# Experimental and Theoretical Studies of Acid-Catalyzed $^{18}O$ Exchange Rates of Conformationally Rigid Ketones. Is the Antiperiplanar Effect Important?†

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The relative rates for the acid-catalyzed addition of $H_2{}^{18}O$ to the carbonyl group of the conformationally fixed bridged biaryl ketone, 1, and several derivatives bearing methyl, chloro, and methoxy substituents in axial-like and equatorial-like orientations have been measured. The effects of axial- versus diaxial-like methyl and chloro substituents produce rate decreases which are consistent with the antiperiplanar (hyperconjugative) interaction proposed by Cieplak; however, the negligible influence of a methoxy group when antiperiplanar is not consistent. Theoretical calculations suggest an unsymmetrical structure for the transition state. On the basis of this structure, the results may be rationalized by a large steric interaction for the first axial methyl or chloro substituent (synperiplanar to the nucleophile) and a small one for the second (antiperiplanar) substituent. An axial methoxy can stabilize the transition state by hydrogen bonding when syn but can only exert the observed small steric retardation in the transition state involving antiperiplanar attack.

More than 30 years ago Cram and co-workers formulated a rule for predicting the preferred face of attack by a nucleophile at a carbonyl group adjacent to an asymmetric center.[1] Subsequently, a number of alternate models were put forward by Cornforth,[2] Karabatsos,[3] and Felkin.[4] The four models which represent different rotameric transition states are shown in Figure 1. Later, theoretical calculations by Anh and Eisenstein[5] supported the Felkin model, particularly when modified to allow nonperpendicular attack by hydride ion.[6] In arriving at this conclusion, they attributed a key role to the strong energetic preference for an antiperiplanar (app) approach to permit an n,$\sigma^*$ interaction between the pair of the electrons of the nucleophile and the $\sigma^*$ antibonding orbital of the antiperiplanar C–L bond.[7] They also compared the relative stabilization energies due to an app C–H, C–C, and C–Cl bond in the transition state for hydride ion addition. The energies were calculated to be 35.5, 37.4, and 59.0 kcal/mol, respectively (relative to unreacting starting material). In contrast, the exact opposite order of stabilization energies was predicted by Cieplak.[8] Based on his extensive analysis of the literature of hydride ion reductions of cyclohexanone, Cieplak put forward the novel proposal that the ubiquitously preferred axial attack was only

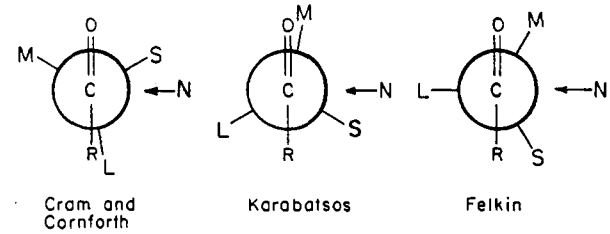


**Figure 1.** Models proposed to explain 1,2-asymmetric induction.

explicable by an orbital interaction, ($\sigma$,$\sigma_{\not\perp}$*) between the app C–H bond (axial and $\alpha$ to the C=O acting as donor) and the incipient bond formed by the hydride ion (antibonding and acting as acceptor).[9] His proposed order of donor strength, based on qualitative considerations of hyperconjugative abilities and electronegativities, was cited as an important influence on any nucleophilic addition to a carbonyl.[10] Recent calculations by Wu and Houk failed to support either of the above predictions regarding the app effect but instead indicated torsional effects as the major influence on the stereoselectivity.[11] The importance of electrostatic interactions has also been advanced.[11e,12] In order to test the validity of these theories, we have studied the effects of an $\alpha$-methyl, $\alpha$-chlorine, and $\alpha$-methoxy versus hydrogen on the rates of addition of $H_2{}^{18}O$ to ketone 1.[13]

† Dedicated to the memory of our colleague Jean-Louis Roustan, deceased September 28, 1992.

