23] are shown in Scheme II; it is clear that in *trans*-2,4-dimethyloxane, the 2-methyl group is close (within 1.2 ppm) to that in the cis isomer and that in 2-methyloxane, suggesting that the group is largely equatorial, whereas the 4-methyl group in the trans isomer is considerably shifted upfield with respect to the cis isomer (by 3.6 ppm), suggesting it is largely axial. Thus, the 2-methyl group should have a substantially larger conformational energy than the 4-methyl, causing the trans-2,4 isomer to exist predominantly with axial Me-4 and equatorial Me-2. That this is indeed so was subse-

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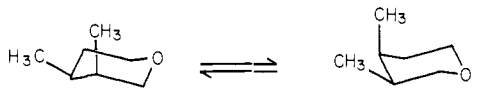
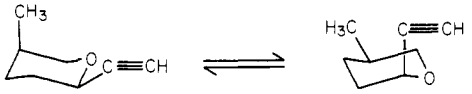
Scheme IV



5, $-\Delta G^\circ$ = 0.76 kcal/mol

8, $-\Delta G^\circ$ = 0.34 kcal/mol



9, $-\Delta G^\circ$ = 1.08 kcal/mol

quently confirmed by our own low-temperature NMR studies (vide infra).

In view of this uncertainty and the general interest in the tetrahydropyran system, we decided to reinvestigate the conformational aspects of the methyltetrahydropyrans using modern low-temperature ^{13}C NMR techniques.

Results

Our results are summarized in Table II. A low-temperature ^{13}C NMR study of 3-methyltetrahydropyran (**1**) directly yielded a $-\Delta G^\circ$ value of 1.44 kcal/mol (K = 65.7). Clearly the larger $-\Delta G^\circ$ values of Me-2 and Me-4 would be impossible to obtain from direct low-temperature area measurements. We therefore set out to determine $-\Delta G^\circ$ for *cis*-2,5- (**4**) and *trans*-2,4-dimethyltetrahydropyran (**3**) (Scheme III). The equilibrium for **3** is well over on the right-hand side (Scheme III), thus confirming the fact that there is a large difference in $-\Delta G^\circ$ between Me-2 and Me-4 (vide supra). The $-\Delta G^\circ$ value for **4** is so large that in the initial experiments (where only a slightly impure sample of **4** was available) the minor conformational isomer could not be found.

There was evident need for a counterpoise group intermediate in size between Me-2 and Me-3. Me-4 is in this category but unfortunately cannot be used; although the conformational equilibrium of *cis*-3,4-dimethyltetrahydropyran (**5**, Scheme IV) was determined, this equilibrium may be affected by differences in vicinal interactions in the two conformers and is therefore not suitable for determination of $-\Delta G^\circ_{4\text{-Me}}$ from $-\Delta G^\circ_{3\text{-Me}}$ using an additivity principle (vide infra).

The conformational equilibrium for the 2-ethynyl group (cf. **8**, Scheme IV) was determined ($-\Delta G^\circ$ = 0.34 kcal/mol, favoring the equatorial conformation); this group is clearly not large enough to act as a suitable counterpoise for the 4-methyl group in *trans*-2-ethynyl-4-methyltetrahydropyran (**15**). It did, however, serve as a counterpoise for the 3-methyl group in *cis*-2-ethynyl-5-methyltetrahydropyran (**9**, Scheme IV); the $-\Delta G^\circ$ value obtained in this way (i.e., assuming additivity) for Me-3 (0.34 + 1.08 = 1.42 kcal/mol) is probably slightly more accurate than the directly determined value of 1.44 kcal/mol (Scheme III) since less one-sided (and hence more accurately measured) equilibria are used in its determination. We have used a mean value of 1.43 kcal/mol for Me-3 (cf. Table III).

The 2-vinyl group then suggested itself as a suitable counterpoise for 5-methyl on one hand and 4-methyl on the other. *cis*-2-(2-Dimethylvinyl)-4-methyltetrahydropyran (rose oxide) is a natural product occurring in Bulgarian rose oil,[24] and both its ^{13}C NMR spectrum and that of its trans isomer tetrahydropyran had already been recorded;[23] from the spectrum of the trans isomer it is clear that both conformers are present. Low-temperature examination of the ^{13}C NMR spectrum of *trans*-2-vinyl-5-methytetrahydropyran (**11**), obtained by semihydrogenation of the corresponding ethynyl compound, indicated an easily measurable equilibrium

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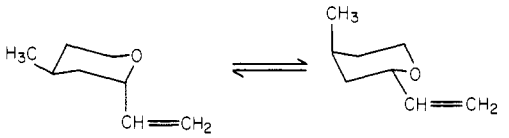
Table III. Conformational Free Energies for Substituted Tetrahydropyrans[a]

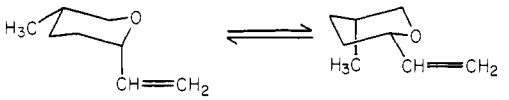
substituent	$-\Delta G^\circ$, kcal/mol
2-CO_2CH_3	1.38 ± 0.04
2-C≡CH	0.34 ± 0.03
2-CH=CH_2	2.27 ± 0.04
2-CH_2OH	2.89[b]
2-CH_3	2.86[b]
3-CH_3	1.43 ± 0.04
4-CH_3	1.95 ± 0.05
2-C_2H_5	2.62[b]

[a] Temperature range 163–183 K; the data refer to CD_2Cl_2 as solvent, except in the case of 2-Me where one of the values (with 4-Me as counterpoise) was obtained in CCl_2=CHCl/CD_3COCD_3 and for 2-CH_2OH where the solvent was CD_2Cl_2/CD_3COCD_3/Cl_2C=CHCl. [b] Because of systematic differences in the three values for 2-CH_3 (see text), a standard deviation cannot be assigned to this value or the derived values of 2-C_2H_5 and 2-CH_2OH. The estimated error in these numbers is ±0.2 kcal/mol.

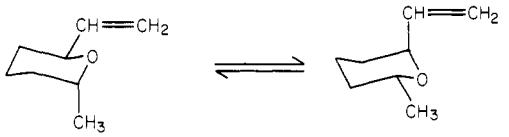
Scheme V



10, $-\Delta G^\circ$ = 0.32 kcal/mol



11, $-\Delta G^\circ$ = 0.84 kcal/mol



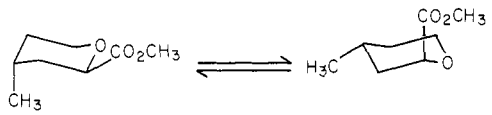
12, $-\Delta G^\circ$ = 0.42 kcal/mol

with $-\Delta G^\circ$ = 0.84 kcal/mol, favoring equatorial vinyl; thus the conformational energy of the 2-vinyl group is 1.43 + 0.84 = 2.27 kcal/mol (Scheme V). Corresponding measurements for *trans*-2-vinyl-4-methyltetrahydropyran (**10**) gave $-\Delta G^\circ$ = 0.32 kcal/mol (Scheme V); hence the conformational energy of 4-methyl is 2.27 − 0.32 = 1.95 kcal/mol. The results for compound **3** from Scheme III then allow one to compute $-\Delta G^\circ_{2\text{-Me}}$ as 1.95 + 0.89 = 2.84 kcal/mol. An alternative value for determining this quantity is from *trans*-2-vinyl-6-methyltetrahydropyran (**12**, Scheme V), $-\Delta G^\circ$ 0.42 kcal/mol; this yields $-\Delta G^\circ_{2\text{-Me}}$ = 2.27 + 0.42 = 2.69 kcal/mol.

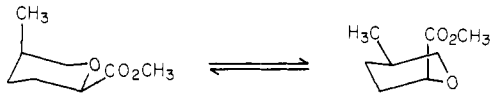
Since the difference between the conformational energies of the 2- and 3-methyl substituents is only of the order of 1.4 kcal/mol (cf. Table III), i.e., of the same order of magnitude as the conformational energy of the 3-methyl group itself, it was not clear why the determination of the conformational equilibrium for **4** (Scheme III) had not been successful. We made a second attempt to determine this equilibrium using, this time, scrupulously purified material; this allowed us to find the minor conformational isomer and to establish the equilibrium constant: K = 86.0, $-\Delta G^\circ$ = 1.62 kcal/mol. This value is somewhat larger than expected and would lead to a $-\Delta G^\circ$ value for 2-Me of 1.62 + 1.43 or 3.05 kcal/mol, appreciably higher than the two values reported above. The discrepancy may reflect some differential molecular deformation of the rings in the various compounds containing 2-methyl groups (**3**, **4**, and **12**), possibly due to buttressing effects, or it may simply reflect the large standard deviations in the determination of large $-\Delta G^\circ$ values. In any case, we have chosen a mean value of 2.86 kcal/mol for $-\Delta G^\circ_{2\text{-Me}}$.