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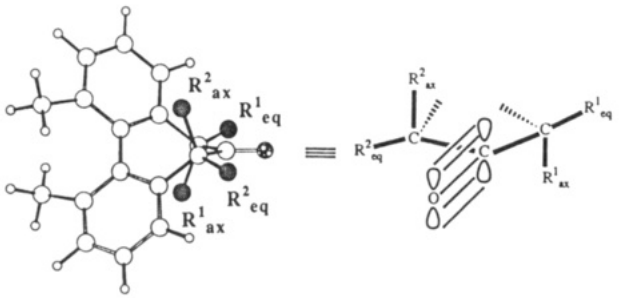


| Compd. | $R^1_{eq}$ | $R^2_{eq}$ | $R^1_{ax}$ | $R^2_{ax}$ | $\Delta\Delta G^{\ddagger}$ (kcal/mol) |
|---|---|---|---|---|---|
| 1 | H | H | H | H | 0 |
| 2 | Me | H | H | H | 0.9 |
| 3 | H | H | Me | H | 2.3 |
| 4 | H | H | Me | Me | 2.7 |
| 5 | Me | Me | H | H | 4.4 |
| 6 | Cl | H | H | H | 1.5 |
| 7 | H | H | Cl | H | 2.8 |
| 8 | H | H | Cl | Cl | 3.5 |
| 9 | Cl | Cl | H | H | 2.2 |
| 10 | Cl | H | H | Cl | 4.1 |
| 11 | OMe | H | H | H | 1.0 |
| 12 | H | H | OMe | H | 0.15 |

**Figure 2.** Structural and 3-dimensional representation of compounds 1–12.

Bridged biaryl ketone 1[14] was chosen for the study of substituent effects in a position app to the attacking nucleophile as it has several advantages over cyclohexanone as a model for studying conformational effects on reactivity. While maintaining axial-like and equatorial-like bonds $\alpha$ to the carbonyl (see Figure 2), the seven membered ring has a greater rigidity[15] and has no intermediate boat conformation.[16] In addition, because 1 possesses a $C_2$ axis, it offers the possibility for the disection of steric from electronic effects (vide infra).

Recently, several novel approaches to the elimination of steric influences on the face selectivity of reactions of a carbonyl group have been described. Cieplak, Tait, and Johnson[10] have studied the effects of electronegative substituents at C-3 of cyclohexanones and methylenecyclohexanes, both of which produced Hammett correlations with face selectivity. Based on their extensive studies of electronegativity on the stereoselectivity of additions to 5-substituted adamantan-2-ones, le Noble and his coworkers have provided valuable data free from steric effects as a consequence of the unique nature of this rigid structure.[17] Mehta and Khan reported nucleophilic additions to substituted norbornanones,[18] and Halterman and McEvoy described hydride reductions of unsymmetrical cyclopentanones.[19] The observed stereoselectivities have been explained by the Cieplak theory. However, calculations by Wu and Houk and by Paddon-Row and Wong have indicated that all of these results can be understood by a combination of geometrical distortions and through-space electrostatic effects caused by the remote substituents.[11e,20]

**Preparation of Derivatives of 1.** Syntheses of the methyl derivatives were accompanied by routine methods. The monoequatorial compound **2** was prepared via alkylation of the *N,N*-dimethylhydrazone of **1**,[14] followed by oxidative hydrolysis. The monoaxial ketone **3** was obtained as the major product of direct alkylation (LDA, $CH_3I$) of **1**. The diaxial derivative **4** was obtained in the same manner by reaction of **3** with 1.2 equiv of base and excess methyl iodide. The diequatorial derivative **5** was obtained by epimerization of **4** with sodium methoxide. Each of the compounds **2–5** was obtained pure by column chromatography. The monoequatorial chloro derivative **6** was prepared in 60% yield by a recently described method[21] using trimethylchlorosilane and dimethyl sulfoxide with bromide ion catalysis. The monoaxial chloro ketone **7** was obtained as a 60:40 mixture with **6** by direct chlorination using sulfuryl chloride.[22] Attempts to obtain pure isomer **7** were not successful since isomerization to **6** occurred during purification. Because a mixture of **6** and **7** was required for determination of relative rates, a 50:50 mixture, fully characterized by $^1H$ and $^{13}C$ NMR and mass spectrometries was prepared. The diaxial dichloro ketone **8** was obtained as the major product when 2 equiv of sulfuryl chloride was used. Column chromatography afforded pure **8**. Isomerization of **8** on active silica gel gave a mixture of diequatorial dichloro ketone **9** and $\alpha$-equatorial, $\alpha$-axial dichloro ketone **10**, which was separated by repeated recrystallizations. The methoxy derivatives **11** and **12** were obtained by methanolysis of **6**. All attempts to obtain either dimethoxy derivative from methanolysis of **8** or **9** failed due to concurrent rearrangement to the geminal dimethoxy derivative. Proof of configuration of the derivatives was provided by NOE