Since the value for $-\Delta G^\circ_{2\text{-Me}}$ obtained in the present work was much larger than that reported earlier,[20] we tried to repeat the earlier observations. In the earlier work the conformational energy

Scheme VI



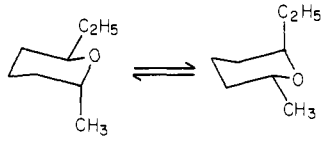
6, $-\Delta G^\circ$ = 0.56 kcal/mol



7, $-\Delta G^\circ$ = 0.05 kcal/mol

13, $-\Delta G^\circ$ = 0.03 kcal/mol

Scheme VII



of the 2-carbomethoxy group was determined as 1.62 kcal/mol by chemically equilibrating (with base) 2-(carbomethoxy)-6-*tert*-butyltetrahydropyran, and the $-\Delta G^\circ$ values of 2-Me, 3-Me, and 4-Me were then determined indirectly by establishing corresponding chemical equilibria for 2-(carbomethoxy)-6-, -5-, and -4-methyltetrahydropyrans. (The original publication[20] should be consulted for the conformational arguments used.) In our hands, equilibration of 2-(carbomethoxy)-4-methyl- and 2-(carbomethoxy)-6-methyltetrahydropyrans was very slow, and we were not able to reach the same final composition starting from the cis and trans isomers.

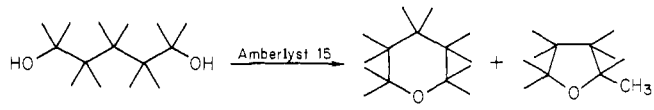
By way of an alternative method of determining the conformational energy of the 2-carbomethoxy group, *cis*-2-(carbomethoxy)-5-methyltetrahydropyran (**7**) was synthesized and its conformational equilibrium (Scheme VI) established by low-temperature ^{13}C NMR spectroscopy. The slight preference for equatorial Me over equatorial CO_2Me (Scheme VI) translates into a $-\Delta G^\circ_{2\text{-}CO_2Me}$ of 1.43 − 0.05 = 1.38 kcal/mol. While it is possible that the difference between the earlier determined[20] value of 1.62 kcal/mol and the present one of 1.38 kcal/mol is due to a difference in solvent (CH_3OH in the earlier work, CD_2Cl_2 in the present), we note that the present value, determined in the less polar solvent (which should maximize the "reverse anomeric effect", if any), is only slightly larger than the accepted value for CO_2CH_3 in cyclohexane (1.27 kcal/mol[25]); thus there is little if any evidence for the earlier postulated[20] reverse anomeric effect in this case, especially since, on steric grounds, one would expect the conformational energy of a carbomethoxy group at C(2) in tetrahydropyran to be somewhat larger than that of the same substituent in cyclohexane.

With the $-\Delta G^\circ$ value of the CO_2Me group in hand, it proved possible to obtain a cross-check on the value for 4-methyl by studying the conformational equilibrium of *trans*-2-(carbomethoxy)-4-methyl-tetrahydropyran (**6**) by low-temperature ^{13}C NMR, (Scheme VI). The value so computed, 1.38 + 0.56 = 1.94 kcal/mol, is in excellent agreement with that derived earlier from the 4-methyl-2-vinyl equilibrium (Scheme V).

From the low-temperature equilibrium of the conformers of *trans*-2-ethyl-6-methyltetrahydropyran (Scheme VII, $-\Delta G^\circ$ = 0.24 kcal/mol), it follows that $-\Delta G^\circ_{2\text{-Et}}$ = 2.86 − 0.24 = 2.62 kcal/mol; the methyl group prefers the 2-equatorial position *more* than ethyl.

(25) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199. Jensen, F. R.; Bushweller, C. H.: Beck, B. H. *J. Am. Chem. Soc.* **1969**, *91*, 344. Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866.

Scheme VIII



The $-\Delta G^\circ$ value of the 2-hydroxymethyl group (2.89 kcal/mol, which may be rounded off to 2.9 kcal/mol) was obtained by counterpoising it against a 2-methyl group (**13**), Scheme VI).

Syntheses

The methyl- and dimethyltetrahydropyrans required in the present study were generally synthesized from appropriately substituted 1,5-diols with Amberlyst 15 (Rohm and Haas) as the acid-cyclization catalyst.[26] In some instances, tetrahydrofurans as well as tetrahydropyrans were formed (Scheme VIII), and it was necessary to separate two stereoisomeric tetrahydrofurans and two stereoisomeric tetrahydrpyrans by gas chromatography. The ^{13}C spectra of the tetrahydrofurans have been previously reported,[27] and those of the tetrahydropyrans not shown in Table IV will be reported in a separate paper.[28]

2-(Carbomethoxy)-5-methyl-3,4-dihydro-2*H*-pyran was synthesized by a hetero-Diels–Alder synthesis from methacrolein and methyl acrylate,[20] purified, and hydrogenated to a mixture of *cis*- and *trans*-2-(carbomethoxy)-5-methyltetrahydropyrans in a 9:1 ratio from which the pure cis isomer (**7**) was isolated by gas chromatography. To obtain pure **4**, we reduced the mixed esters to 2-(hydroxymethyl)-5-methyltetrahydropyran, which was converted to the crystalline *p*-bromobenzenesulfonate of the cis isomer, which was purified by recrystallization and reduced with hydride to **4**. *trans*-2-(Carbomethoxy)-4-methyltetrahydropyran (**6**) was similarly synthesized from isoprene and *n*-butyl glyoxylate[29] followed by hydrogenation and transesterification. Ethynyl compounds were obtained by the action of ethynylmagnesium bromide on the appropriately substituted 2-chlorotetrahydropyran, which in turn resulted from the HCl addition to the 2,3 double bond in the pertinent dihydropyran precursor. It is of interest that in the conformationally biased systems only the stereoisomer with axial ethynyl at C(2) resulted; presumably this reflects approach of the ethynyl group to an intermediate oxocarbonium ion (formed by loss of chloride) from the axial side of the chair, i.e., along the direction of the vacant p orbital on the less hindered side. A similar situation is found in reactions of 2-alkoxy-1,3-dioxanes with Grignard reagents to give axial 2-alkyl-1,3-dioxanes,[30] and the mechanism has been discussed earlier.[30] Surprisingly, the reaction of *trans*-2-chloro-6-methyltetrahydropyran with vinylmagnesium bromide is stereochemically less clean, giving rise to some *cis*-2-vinyl-6-methyltetrahydropyran along with a major amount of the trans isomer **12**. This may be a manifestation of Deslongchamps postulate[31] that it generally requires *two* antiperiplanar lone pairs (as in axially substituted 2-alkoxy-1,3-dioxanes) to obtain maximum stereoelectronic control. In the present case, stereoelectronic control favoring axial approach is opposed by steric factors impeding it; it would appear that the stereoelectronic effect dominates completely in the case of the small ethynyl group (even though there is only one antiperiplanar electron pair on oxygen), but steric factors make themselves felt with the larger vinyl group so that its approach is no longer exclusively from the axial side. The remaining vinyl compounds were therefore obtained by semihydrogenation of ethynyl precursors. While semihydrogenation of 2-ethynyltetrahydropyran (**8**) was quite selective, yielding the vinyl compound in good yield, the corresponding hydrogenation of the *trans*-4- (**15**), *cis*-5- (**9**), and also the *trans*-6- (**16**)[28] homologues led to nearly statistical

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(30) Eliel, E. L.; Nader, F. W. *J. Am. Chem. Soc.* **1970**, *92*, 584. Bailey, W. F.; Croteau, A. A. *Tetrahedron Lett.* **1981**, *22*, 545.
(31) Deslongchamps, P. *Heterocycles* **1977**, *7*, 1271.

mixtures of recovered ethynyl, vinyl, and ethyl compounds (1:2:1). One might hypothesize that the nearly complete existence of **9**, **15**, and **16** in the conformation with axial ethynyl slows down the first stage of the hydrogenation (since the axial ethynyl group is not readily adsorbed on the catalyst). One the vinyl stage is reached, no such inhibition persists—since the vinyl group is predominantly equatorial—and further reduction to the 2-ethyl compounds occurs readily. Indeed, 2-ethyl- and *trans*-2-ethyl-6-methyltetrahydropyran (**14**) were easily prepared by hydrogenation of the corresponding vinyl compounds.