(13) The effects of methyl substituents were described in a preliminary communication. Fraser, R. R.; Stanciulescu, M. *J. Am. Chem. Soc.* **1987**, *109*, 1580–1581. In this paper we interpreted the effects of methyl substitution in terms of Anh's theory only, an oversight properly corrected by Cieplak, Tait, and Johnson.[10]

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(15) A clear indication of the strong resistance of 1 to conformational change is provided by the value of 39 kcal/mol for the barrier to racemization (by ring inversion). Mislow, K.; Gordon, A. J. *Am. Chem. Soc.* **1963**, *85*, 3521–3521. The much larger stereoselectivity observed in the base-catalysed H–D exchange of 1 (73:1) compared to 4-*tert*-butylcyclohexanone (5:1) supports this contention. Fraser, R. R.; Champagne, P. J. *Can. J. Chem.* **1976**, *54*, 3809–3811. More precise evidence regarding the conformational properties of 1–5 and their rigidity has been obtained from X-ray data and MMX calculations respectively (*Can. J. Chem.*, in press).

(16) The involvement of boat conformations as intermediates has been suggested as an explanation for the lack of appreciable stereoselectivity in the alkylation of cyclohexanones. House, H. O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935–940.

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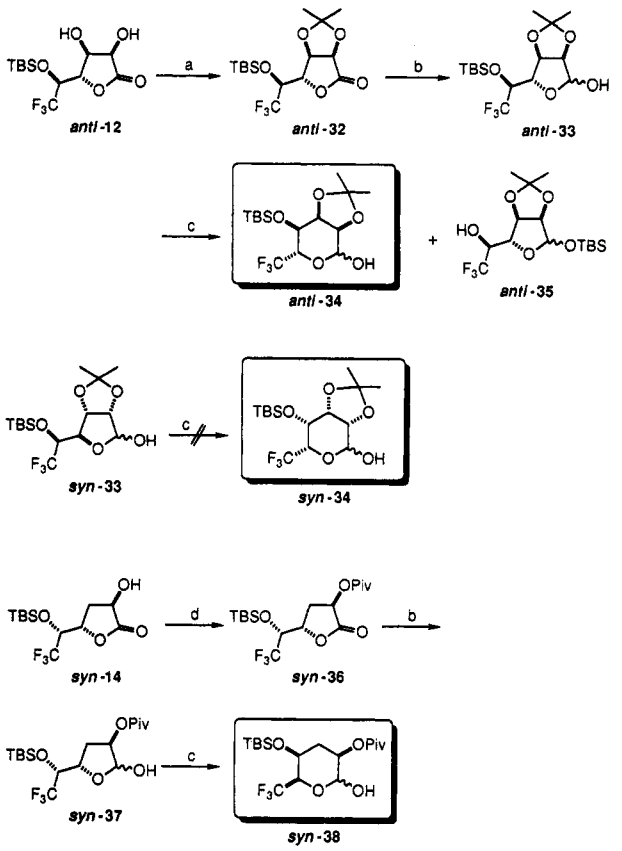
**Scheme VII**[a]




[a] Key: (a) $Me_2C(OMe)_2$, $H^+$; (b) DIBAL-H; (c) $KOBu^t$; (d) pivaloyl chloride, pyr.