Finally, the *trans*-2-(hydroxymethyl)-6-methyl compound (**13**) was obtained by hydride reduction of the corresponding ester.

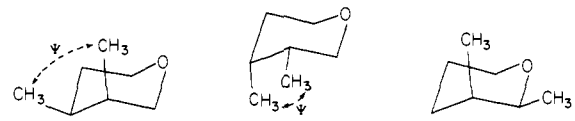
Discussion

Comparison of the conformational free energies of methyl groups in the different positions in tetrahydropyran (Table III) with the expectation values (vide supra) shows reasonable agreement; in particular, the expected large value for $-\Delta G°_{2\text{-Me}}$ is borne out by experiment. The 2-Me group, is, of course, engaged in a syn-axial interaction with H(6-a)—which is very close by because of the short C–O bond distances—as well as with the more distant H(4-a); this explains the large $-\Delta G°$ value. The values for $-\Delta G°_{3\text{-Me}}$ and $-\Delta G°_{4\text{-Me}}$ are slightly larger than expected; this is particularly surprising for the Me-4 value, in view of the fact[4] that the puckering of tetrahydropyran is about the same of that of cyclohexane. Yet the precision of our data is such as to leave no doubt that the conformational energy in 4-methyltetrahydropyran (1.95 ± 0.05 kcal/mol) is larger than that in cyclohexane[22] (1.74 ± 0.06 kcal/mol). The only apparent explanation is to postulate that deformation potentials (deformation leading to minimization of energy) are larger in tetrahydropyran than in cyclohexane.

The $-\Delta G°_{2\text{-C}\equiv\text{CH}}$ value is small, though perhaps still larger than one might have expected on the basis of the range of values for ethynylcyclohexane, 0.2–0.5 kcal/mol,[25] and on the basis of the observation[32] that 2-ethynyl in 1,3-dioxane (in solvent CCl_4) prefers the axial position by 0.21 kcal/mol because of an anomeric effect. We note, however, that the value of 1,3-dioxane is extremely solvent sensitive, changing to 0.94 kcal/mol in favor of the *equatorial* position in solvent acetonitrile. This is the kind of situation one would expect if a steric effect opposes a polar one, with the polar effect dominating in nonpolar solvents and the steric one in polar solvents. In our case, the polarity of the solvent (CD_2Cl_2) is intermediate, the steric effect is less than at C(2) in 1,3-dioxane, and the anomeric (polar) effect is also less—perhaps, following Deslongchamps (vide supra), considerably less. It is therefore not possible to predict where the balance of these effects will lie, and the result, after the fact, does not appear unreasonable. In contrast, the 2-vinyl value is quite large, though less so than 2-methyl. This is reasonable for a purely steric effect; in cyclohexane, $-\Delta G°$ for vinyl (1.68 kcal/mol[33]) is slightly smaller than the methyl value. In axial vinylcyclohexane the vinyl group appears to be eclipsed with a C–C (rather than C–H) bond.[33,34] If the major orientation of the axial 2-vinyl group in tetrahydropyran is such as to eclipse the C–O bond, some relief of strain relative to cyclohexane would be expected because of absence of H substituents at the 1-position. This may explain why the $-\Delta G°$ difference between axial 2-vinyl and 2-methyl in tetrahydropyran (0.58 kcal/mol) is so much larger than the corresponding difference in cyclohexane (0.06 kcal/mol); however, the alternative possibility of a (small) anomeric effect for the 2-vinyl group is not excluded.

Interestingly $-\Delta G°$ for 2-ethyl (2.62 kcal/mol) is appreciably smaller than that for 2-methyl (2.86) at 163 K. Allinger[35] has already pointed out that the conformational *enthalpy*, $-\Delta H°$, favors equatorial ethyl less than equatorial methyl, it is only because of an *entropy* disadvantage (more rotamers possible for

Scheme IX



equatorial CH_2CH_3 than for axial) that axial ethyl is more disfavored (in terms of K or $\Delta G°$) at room temperature. However, the entropy factor is less important at low temperature (since $\Delta G° = \Delta H° - T\Delta S°$), and Booth[36] has, in fact, shown by low-temperature NMR study of *cis*-1-ethyl-4-methylcyclohexane that the conformation with axial ethyl is preferred (by 0.06 kcal/mol) at 141 K. The situation with *trans*-2-ethyl-6-methyltetrahydropyran (**14**) is evidently similar at 163 K; however, the ambient temperature (ca. 300 K) NMR spectrum suggests that axial ethyl may be slightly preferred even at room temperature in this case.

We have already discussed the $-\Delta G°$ value of the 2-carbomethoxy group, which is of about the same "size" as an axial carbomethoxy group in cyclohexane. This may well be due to a compensation of various steric and polar effects. Finally we draw attention to the large $-\Delta G°$ value (2.89 kcal/mol) for a hydroxymethyl (CH_2OH) group at C(2); this value is of interest because of the occurrence of this group in the pyranose form of aldohexoses. It is considerably larger than the value previously assumed in aldohexoses (2 kcal/mol[37]), which, however, is affected by vicinal interactions with adjacent hydroxyl groups at C(5) (C-4 in sugar numbering). We note that the value for 2-CH_2OH is only faintly larger (by 0.03 kcal/mol) than the value for 2-Me, suggesting either that dipolar and hydrogen-bonding[38] effects are unimportant or that they compensate each other.

We indicated earlier that the $-\Delta G°$ value for *cis*-3,4-dimethyltetrahydropyran (**5**), 0.76 kcal/mol, might be affected by a vicinal interaction. From the data in Table III, it is clear that this is in fact so; the calculated value $(-\Delta G°_{4\text{-Me}}) - (-\Delta G°_{3\text{-Me}})$ is only 0.52 kcal/mol, and the **3a**/**4e** conformation is evidently favored over **3e**/**4a** by an extra 0.24 kcal/mol. Measurements on Dreiding models suggest that this discrepancy may be due to a larger dihedral angle between methyl groups in the **3a**/**4e** as compared to the **3e**/**4a** conformer (Scheme IX) leading to greater vicinal interaction in the latter; similar differences have been found earlier in *cis*-2-methylcyclohexanols[39] and in *cis*-2,3- and 3,4-dimethylthianes.[40a] Attempts to measure the corresponding equilibrium in *cis*-2,3-dimethyltetrahydropyran (**2**) (Scheme IX) foundered because this equilibrium is too one-sided in favor of the **2e**/**3a** conformation.

The room-temperature and low-temperature ^{13}C NMR spectra used to obtain the data in Table II are shown in Table IV. A more detailed discussion of these data and others will be published elsewhere.[28] Of particular interest is the fact that in the case of the ethynyl group the α_a effect (downfield shifting) is considerably larger than the α_e effect (cf. the low-temperature spectrum of 2-ethynyltetrahydropyran), in contrast to what is almost universally observed for methyl substituents.[41] We also note that the C=O signal of the axial CO_2CH_3 group at C(2) is downfield of that of the equatorial, in contrast to what has been seen in cyclohexanecarboxylates.[42]

Experimental Section

General Information. Proton NMR spectra were recorded on JEOL C-604 (60 MHz), Perkin-Elmer R24B (60 MHz), Varian XL-100 (100 MHz), or Bruker Spectrospin WM-250 (250 MHz) spectrometers. Carbon-13 NMR spectra were similarly recorded on the Varian XL-100