Hz), 6.55 (1 H, d, $J$ = 1.63 Hz), 6.62 (1 H, d, $J$ = 1.63 Hz); $^{13}C$ NMR $\delta$ -6.73, 16.54, 20.26, 26.01, 65.74 (q, $J$ = 35.1 Hz), 111.50, 121.53, 122.61 (q, $J$ = 281.4 Hz), 148.55, 161.64, 168.91; $^{19}F$ NMR $\delta$ 3.0 (d, $J$ = 5.9 Hz); IR (neat) $\nu$ 2950, 2925, 2900, 2850, 1770; HRMS calcd for $C_{14}H_{21}F_3O_3Si$ 322.1212, found $m/e$ 322.1207. **2-[2′,2′,2′-Trifluoro-1′-(isobutyroyloxy)ethyl]-5-(trimethylsilyl)furan (3c)**: yield 95%; bp 70–75 °C/2.0 mmHg; $R_f$ 0.60 (AcOEt:Hex = 1:7); $^1H$ NMR $\delta$ 0.24 (9 H, s), 1.17 (3 H, d, $J$ = 7.00 Hz), 1.20 (3 H, d, $J$ = 6.96 Hz), 2.66 (1 H, sep, $J$ = 7.02 Hz), 6.32 (1 H, q, $J$ = 6.68 Hz), 6.51 (1 H, d, $J$ = 3.30 Hz), 6.58 (1 H, d, $J$ = 3.18 Hz); $^{13}C$ NMR $\delta$ -2.08, 18.41, 18.50, 33.59, 65.61 (q, $J$ = 35.0 Hz), 111.21 (q, $J$ = 1.2 Hz), 120.30, 122.66 (q, $J$ = 281.6 Hz), 148.59 (q, $J$ = 1.4 Hz), 162.93, 175.07; $^{19}F$ NMR $\delta$ 3.0 (d, $J$ = 6.8 Hz); IR (neat) $\nu$ 2975, 1760; HRMS calcd for $C_{13}H_{19}F_3O_3Si$ 308.1056, found $m/e$ 308.1039. **2-(*tert*-Butyldimethylsilyl)-5-[(1′-isobutyroyloxy)-2′,2′,2′-trifluoroethyl]furan (3d)**: yield 90%; bp 86–89 °C/0.8 mmHg; $R_f$ 0.68 (AcOEt:Hex = 1:7); $^1H$ NMR $\delta$ 0.21 (6 H, s), 0.88 (9 H, s), 1.16 (3 H, d, $J$ = 6.96 Hz), 1.20 (3 H, d, $J$ = 6.87 Hz), 2.65 (1 H, sep, $J$ = 6.99 Hz), 6.31 (1 H, q, $J$ = 6.69 Hz), 6.51 (1 H, d, $J$ = 3.30 Hz), 6.60 (1 H, d, $J$ = 3.14 Hz); $^{13}C$ NMR $\delta$ -6.76, 16.54, 18.45, 26.02, 33.63, 65.70 (q, $J$ = 35.2 Hz), 111.20, 121.51, 122.74 (q, $J$ = 282.2 Hz), 148.74, 161.64, 175.00; $^{19}F$ NMR $\delta$ 2.6 (d, $J$ = 6.7 Hz); IR (neat) $\nu$ 2975, 2950, 2875, 2850, 1760; HRMS calcd for $C_{16}H_{25}F_3O_3Si$ 350.1525, found $m/e$ 350.1551.

**Enzymatic Hydrolysis.** To a 0.1 M solution of an ester in $H_2O$ was added lipase (6000 unit for 1 mmol of the substrate), and the reaction mixture, maintained at about pH 7 by titration with 1 N NaOH aq, was stirred at 40 °C. When the conversion was found to reach to about 50%, flocculant (P-713, Daiichi Kogyo Seiyaku, Japan) was added. The whole was filtered through Celite-545 to remove the enzyme, and the aqueous phase was treated as usual. Isolation by silica gel column chromatography gave an optically active alcohol and an ester. Physical properties of the obtained materials were identical to those of the corresponding racemic compounds expect for their optical rotations. The enantiomeric excess was determined by capillary GC after derivatization into the corresponding MTPA esters. **(1′*S*)-2-[1′-(2′,2′,2′-Trifluoro-1′-hydroxyethyl)]-5-(trimethylsilyl)furan (2a)**: $[\alpha]^{27}_D$ +7.45° (*c* 1.10, MeOH), 97.6% ee. **(1′*R*)-2-[1′-(1′-Acetoxy-2′,2′,2′-trifluoroethyl)]-5-(trimethylsilyl)furan (3a)**: $[\alpha]^{29}_D$ -102.68° (*c* 1.28, MeOH), 94.3% ee. **(1′*S*)-2-(*tert*-Butyldimethylsilyl)-5-[1′-(2′,2′,2′-trifluoro-1′-hydroxyethyl)]furan (2b)**: $[\alpha]^{19}_D$ +14.33° (*c* 1.13, MeOH), 98.4% ee. **(1′*R*)-2-[1′-(2′,2′,2′-Trifluoro-ethyl-1′-isobutyroyloxy)]-5-(trimethylsilyl)furan (3c)**: $[\alpha]^{19}_D$ -3.3° (*c* 0.77, MeOH), 39.1% ee. **(1′*R*)-2-[1′-(1′-Acetoxy-2′,2′,2′-trifluoroethyl)]-5-(*tert*-butyldimethylsilyl)furan (3b)**: $[\alpha]^{20}_D$ -68.33° (*c* 1.47, MeOH), 88.2% ee. The obtained esters were hydrolyzed by methanolic $K_2CO_3$ (1.2 equiv) at 0 °C, and the usual workup and purification afforded the hydrolyzed alcohols in >95% yield.