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Table IV. Carbon-13 Chemical Shift Data for Substituted Tetrahydropyrans 1-14 at Ambient and Low Temperatures[a]

compd	substituents	temp, °C	conformer	C_2	C_3	C_4	C_5	C_6	Me[b]	Me[c]	C_α	C_ω
1	3-Me	amb[d]		74.80	31.18	32.17	26.11	68.18	17.47			
		−100	major	*74.62*	31.48	32.15	*26.45*	67.99	17.88			
			minor	*73.00*	(28.54)[e]	(28.74)	*21.24*	68.98	16.56			
2	*cis*-2,3-di-Me	amb[d]		75.69	32.63	30.65	21.34	68.05	18.41	12.02		
		−100	major	76.70	32.85	31.55	21.00	69.46	19.75	11.65		
			minor[f]									
3	*trans*-2,4-di-Me	amb[d]		68.04	39.44	24.99	32.27	62.34	21.05	18.73		
		−100[g]	major	67.77	39.17	25.41	*31.13*	*62.65*	22.48	17.49		
			minor	65.58	*h*	24.91	*34.97*	*59.82*	16.99	*h*		
4	*cis*-2,5-di-Me	amb[d]		73.70	(28.86)	(29.16)	28.34	72.52	21.58	16.73		
		−90	major	73.74	(*27.80*)	(28.33)	*27.13*	72.33	*21.74*	15.95		
			minor	72.89	*31.58*	*h*	*30.29*	*h*	*16.86*	*h*		
5	*cis*-3,4-di-Me	amb[d]		73.15	34.18	32.25	30.61	67.18	11.75	17.62		
		−100[g]	major	*74.17*	34.26	33.11	29.21	68.56	10.93	*20.27*		
			minor	*68.28*	(34.09)	(30.21)	(33.70)	*61.92*	*h*	*15.10*		
6	*trans*-2-CO_2Me-4-Me	amb		72.55	35.07	26.00	33.25	63.90	20.80		172.79	51.86
		−110	major	*72.91*	35.00	*26.76*	*33.91*	*64.17*	*22.50*		173.22	52.64
			minor	*70.88*	34.53	*24.82*	*30.29*	*62.82*	*16.74*		173.22	52.64
7	*cis*-2-CO_2Me-5-Me	amb		74.52	26.10	29.06	29.80	71.78	17.11		172.66	51.88
		−110	major	72.44	*28.59*	30.75	*30.75*	70.35	*17.71*		*173.31*	52.93
			minor	76.51	*24.15*	26.99	*27.42*	73.06	*16.40*		*172.96*	52.93
8	2-C≡CH	amb		73.28	31.98	21.52	25.69	(66.24)			82.82	(66.60)
		−90	major	72.82	*32.55*	*23.09*	*25.31*	(68.75)			*83.42*	(*67.56*)
			minor	75.23	*30.41*	*18.95*	*25.90*	(62.77)			*81.97*	(*64.50*)
9	*cis*-2-C≡CH-5-Me	amb		74.21	30.65	28.19	30.90	69.56	17.38		82.68	64.85
		−100	major	75.09	30.40	27.55	31.05	*68.66*	*17.31*		82.12	63.90
			minor	(72.66)	*h*	*h*	*h*	(*73.09*)	*16.31*		83.52	68.06
10	*trans*-2-CH=CH_2-4-Me	amb		72.98	37.84	25.41	33.17	62.51	19.58		139.94	114.94
		−100	major	72.66	*37.35*	25.08	*30.96*	*62.84*	*17.32*		*140.12*	*114.21*
			minor	72.66	*36.46*	25.08	*34.93*	*61.66*	*22.88*		*138.59*	*116.74*
11	*cis*-2-CH=CH_2-5-Me	amb		77.72	27.49	29.11	28.99	72.16	16.85		140.00	114.48
		−100	major	79.66	(28.64)	(27.64)	26.61	*72.78*	*16.53*		*139.67*	*114.39*
			minor	72.60	(31.58)	*h*	(29.64)	*71.98*	*17.88*		*138.09*	*116.96*
12	*trans*-2-CH=CH_2-6-Me	amb		72.46	29.53	19.06	32.76	67.35	20.79		139.72	115.43
		−110	major	73.38	*27.17*	18.97	*33.61*	66.49	22.59		*138.66*	*116.67*
			minor	(69.08)	*29.03*	17.97	*32.20*	(69.85)	16.82		*140.34*	*114.28*
13	*trans*-2-CH_2OH-6-Me	amb		71.57	26.92	18.57	31.42	67.96	19.15		64.31	
		−110[l]	major	*69.06*	*26.63*	*16.57*	28.29	*65.11*	*15.68*		*64.39*	
			minor	*73.33*	*24.20*	*18.35*	32.51	*68.12*	*21.50*		*58.87*	
14	*trans*-2-Et-6-Me	amb		72.78	66.81	19.01	32.36	66.84	20.14		26.43	10.52
		−110	major	73.65	*27.30*	*18.04*	*32.80*	63.65	21.86		21.86	10.07
			minor	*69.12*	*30.95*	*17.36*	*29.16*	68.03	16.04		28.72	10.07

[a] Shifts in parts per million from Me_4Si in CD_2Cl_2 unless otherwise indicated. The peaks which were integrated to obtain data in Table II are italicized in the low-temperature spectra. [b] Methyl group attached to lower numbered carbon. [c] Methyl group attached to higher numbered carbon. [d] Ambient-temperature spectrum in $CDCl_3$. [e] Parenthesized chemical shift values may be interchanged (horizontally). [f] Peaks of the minor isomers too small to be recorded. [g] For this low-temperature measurement, a mixture of $(CD_3)_2CO$ and $Cl_2C{=}CHCl$ (35:65) was used as solvent. [h] Peak not clearly discernible. [l] In 50% CD_2Cl_2, 30% acetone-d_6, 20% $CHCl{=}CCl_2$; 0.2 M solution. In pure CD_2Cl_2 solubility is quite low and signals are broad, but the measured $-\Delta G^\circ$ at −110 °C varies by less than 0.1 kcal/mol.

(25.12 MHz) or Bruker Spectrospin WM-250 (62.89 MHz) instrument operated in pulsed Fourier transform mode and locked on solvent deuterium. Samples were prepared as 10–15% solutions in CD_2Cl_2, $CDCl_3$ or 65% $CCl_2{=}CHCl$/35% $(CD_3)_2CO$ mixture with 2–5% Me_4Si as internal reference in 5- or 10-mm o.d. tubes. Temperature readings in the Varian XL-100 instrument were measured as previously described.[40b] The temperature indicator of the Bruker WM-250 spectrometer was calibrated by recording low-temperature proton spectra of acidulated methanol and using the known C–H/O–H shift for assessment of temperature.

Analytical gas–liquid partition chromatography was carried out in Hewlett-Packard 5750 research chromatographs equipped with either a thermal conductivity or flame ionization detector. Columns used were 12 ft × 0.125 in. Carbowax 20M + 10% KOH on Chromosorb W, 80/100 mesh; 12 ft × 0.125 in. 25% TCEP on Firebrick 60/80 mesh; 12 ft × 0.125 in. 20% SE-30 on Chromosorb W 80/100 mesh; 6 ft × 0.125 in. 10% UC-W98 on Chromosorb W AW 80/100 mesh, at temperatures between 60 and 100 °C. For preparative GLPC a Varian Aerograph series 2700 model equipped with one of the following columns was used: 20% UC-W98 on Chromosorb P 40/60 mesh (20 ft × 0.375 in.); 20% TCEP on Chromosorb P 40/60 mesh (20 ft × 0.375 in.); 30% SE-30 on Chromosorb A 60/80 mesh (12 ft × 0.375 in.); 20% Carbowax 20M + 10% KOH on Chromosorb W 60/80 mesh (12 ft × 0.375 in.); 30% SE-52 on Chromosorb A (12 ft × 0.375 in.).

High performance liquid chromatography was carried out in a Waters Prep LC/system 500 A instrument with two Prep PAK-500 silica gel normal phase columns and a refractive index detector.

Microanalyses, by Galbraith Laboratories, Inc., and M-H-W Laboratories, were, in general, performed on mixtures of isomers. Melting points and boiling points are uncorrected.

Methyltetrahydropyrans. General Procedure.[26] Five grams of the appropriate 1,5-diol and 0.5 g of Amberlyst 15 (Rohm and Haas beaded poly(styrenesulfonic acid)) were placed in a 25-mL flask equipped with a magnetic stirrer and distilling head. The reaction mixture was heated slowly to 140–160 °C on the oil bath and the product distilled initially as an azeotrope with water and then as a clear liquid. The water layer was separated and the combined colorless organic product dried over molecular sieves and redistilled at atmospheric pressure.

3-Methyltetrahydropyran (1) and 2,2-Dimethyltetrahydrofuran. 2-Methyl-1,5-pentanediol[40] was converted into the cyclic ether in 86.2% yield by the procedure described above, bp 107 °C (lit.[43] 109 °C (733 mm)). Gas chromotographic analysis (UC-W98, 60 °C) revealed the presence of two side products (3% and 4%), and one of them (3%) having the shortest retention time was collected during purification of 3-methyltetrahydropyran by preparative GLC (TCEP, 70 °C) and found to be 2,2-dimethyltetrahydrofuran.[44] The other contaminant was not identified.

3-Methyltetrahydropyran (1): ^1H NMR ($CDCl_3$) δ 0.78 (d, J = 6.0 Hz, 3 H, CH_3), 1.10–1.93 (m, 5 H), 2.75–3.48 (m, 2 H), 3.6–4.0 (m, 2 H); ^{13}C NMR, Table V.

(43) Hanschke, E. *Chem. Ber.* **1955**, *88* 1048.
(44) Ansell, M. F.; Thomas, D. A. *J. Chem. Soc.* **1958**, 1163.

2,2-Dimethyltetrahydrofuran: ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 6 H), 1.5–2.3 (m, 4 H), 3.81 (bt, J = 7.0 Hz, 2 H); ^{13}C NMR.[27]

***cis*- and *trans*-2,3-Dimethyltetrahydropyrans.** Since attempted synthesis of 2,3-dimetyltetrahydropyran by treatment of 4-methyl-1,5-hexanediol with Amberlyst 15 afforded almost exclusively 2-ethyl-2-methyltetrahydrofuran,[27] an alternative route was developed. A solution of 21 g (0.111 mol) of *p*-toluenesulfonyl chloride and 9.9 g (0.075 mol) of 4-methyl-1,5-hexanediol[40] in ca. 50 mL of pyridine was kept at 80 °C overnight, cooled, and poured over a mixture of ice and hydrochloric acid. Extraction with ether (3 × 100 mL) followed by drying over anhydrous magnesium sulfate and concentration and distillation of the colorless residue through a short Vigreux column afforded 4.3 g (51%) of isomeric 2,3-dimethyltetrahydropyrans, bp 121–123 °C (lit.[45] 123–123.5 °C). The isomeric products were separated by preparative GLC on a TCEP column. The short and long retention time products were identified as *trans*- (82%) and *cis*-2,3-dimethyltetrahydropyrans (18%), respectively, on the basis of their ^{1}H and ^{13}C NMR spectra.

***cis*-2,3-Dimethyltetrahydropyran (2)**: ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.0 Hz, 3 H), 1.08 (d, J = 6.5 Hz, 3 H), 1.2–1.8 (m, 5 H), 3.0–4.0 (m, 3 H); ^{13}C NMR, Table IV.

***trans*-2,3-Dimethyltetrahydropyran**: ^{1}H NMR ($CDCl_3$) δ 0.82 (d, J = 6.0 Hz, 3 H), 1.13 (d, J = 6.0 Hz, 3 H), 1.1–1.9 (m, 5 H), 2.75–4.1 (m, 3 H); ^{13}C NMR.[28]

***cis*- and *trans*-2,4-Dimethyltetrahydropyrans and *cis*- and *trans*-2-Ethyl-3-methyltetrahydrofurans.** These compounds were prepared from 3-methyl-1,5-hexanediol[40] by treatment with Amberlyst 15 in the manner described above. The products were formed in 82% combined yield, bp 118–121 °C (lit.[46] bp 118–119 °C for **3**), and constituted a mixture of four isomeric cyclic ethers. The four isomers were separated by preparative GLC (TCEP, 80 °C) and their structures assigned on the basis of ^{1}H and ^{13}C NMR as (in order of increasing retention time) *cis*-2,4-dimethyltetrahydropyran (65%), *trans*-2-ethyl-3-methyltetrahydrofuran (6%), *trans*-2,4-dimethyltetrahydropyran (**3**, 27%), and *cis*-2-ethyl-3-methyltetrahydropyran (2%). Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.45; H, 12.33. (Four-component mixture.)

***trans*-2,4-Dimethyltetrahydropyran (3)**: ^{1}H NMR ($CDCl_3$) δ 1.03 (d, 6.5 Hz, 3 H), 1.18 (d, J = 6.5 Hz, 3 H), 1.1–2.2 (m, 5 H), 3.4–4.0 (m, 3 H); ^{13}C NMR, Table IV.

***cis*-2,4-Dimethyltetrahydropyran**: ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6 Hz, 3 H), 1.17 (d, J = 6 Hz, 3 H), 1.15–1.7 (m, 5 H), 2.95–3.6 (m, 2 H), 3.75–4.1 (m, 1 H); ^{13}C NMR.[28]

***cis*-2-Ethyl-3-methyltetrahydrofuran**: ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 7.3 Hz, 3 H), 0.93 (t, J = 6.8 Hz, 3 H), 1.1–2.0 (m, 5 H), 3.5–3.9 (m, 3 H); ^{13}C NMR.[27]

***trans*-2-Ethyl-3-methyltetrahydrofuran**: ^{1}H NMR ($CDCl_3$) δ 1.1 (t, J = 7 Hz, 3 H), 1.12 (d, J = 7 Hz, 3 H), 1.2–1.8 (m, 5 H), 3.45–3.8 (m, 3 H); ^{13}C NMR.[27]

***cis*- and *trans*-2,5-Dimethyltetrahydropyrans and *cis*- and *trans*-2-Ethyl-4-methyltetrahydrofurans. A. From 2-Methyl-1,5-hexanediol.** Treatment of this diol with Amberlyst 15 as described above afforded, in 76% yield, a crude product, bp 123 °C (lit.[47] bp 116 °C), shown to be a mixture resolved by gas chromatography into three peaks. The three comopunds were separated by preparative GLC (TCEP, 80 °C) and their structures assigned on the basis of ^{1}H and ^{13}C NMR spectroscopy as *trans*-2,5-dimethyltetrahydropyran (38.3%), *cis*-2,5-dimethyltetrahydropyran (36.4%), and *cis*- andd *trans*-2-ethyl-methyltetrahydrofurans (25.3%) in order of increasing retention time. Since the third fraction appeared to be an inseparable 1:1 mixture, inconvenient for spectral interpretation, an alternate synthesis was accomplished utilizing the procedure published by Brown et al.[48] with 2-methylhex-5-en-1-ol[47] as the starting material. This synthesis gave 27% of *trans*-2,5-dimethyltetrahydropyran and 73% of a mixture of *cis*- and *trans*-2-ethyl-4-methyltetrahydrofurans. After separation of the constitutional isomers by preparative GLC, the mixture of tetrahydrofurans was used for ^{13}C NMR measurement and its composition established as 76% cis and 24% trans isomer.[27]

***cis*-2,5-Dimethyltetrahydropyran (4)**: ^{1}H NMR ($CDCl_3$) δ 1.04 (d, J = 6.5 Hz, 3 H), 1.11 (d, J = 6.5 Hz, 3 H), 1.2–1.85 (m, 5 H), 3.1–3.7 (m, 3 H); ^{13}C NMR, Table IV.

***trans*-2,5-Dimethyltetrahydropyran**: ^{1}H NMR ($CDCl_3$) δ 0.79 (d, J = 6.5 Hz, 3 H), 1.15 (d, J = 6.5 Hz, 3 H), 0.95–1.9 (m, 5 H), 2.7–3.6 (m, 2 H), 3.6–4.0 (m, 1 H); ^{13}C NMR.[28]

***cis*- and *trans*-2-Ethyl-4-methyltetrahydrofurans**: ^{1}H NMR ($CDCl_3$) δ 0.75–1.2 (m, 6 H), 1.2–1.78 (m, 3 H), 1.81–2.6 (m, 2 H), 3.1–3.45 (m, 1 H), 3.5–4.1 (m, 2 H); ^{13}C NMR.[27]

B. From *cis*-2-(Hydroxymethyl)-5-methyltetrahydropyran. In order to obtain a sample of **4** of very high purity, **7** (vide infra) was reduced with $LiAlH_4$ in ether to provide, after the usual workup, *cis*-2-(hydroxymethyl)-5-methyltetrahydropyran in 97% yield: bp 105–110 °C (27 mm) (Kugelrohr); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.08 (d, J = 6.4 Hz, 3 H, CH_3), 1.27–1.41 (m, 1 H), 1.48–1.65 (m, 2 H), 1.66–1.81 (m, 2 H), 2.49 (bs, 1 H, OH), 3.53–3.62 (m, 2 H, 6-H), 3.62–3.68 (m, 2 H, CH_2OH); ^{13}C NMR, see ref 28. This compound was converted to its brosylate in 62% yield by treatment with *p*-bromobenzenesulfonyl chloride in pyridine. The crude brosylate was carefully purified by crystallization from 95% ethanol: mp 94.5 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.01 (d, J = 7 Hz, 3 H, CH_3), 1.2–1.84 (m, 5 H, 3-H_2, 4-H_2, and 5-H), 3.45–3.75 and 4.0–4.18 (2 m, 5 H, 2-H, 6-H_2, and CH_2OBs), 7.6–7.85 (m, 4 H, aromatic protons). Reduction of the pure brosylate with $LiAlH_4$ in ether gave, after the usual workup, the desired *cis*-2,5-dimethyltetrahydropyran (**4**), purified by preparative GLC (using a TCEP column) prior to the NMR measurements. Anal. Calcd for $C_7H_{14}O$: C, 73.68; H, 12.28. Found: C, 73.71; H, 12.32.