**Silylation of Furyl Alcohols.** A 0.5 M $CH_2Cl_2$ solution of furyl alcohol **2** (70.00 mmol) was treated with imidazole and an appropriate silyl chloride (both 1.2 equiv) under $N_2$ at 0 °C. The reaction mixture was stirred overnight at room temperature. The usual workup followed by distillation furnished the desired silyl ether. **(1′*S*)-2-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]-5-(*tert*-butyldimethylsilyl)furan (5a)**: quantitative yield; bp 93–95 °C/0.8 mmHg; $[\alpha]^{17}_D$ +46.25° (*c* 1.33, MeOH), 98.4% ee; $R_f$ 0.79 (AcOEt:Hex = 1:7); $^1H$ NMR $\delta$ -0.02 (3 H, s), -0.01 (3 H, s), 0.21 (6 H, s), 0.86 (9 H, s), 0.90 (9 H, s), 5.02 (1 H, dq, $J$ = 0.52, 6.28 Hz), 6.43 (1 H, d, $J$ = 3.30 Hz), 6.60 (1 H, d, $J$ = 3.26 Hz); $^{13}C$ NMR $\delta$ -6.71, -6.62, -5.72, -5.52, 16.52, 17.93, 25.27, 26.07, 68.21 (q, $J$ = 34.1 Hz), 109.31, 121.68, 123.72 (q, $J$ = 283.1 Hz), 153.10, 159.93; $^{19}F$ NMR $\delta$ -0.0 (d, $J$ = 5.6 Hz); IR (neat) $\nu$ 2975, 2925, 2900, 2850; HRMS calcd for $C_{18}H_{33}F_3O_2Si_2$ 394.1971, found $m/e$ 394.1953. **(1′*S*)-2-[2′,2′,2′-Trifluoro-1′-(trimethylsiloxy)ethyl]-5-(trimethylsilyl)furan (5b)**: yield 98%; bp 71–73 °C/1.3 mmHg; $[\alpha]^{27}_D$ +43.61° (*c* 0.57, MeOH), 97.6% ee; $R_f$ 0.87 (AcOEt:Hex = 1:5); $^1H$ NMR $\delta$ 0.09 (9 H, s), 0.24 (9 H, s), 5.03 (1 H, q, $J$ = 6.46 Hz), 6.21 (1 H, d, $J$ = 3.28 Hz), 6.57 (1 H, d, $J$ = 3.26 Hz); $^{13}C$ NMR $\delta$ -1.98, -0.67, 68.79 (q, $J$ = 34.3 Hz), 109.49, 120.52, 120.38 (q, $J$ = 282.5 Hz), 152.73, 161.64; $^{19}F$ NMR $\delta$ 0.6 (d, $J$ = 5.9 Hz); IR (neat) $\nu$ 2975, 2925; HRMS calcd for $C_{12}H_{21}F_3O_2Si_2$ 310.1032, found $m/e$ 310.1023. **(1′*R*)-2-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]-5-(trimethylsilyl)furan (5c)**: yield 93%; bp 67–69 °C/mmHg; $[\alpha]^{27}_D$ -36.72° (*c* 1.15, MeOH), 94.3% ee; $R_f$ 0.46 (hexane); $^1H$ NMR $\delta$ 0.03 (3 H, s), 0.08 (3 H, s), 0.24 (9 H, s), 0.86 (9 H, s), 5.03 (1 H, q, $J$ = 6.37 Hz), 6.41 (1 H, d, $J$ = 3.25 Hz), 6.57 (1 H, dq, $J$ = 3.26, 0.45 Hz); $^{13}C$ NMR $\delta$ -5.72, -5.60, -1.99, 17.95, 25.27, 68.22 (q, $J$ = 34.4 Hz), 109.29 (q, $J$ = 1.7 Hz), 120.45, 123.75 (q, $J$ = 283.2 Hz), 152.96 (q, $J$ = 1.6 Hz), 161.63; $^{19}F$ NMR $\delta$ 0.5 (d, $J$ = 6.3 Hz); IR (neat) $\nu$ 2950, 2875; HRMS calcd for $C_{15}H_{28}F_3O_2Si_2$ (M + H) 353.1574, found $m/e$ 353.1580. Anal. Calcd for $C_{15}H_{27}F_3O_2Si_2$: C, 51.10; H, 7.72. Found: C, 50.88; H, 7.53.