***cis*- and *trans*-3,4-Dimethyltetrahydropyrans.** 2,3-Dimethyl-1,5-pentanediol[40] upon treatment with Amberlyst 15 was converted into a mixture of *cis*- and *trans*-3,4-dimethyltetrahydropyrans in 86% yield; bp 127–128 °C. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.43; H, 12.29.

The isomeric products were separated by preparative GLC (TCEP, 80 °C). The short and long retention time products were assigned the trans (51%) and cis (49%) structures, respectively, on the basis of their ^{1}H and ^{13}C NMR spectra.

***cis*-3,4-Dimethyltetrahydropyran (5)**: ^{1}H NMR ($CDCl_3$) δ 0.9 (d, J = 6.5 Hz, 6 H, 2 CH_3), 1.2–2.0 (m, 4 H, 3-H, 4-H, and 5-H_2), 3.1–3.98 (m, 4 H, 2-H_2 and 6-H_2); ^{13}C NMR, Table IV.

***trans*-3,4-Dimethyltetrahydropyran**: ^{1}H NMR ($CDCl_3$) δ 0.80 (d, J = 6.5 Hz, 3 H, CH_3), 0.94 (d, J = 6.5 Hz, 3 H, CH_3), 0.85–1.6 (m, 4 H, 3-H, 4-H, and 5-H_2), 2.7–4.05 (m, 4 H, 2-H_2 and 6-H_2); ^{13}C NMR.[28]

***trans*-2-(Carbomethoxy)-4-methyltetrahydropyran (6).**[20] The modification of the synthesis of this compound from isoprene and butyl glyoxylate[29] followed by hydrogenation and transesterification will be described in detail elsewhere.[28]

***trans*- and *cis*-2-(Carbomethoxy)-5-methyltetrahydropyran (7)** were synthesized according to a modification of the reported method.[20]

2-(Carbomethoxy)-5-methyl-3,4-dihydro-2*H*-pyran. Diels–Alder reaction of 42.5 g (0.61 mol) of methacrolein and 150 g (1.74 mol) of methyl acrylate with 1 g of hydroquinone as inhibitor at 200 °C yielded 40 g of a liquid boiling around 220 °C. HPLC separation (two Prep-PAK/500 silica gel normal phase columns, 10% ethyl acetate/hexane mixture eluent) yielded pure 2-(carbomethoxy)-5-methyl-3,4-dihydro-2*H*-pyran (21% yield) and methacrolein dimer in about a 1:1 ratio: ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.58–1.59 (d, J = 1.5 Hz, 3 H, CH_3), 1.9–2.2 (m, 4 H, H_2-3, H_2-4), 3.8 (s, 3 H, $COOCH_3$), 4.3–4.48 (m, 1 H, H-2), 6.24–6.25 (d, J = 1.5 Hz, —CH═); ^{13}C NMR.[28]

Hydrogenation of 2-(carbomethoxy)-5-methyl-3,4-dihydro-2*H*-pyran (5 g, 0.032 mol) was carried out at room temperature and atmospheric pressure with 1 g of 10% Pt on carbon in 50 mL of 95% ethanol. When the reaction stopped after ca. 12 h, fresh catalyst (0.5 g) was added and hydrogenation continued until the theoretical amount of hydrogen was consumed. After filtration and evaporation of the solvent, the residual liquid was distilled (bp 90–95 °C (25 mm), lit.[20] 70–74 °C (5 mm)) to give 4.85 g (95%) of a 9:1 mixture of *cis*- and *trans*-2-(carbomethoxy)-5-methyltetrahydropyrans as analyzed by ^{13}C NMR spectroscopy. This mixture was separated on a SE-52 GLC column at 150 °C, the cis isomer emerging first.

***cis*-2-(Carbomethoxy)-5-methyltetrahydropyran (7)**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.97–1.00 (d, J = 6.6 Hz, 3 H, CH_3). A set of three multiplets comprising hydrogens at 3, 4, and 5: 1.30–1.45 (1 H), 1.71–1.92 (3 H) and 1.93–2.08 (1 H), 3.55–3.78 (8 lines, 2 H, H_2-6), 3.78 (s, 3 H, $COOCH_3$), 4.2–4.28 (t, J = 3.3 Hz, 1 H, H-2); ^{13}C NMR, Table IV.

***trans*-2-(Carbomethoxy)-5-methyltetrahydropyran**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.82–0.85 (d, J = 6.6 Hz, 3 H, CH_3), 1.09–1.18 and 1.55–2.00 (m, 5 H, H_2-3, H_2-4, H-5), 3.00–3.11 (doublet of doublet appearing as triplet, J = 7.4 Hz, 1 H, H-6 (ax)), 3.75 (s, 3 H, $COOCH_3$), 3.87–3.96 (q, 1 H, H-6 (eq)), 3.96–4.06 (broad q, 1 H, H-2); ^{13}C NMR.[28]

2-Ethynyltetrahydropyran (8). This compound was synthesized from 2-chlorotetrahydropyran and ethynylmagnesium bromide as previously described:[49] bp 72 °C (60 mm) (lit.[49] 56 °C (25 mm)), yield 40%.

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Additional purification by preparative GLPC (30% SE-30 on Chromosorb W) was performed prior to recording the ^{13}C NMR spectra (Table IV).

***cis*-2-Ethynyl-5-methyltetrahydropyran (9). 2-Ethoxy-5-methyltetrahydropyran.** 2-Ethoxy-5-methyl-3,4-dihydro-2*H*-pyran[50] was hydrogenated at room temperature and atmospheric pressure with 5% Pd/C as catalyst and ether as solvent. The hydrogenation afforded 2-ethoxy-5-methyltetrahydropyran in essentially quantitative yield as determined by analytical GC (30% SE 30 on Chromosorb W, 90 °C) after the normal workup: ^1H NMR ($CDCl_3$) δ 0.82 (d, J = 6.5 Hz, 3 H, 5-CH_3), 1.20 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.4–2.0 (m, 5 H, 3-H_2, 4-H_2, and 5-H), 3.15–4.0 (m, 4 H, 6-H_2 and OCH_2CH_3), 4.70 (bs, 1 H, 2-H).

3-Methyl-3,4-dihydro-2*H*-pyran. Distillation of crude 2-ethoxy-5-methyltetrahydropyran from a catalytical amount of *p*-toluenesulfonic acid provided 3-methyl-3,4-dihydro-2*H*-pyran in 68.8% yield: bp 64–66 °C (180 mm) (Kugelrohr); ^1H NMR ($CDCl_3$) δ 0.92 (d, J = 6.8 Hz, 3 H, 3-CH_3), 1.4–2.1 (m, 3 H, 3-H and 4-H_2), 3.4–3.65 (m, 2 H, 2-H_2), 4.35 (m, 1 H, 5-H), 6.3 (m, 1 H, 6-H); ^{13}C NMR.[28]

2-Chloro-5-methyltetrahydropyran. Addition of hydrogen chloride to 3-methyl-;3,4-dihydro-2*H*-pyran was carried out as described,[11,51] the 2-chloro-5-methyltetrahydropyran thus obtained being used without distillation.

***cis*-2-Ethynyl-5-methyltetrahydropyran.** Reaction of 2-chloro-5-methyltetrahydropyran with ethynylmagnesium bromide[49] provided crude 2-ethynyl-5-methyltetrahydropyran (**9**) in 15.1% yield, bp 94–96 °C (66 mm) (Kugelrohr), further purified by preparative GLPC using 30% SE 30 on Chromosorb A column at 100 °C. The cis configuration of **9** was assigned on the basis of its ^1H and ^{13}C NMR spectra: ^1H NMR ($CDCl_3$) δ 0.86 (d, J = 7 Hz, 3 H, 5-CH_3), 1.4–2.0 (m, 5 H, 3-H_2, 4-H_2, and 5-H), 2.45 (d, J = 2 Hz, 1 H, –C≡CH), 3.54–3.70 (m, 2 H, 6-H_2), 4.58–4.70 (m, 1 H, 2-H); ^{13}C NMR, Table IV.