**Peracid Oxidation of Silylfurans.** To a solution of silylfuran was added peracid (3 equiv) in an appropriate solvent (acetic acid or chloroform, 0.3 M). The reaction was quenched with dimethyl sulfide, and the whole was concentrated in vacuo (when MMPP was used, the resulting solid was removed by filtration). After the usual extractive workup (ethyl acetate), a mixture of butenolides and the starting material were obtained. **(1′*S*,4*S*)-4-[1′-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]-2-buten-4-olide (*anti*-6c)**: bp 95–100 °C/0.5 mmHg; $[\alpha]^{27}_D$ +98.24° (*c* 1.00, MeOH), 94.3% ee; $R_f$ 0.27 (AcOEt:Hex = 1:7); $^1H$ NMR $\delta$ 0.05 (3 H, s), 0.07 (3 H, s), 0.80 (9 H, s), 4.41 (1 H, dq, $J$ = 2.40, 7.09 Hz), 5.21 (1 H, m), 6.20 (1 H, ddd, $J$ = 0.67, 2.03, 5.86 Hz), 7.45 (1 H, m); $^{13}C$ NMR $\delta$ -5.80, -5.47, 17.75, 25.15, 70.97 (q, $J$ = 31.0 Hz), 80.82 (q, $J$ = 1.8 Hz), 123.65 (q, $J$ = 284.5 Hz), 123.95, 151.95 (q, $J$ = 2.1 Hz), 172.12; $^{19}F$ NMR $\delta$ 2.1 (d, $J$ = 6.3 Hz); IR (neat) $\nu$ 2975, 2950, 2900, 2875, 1780; HRMS calcd for $C_{12}H_{20}F_3O_3Si$ (M + H) 297.1134, found $m/e$ 297.1163. Anal. Calcd for $C_{12}H_{19}F_3O_3Si$: C, 48.63; H, 6.46. Found: C, 48.34; H, 6.44. **(1′*S*,4*R*)-4-[1′-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]-2-buten-4-olide (*syn*-6c)**: mp 64.5–65.5 °C; $[\alpha]^{27}_D$ +87.86° (*c* 0.66, MeOH), 97.6% ee; $R_f$ 0.11 (AcOEt:Hex = 1:7); $^1H$ NMR $\delta$ 0.10 (3 H, s), 0.11 (3 H, s), 0.87 (9 H, s), 4.09 (1 H, dq, $J$ = 5.01, 6.45 Hz), 5.11 (1 h, dt, $J$ = 5.02, 6.45 Hz), 6.22 (1 H, dd, $J$ = 2.12, 5.78 Hz), 7.44 (1 H, m); $^{13}C$ NMR $\delta$ -5.21, -4.89, 18.22, 25.60, 72.04 (q, $J$ = 31.2 Hz), 81.78 (q, $J$ = 1.7 Hz), 123.90 (q, $J$ = 284.7 Hz), 124.05, 152.04 (q, $J$ = 1.7 Hz), 172.37; $^{19}F$ NMR $\delta$ 2.4 (d, $J$ = 6.0 Hz); IR (neat) $\nu$ 2975, 2950, 2900, 2875, 1770; HRMS calcd for $C_{12}H_{20}F_3O_3Si$ (M + H) 297.1134, found $m/e$ 297.1130. Anal. Calcd for $C_{12}H_{19}F_3O_3Si$: C, 48.63; H, 6.46. Found: C, 48.45; H, 6.36. 4-[1′-[1′-(*tert*-Butyldimethylsiloxy)-

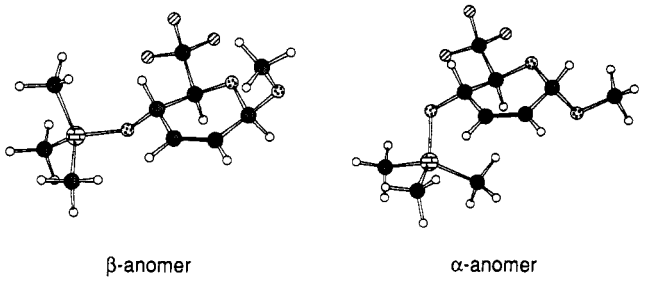



**Figure 1.** Most stable calculated conformations of anomeric *anti*-24.

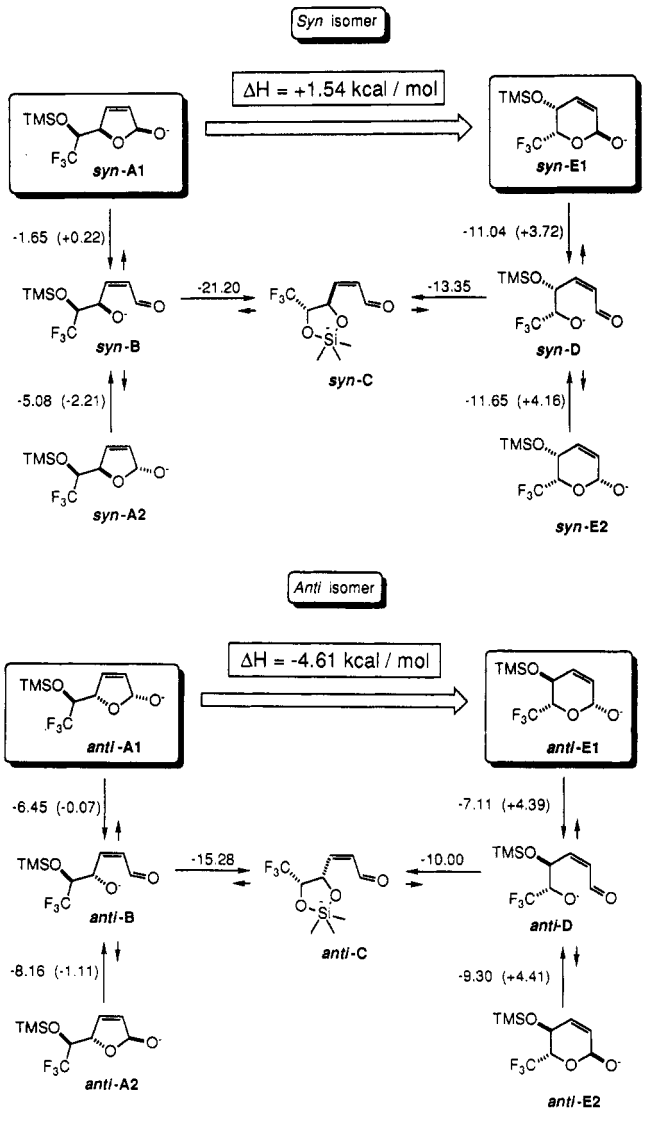



**Figure 2.** Energy profiles for the present isomerization process. Energy differences between two conformers are described in kcal/mol, and in parentheses are shown the energy differences between the corresponding protonated materials.