***cis*-2-Vinyl-5-methyltetrahydropyran (11).** Compound **9** (300 mg) was hydrogenated by using 30 mg of Lindlar's catalyst and a drop of quinoline in 1.5 mL of hexane at room temperature and atmospheric pressure until the theoretical quantity of hydrogen (54.3 mL) was absorbed. Filtration followed by Kugelrohr distillation (130 °C) gave a three-component mixture separated by preparative GLC (20% Carbowax 20M + 10% KOH; 90 °C) to yield pure **11** as the middle fraction (50%): ^1H NMR (CD_2Cl_2, 250 MHz) δ 1.01–1.04 (d, J = 7 Hz, 3 H, CH_3), 1.48–1.77 (m, 5 H, 3-H_2, 4-H_2, 5-H), 3.58–3.59 (m, sharp, 2 H, 6-H_2), 3.81–3.88 (m, broad, 1 H, 2-H (allylic)), 5.03–5.22 (AB part of ABMX system, 12 lines, J_t = 17.54 Hz, J_c = 11 Hz, $J_{allylic}$ = J_{gem} = 1.83 Hz, 2 H, =CH_2), 5.79–5.93 (M part of ABMX system, 8 lines, J_t = 17.54 Hz, J_c = 11 Hz, J_{vic} = 5.5 Hz, 1 H, –CH=); ^{13}C NMR, Table IV. Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.95; H, 11.07.

***trans*-2-Vinyl-4-methyltetrahydropyran (10). *trans*-2-Ethynyl-4-methyltetrahydropyran (15).** Coupling of 2-chloro-4-methyl-tetrahydropyran[11] with ethynylmagnesium bromide yielded *trans*-2-ethynyl-4-methyltetrahydropyran in 13% yield, bp 80–83 °C (22 mm) (Kugelrohr). This was purified as described above for the corresponding 5-methyl isomer (**9**). The trans configuration of the product was assigned on the basis of ^1H and ^{13}C NMR[28] spectra: ^1H NMR ($CDCl_3$, 100 MHz) δ 0.98–1.01 (d, J = 6.5 Hz, 3 H, CH_3), 1.02–2.2 (m, 5 H, 3-H_2, 4-H_2, and 5-H), 2.45 (d, J = 2 Hz, 1 H, acetylenic), 3.58–4.08 (d,d,d, 2 H, 6-H_2), 4.62–4.78 (quintet, 1 H, 2-H_2).

***trans*-2-Vinyl-4-methyltetrahydropyran.** Catalytic reduction of 2-ethynyl-4-methyltetrahydropyran as described above for 2-ethynyl-5-methyltetrahydropyran gave a 1:2:1 mixture of 2-ethyl-, 2-vinyl-, and 2-ethynyl-4-methyltetrahydropyrans, which was separated by preparative GLC (20% Carbowax 20M + 10% KOH column, 100 °C) to yield pure **10** for NMR measurements: ^1H NMR (CD_2Cl_2, 250 MHz) δ 1.03–1.06 (d, J = 7 Hz, 3 H, CH_3), a set of four multiples 1.17–1.31 (1 H), 1.35–1.47 (1 H), 1.58–1.77 (2 H), 1.86–2.05 (1 H), (hydrogens at 3, 4, and 5), 3.59–3.76 (m, 2 H, H_2-6), 4.14–4.23 (m, broad, 1 H, H-2), 5.06–5.26 (AB part of ABMX spectrum, 12 lines, J_t = 17.5 Hz, J_c = 10.5 Hz, J_{gem} = J_{allyic} = 2 Hz, 2 H, =CH_2), 5.74–5.96 (M part of ABMX system, 8 lines, J_t = 17.5 Hz, J_c = 10.5 Hz, J_{vic} = 5.5 Hz, 1 H, —CH=); ^{13}C NMR, Table IV. Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.11; H, 11.26.

***cis*- and *trans*-2-Vinyl-6-methyltetrahydropyrans. 3,4-Dihydro-2*H*-pyran-2-methanol.** The sodium salt of 3,4-dihydro-2*H*-pyran-2-carboxylic acid (Aldrich Chemical Co.) was reduced with $LiAlH_4$ in refluxing THF to give 3,4-dihydro-2*H*-pyran-2-methanol in 84% yield: bp 90–92 °C (22 mm) (lit.[52] bp 81–82 °C (13 mm)); ^1H NMR ($CDCl_3$, 100 MHz) δ 1.41–1.95 (m, 2 H, 3-H_2), 1.96–2.31 (m, 2 H, 4-H_2), 3.18 (s, 1 H, OH), 3.6–3.8 (m, 2 H, CH_2OH), 3.8–4.06 (m, 1 H, 2-H); ^{13}C NMR.[28]

2-Methyl-3,4-dihydro-2*H*-pyran. 3,4-Dihydro-2*H*-pyran-2-methanol yielded an oily tosylate on treatment with *p*-toluenesulfonyl chloride–pyridine followed by the standard workup. The *p*-toluenesulfonate was crystallized from petroleum ether and reduced with $LiAlH_4$ in ether to yield 2-methyl-3,4-dihydro-2*H*-pyran in 72% yield: bp 220 °C (lit.[53] bp 62 °C (150 mm)); ^1H NMR ($CDCl_3$, 100 MHz) δ 1.25 (d, J = 6.6 Hz, 3 H, 2-CH_3), 1.35–1.9 (m, 2 H), 1.90–2.19 (m, 2 H), 3.95 (m, 1 H, 2-H), 4.58–4.77 (m, 1 H, 5-H), 6.37 (dt, J = 6.4 Hz, 2 Hz, 1 H, 6-H); ^{13}C NMR.[28]

2-Chloro-6-methyltetrahydropyran was prepared by bubbling dry hydrogen chloride gas into 2-methyl-3,4-dihydro-2*H*-pyran (14 g, 0.143 mol) in 100 mL of dry ether at –10 °C for 3 h. Gentle vacuum was applied to the solution followed by bubbling dry nitrogen through it to remove excess hydrogen chloride. The resulting product was used without further purification. Vinyl bromide (61.0 g, 0.57 mol) in 100 mL of THF was added to 14.4 g (0.6 mol) of magnesium turnings in a flask equipped with an acetone–dry ice reflux condenser. To the resulting Grignard reagent was added 10 drops of 10% $FeCl_3$ solution in THF[54] followed by dropwise addition of the etheral solution of 2-chloro-6-methyltetrahydropyran.[55] The acetone–dry ice condenser was replaced by a water condenser and the solution stirred overnight. The usual workup followed by distillation gave 10.5 g (0.083 mol, 58% from the dihydropyran) of product, bp 144–150 °C, found to be a 1:3 mixture of *cis*- and *trans*-2-vinyl-6-methyltetrahydropyrans as shown by ^1H and ^{13}C NMR analysis. The mixture was separated by preparative GLC (20% Carbowax 20M + 10% KOH column, 100 °C), with the cis isomer having a shorter retention time.

***trans*-2-Vinyl-6-methyltetrahydropyran (12):** ^1H NMR ($CDCl_3$, 250 MHz) δ 1.16–1.19 (d, J = 6.6 Hz, 3 H, CH_3), 1.23–1.38 (m, 1 H, axial hydrogen at 4[56]), 1.51–1.78 (m, 5 H, 3-H_2, 4-H_1 (eq), 5-H_2), 3.83–3.97 (m, 1 H, 6-H), 4.33–4.39 (m, 1 H, 2-H), 5.15–5.26 (12 lines, AB part of ABMX spectrum, J_t = 17.1 Hz, J_c = 10.5 Hz, $J_{allylic}$ = J_{gem} = 1.8 Hz, 2 H, =CH_2), 5.88–6.01 (8 lines, M part of ABMX spectrum, J_t = 17.1 Hz, J_c = 10.5 Hz, J_{vic} = 4.9 Hz, 1 H, —CH=); ^{13}C NMR, Table IV. Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.05; H, 11.16.

***cis*-2-Vinyl-6-methyltetrahydropyran:** ^1H NMR ($CDCl_3$, 250 MHz) δ 1.19–1.22 (d, J = 6.5 Hz, 3 H, CH_3); a set of three multiplets comprising hydrogens at 3, 4, and 5: 1.11–1.41 (2 H), 1.45–1.70 (3 H), and 1.79–1.91 (1 H), 3.44–3.57 (12 lines, 1 H, 6-H), 3.79–3.89 (m, 1 H, 2-H), 5.06–5.33 (AB part of ABMX spectrum, 12 lines, J_t = 17.1 Hz, J_c = 10.5 Hz, $J_{allylic}$ = J_{gem} = 1.65 Hz, 2 H, =CH_2), 5.81–5.96 (M part of ABMX spectrum, 8 lines, J_t = 17.1 Hz, J_c = 10.5 Hz, J_{vic} = 6 Hz, 1 H, —CH=); ^{13}C NMR.[28]

***trans*-2-(Hydroxymethyl)-6-methyltetrahydropyran (13).** *trans*-2-Carbomethoxy)-6-methyltetrahydropyran[20,28] (200 mg, 0.0013 mol) was reduced with 40 mg of $LiAlH_4$ in 20 mL of absolute ether. After the reaction was quenched by dropwise addition of saturated sodium sulfate solution, the ether solution was filtered and dried over anhydrous K_2CO_3, concentrated, and distilled (Kugelrohr, bp 110–115 °C (33 mm) to yield 156 mg (89%) of **13**: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.13–1.16 (d, J = 6.8 Hz, 3 H, CH_3 (6)), 1.23–1.37 (m, 2 H), and 1.48–1.68 (m, 4 H, comprising H_2-3, H_2-4, and H_2-5), 2.55 (s, broad, OH), 3.37–3.41 and 3.56–3.64 (4 lines each, 2 H, CH_2OH), 3.71–3.80 (7 lines, 1 H, H-6), 3.88–4.00 (m, 1 H, H-2); ^{13}C NMR, Table IV. Anal. Calcd for $C_7H_{14}O_2$: C, 64.62; H, 10.77. Found: C, 64.40; H, 10.98.

***trans*-2-Ethyl-6-methyltetrahydropyran (14).** Catalytic hydrogenation of *trans*-2-vinyl-6-methyltetrahydropyran (**12**, 200 mg, 0.0016 mol) with 20 mg of 5% rhodium on alumina in 0.5 mL of hexane at atmospheric pressure afforded 140 mg (0.0012 mol, 75%) of **14** after distillation, bp 141–143 °C (760 mm) (Kugelrohr) (lit.[57] bp 34–35 °C (15 mm)). The NMR sample was obtained by passing the distillate through a SE-52 preparative GLC column: ^1H NMR (CD_2Cl_2, 250 MHz) δ 0.84–0.90 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.11–1.13 (d, J = 6.8 Hz, 6-CH_3), 1.20–1.44 (m, 3 H, CH_2CH_3 and one of the hydrogens at 3, 4, or 5), 1.55–1.70 (m, 5 H, hydrogens at 3, 4, and 5), 3.53–3.61 (m, 1 H, H-6), 3.79–3.85 (m, 1 H, H-2); ^{13}C NMR, see Table IV.

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Registry No. 1, 26093-63-0; *cis*-**2**, 81554-06-5; *trans*-**2**, 81571-95-1; *cis*-**3**, 67217-63-4; *trans*-**3**, 67217-62-3; *cis*-**4**, 81554-07-6; *trans*-**4**, 81554-08-7; *cis*-**5**, 81554-09-8; *trans*-**5**, 81554-10-1; **6**, 16831-15-5; *cis*-**7**, 16831-12-2; *trans*-**7**, 16831-13-3; **8**, 76928-53-5; **9**, 81554-11-2; **10**, 81554-12-3; **11**, 81554-13-4; *cis*-**12**, 81554-14-5; *trans*-**12**, 81554-15-6; **13**, 81554-16-7; **14**, 81554-17-8; **15**, 81554-18-9; 2-methyl-1,5-pentanediol, 42856-62-2; *cis*-2-ethyl-3-methyltetrahydrofuran, 73435-16-2; *trans*-2-ethyl-3-methyltetrahydrofuran, 73435-17-3; 3-methyl-1,5-hexanediol, 4089-71-8; *cis*-2-ethyl-4-methyltetrahydrofuran, 73435-18-4; *trans*-2-ethyl-4-methyltetrahydrofuran, 73435-19-5; *cis*-2-(hydroxymethyl)-5-methyltetrahydropyran brosylate, 81554-19-0; 2,3-dimethyl-1,5-pentanediol, 81554-20-3; 2-(carbomethoxy)-5-methyl-3,4-dihydro-2*H*-pyran, 81554-21-4; methacrolein, 78-85-3; methyl acrylate, 96-33-3; ethynyl bromide, 593-61-3; 2-ethoxy-5-methyltetrahydropyran, 81554-22-5; 2-ethoxy-5-methyl-3,4-dihydro-2*H*-pyran, 2397-94-6; 2-chloro-5-methyltetrahydropyran, 81554-23-6; 2-chloro-4-methyltetrahydropyran, 79543-42-3; 3,4-dihydro-2*H*-pyran-2-methanol, 3749-36-8; 3,4-dihydro-2*H*-pyran-2-carboxylic acid sodium salt, 16698-52-5; 2-methyl-3,4-dihydro-2*H*-pyran, 13039-50-4; 2-chloro-6-methyltetrahydropyran, 81554-24-7; vinyl bromide, 593-60-2; *trans*-2-(carbomethoxy)-6-methyltetrahydropyran, 16831-11-1; 2-chlorotetrahydropyran, 3136-02-5; 3-methyl-3,4-dihydro-2*H*-pyran, 15990-72-4.

Porphyrins with Multiple Crown Ether Voids: Novel Systems for Cation Complexation Studies

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Abstract: Porphyrins appended with crown ether, benzo-15-crown-5, at the methine positions have been synthesized and characterized. The fully and partially substituted porphyrins and their metallo (Co, Cu, and Zn) derivatives describe one or more ether cavities in the periphery that are capable of recognizing spherical cations. The ability of these macrocycles to complex cations (Na^+, K^+, Mg^{2+}, Ca^{2+}, Ba^{2+}, and NH_4^+) is investigated by use of visible, ^1H NMR, ESR, and emission spectral studies. The tetrasubstituted crown porphyrin (TCP) exhibits very high selectivity for K^+. The cations (K^+, Ba^{2+}, and NH_4^+) that require two crown ether cavities for complexation promote dimerization of the porphyrins. The ESR study of the cation-induced porphyrin dimers reveals axial symmetry with the porphyrin planes separated by ~4.2 Å. This distance increases from the fully substituted to partially substituted porphyrins. The cations (K^+, Ba^{2+}, and NH_4^+) quench efficiently the fluorescence of the free base porphyrins and their metallo derivatives. The quenching process is attributed to the steric geometry of the dimers.

There has been considerable research interest in the synthesis of porphyrins with different substitutents in the periphery in view of their utility as models to mimic several biofunctions such as heme oxygenation, cytochrome activity, and photosynthetic electron transport. The design of model compounds depends on the judicious choice of the nature of the substituent and the peripheral position being substituted. Thus, covalently linked porphyrin dimers,[1] sterically crowded porphyrins,[2] and porphyrins appended with organic moieties with acceptor functionalities[3] have been studied to elucidate molecular mechanisms involved in energy transfers, reversible oxygenations, and light-induced electron transport, respectively. We have been interested in the macrocyclic compounds to model carriers for specific cation (Na^+/K^+) transport across biomembranes. Molecular entities endowed with cavities that are capable of recognizing spherical cations containing a central fluorescent porphyrin group form attractive systems to study the movement of cations during transport. The novel cavity-bearing porphyrins can be used with advantage as ionophores, and the ionophoric behavior monitored by the change in fluorescence may also be correlated with properties like the inhibition of oxidative phosphorylation in the respirating mitochondrial systems.

A majority of the synthesized porphyrins normally have substituents in pyrrole units containing paraffinic,[4] ether,[5] and/or amide[1d] linkages. Here, we report the preparation and characterization of porphyrins functionalized at the methine positions with macrocyclic polyethers as first examples of porphyrins with multiple host sites. These sites offer an opportunity to study cation complexation behavior of the porphyrin macrocycle.

Experimental Section

All solvents and reagents used in the synthesis work were of reagent grade quality. The solvents for spectroscopic work were purified and distilled prior to use. The spectrometers employed in the present study are the same as described in the earlier work.[6]

Benzo-15-crown-5 was synthesized according to Pederson[7] and was then converted into an 4′-aldehyde by using the method described in literature.[8] The 4′-aldehyde crown ether (50 mmol) and pyrrole (50 mmol) in propionic acid (300 mL) were refluxed for 45 min. The mixture was worked up in a manner similar to the one employed for the

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