**2′,2′,2′-trifluoroethyl]]-3-buten-4-olide (7b)**: bp 100–105 °C/0.6 mmHg; $R_f$ 0.36 (AcOEt:Hex = 1:7); $^1$H NMR δ 0.13 (3 H, s), 0.16 (3 H, s), 0.92 (9 H, s), 3.29 (2 H, m), 4.65 (1 H, dq, $J$ = 1.59, 6.07 Hz), 5.68 (1 H, dt, $J$ = 1.14, 2.48 Hz); $^{13}$C NMR δ −5.73, −5.46, 17.91, 25.22, 33.47, 67.83 (q, $J$ = 34.1 Hz), 104,10, 123.00 (q, $J$ = 286.1 Hz), 150.79, 176.41; $^{19}$F NMR δ 0.7 (d, $J$ = 5.8 Hz); IR (neat) ν 2975, 2950, 2900, 2875, 1820. **(1′*S*,4*S*)-4-[1′-(2′,2′,2′-Trifluoro-1′-hydroxyethyl)]-2-buten-4-olide (*anti*-6b)**: bp 170–180 °C/0.15 mmHg; $[\alpha]^{26}_D$ −67.74° (*c* 1.44, $CHCl_3$), 97.6% ee; $R_f$ 0.41 (AcOEt:Hex = 1:1); $^1$H NMR δ 4.38 (1 H, d, $J$ = 6.22 Hz), 4.45 (1 H, m), 5.31 (1 H, ddd, $J$ = 1.67, 1.67, 3.32 Hz), 6.29 (1 H, ddd, $J$ = 0.53, 1.99, 5.86 Hz), 7.57 (1 H, ddd, $J$ = 1.36, 1.36, 5.84 Hz); $^{13}$C NMR δ 69.83 (q, $J$ = 31.5 Hz), 81.16 (q, $J$ = 2.2 Hz), 123.90 (q, $J$ = 283.2 Hz), 124.24, 152.69, 173.78; $^{19}$F NMR δ 2.0 (d, $J$ = 6.2 Hz); IR (neat) ν 3000, 1760; HRMS calcd for $C_6H_6F_3O_3$ (M + H) 183.0269, found *m/e* 183.0248. Anal. Calcd for $C_6H_5F_3O_3$: C, 39.58; H, 2.77. Found: C, 39.45; H, 2.94. **(1′*S*,4*R*)-4-[1′-(2′,2′,2′-Trifluoro-1′-hydroxyethyl)]-2-buten-4-olide (*syn*-6b)**: mp 103.0–103.5 °C; $[\alpha]^{27}_D$ +87.86° (*c* 0.66, MeOH), 97.6% ee; $R_f$ 0.27 (AcOEt:Hex = 1:1); $^1$H NMR (acetone-$d_6$) δ 4.60 (1 H, ddq, $J$ = 2.54, 8.23, 7.45 Hz), 5.45 (1 H, ddd, $J$ = 1.69, 2.23, 2.45 Hz), 5.77 (1 H, d, $J$ = 8.24 Hz), 6.29 (1 H, dd, $J$ = 2.16, 5.78 Hz), 7.67 (1 H, dd, $J$ = 1.77, 5.80 Hz); $^{13}$C NMR (acetone-$d_6$) δ 69.62 (q, $J$ = 30.6 Hz), 81.36 (q, $J$ = 2.1 Hz), 123.86, 125.83 (q, $J$ = 283.2 Hz), 154.75, 173.67; $^{19}$F NMR (acetone-$d_6$) δ 1.3 (d, $J$ = 8.0 Hz); IR (neat) ν 3400, 2950, 2900, 1750; HRMS calcd for $C_6H_6F_3O_3$ (M + H) 183.0269, found *m/e* 183.0241. Anal. Calcd for $C_6H_5F_3O_3$: C, 39.58; H, 2.77. Found: C, 39.66; H, 2.87. **4-[1′-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]-2-(*tert*-butyldimethylsilyl)-2-buten-4-olide (*syn*- and *anti*-6a)**: inseparable diastereomer mixture; $R_f$ 0.60 (AcOEt:Hex = 1:5); IR (neat) ν 2975, 2950, 2900, 2875, 1775, 1600. ***anti*-6a** $^1$H NMR δ 0.04–0.21 (12 H, m), 0.80 (9 H, s), 0.90 (9 H, s), 4.38 (1 H, dq, $J$ = 2.54, 7.20 Hz), 5.12 (1 H, dd, $J$ = 1.55, 2.52 Hz), 7.49 (1 H, m); $^{13}$C NMR δ −6.70, −6.57, −5.95, −5.13, 16.35, 17.78, 25.25, 26.24, 71.15 (q, $J$ = 31.1 Hz), 80.92, 125.41 (q, $J$ = 284.6 Hz), 136.21, 160.65, 175.02; $^{19}$F NMR δ 2.8 (d, $J$ = 7.0 Hz). ***syn*-6a**: $^1$H NMR δ 0.04–0.21 (12 H, m), 0.88 (9 H, s), 0.89 (9 H, s), 4.08 (1 H, dq, $J$ = 4.98, 6.53 Hz), 4.98 (1 H, dd, $J$ = 1.57, 4.99 Hz), 7.49 (1 H, m); $^{13}$C NMR δ −6.70, −6.57, −5.56, −5.26, 16.41, 17.86, 25.29, 26.16, 71.91 (q, $J$ = 31.2 Hz), 81.82, 126.87 (q, $J$ = 297.3 Hz), 135.69, 160.21, 174.80; $^{19}$F NMR δ 3.6 (d, $J$ = 6.0 Hz).

**Isomerization of 3-Butenolides to 2-Butenolides.** A THF solution (10 mL) of LDA, prepared from diisopropylamine (1.7 mL, 12 mmol) and *n*-BuLi (2.5 M in hexane, 4.4 mL, 11 mmol), was added to a mixture of 3-butenolide **7b** and unchanged silylfuran **5c** at −78 °C (the crude reaction mixture from the above peracid oxidation process on a 10 mmol scale), and the whole was stirred for 30 min. The reaction mixture was then quenched with anhydrous acetic acid (3 mL) at the same temperature. The usual workup and purification by silica gel column chromatography furnished 2-butenolide *syn*- and *anti*-**6c** in a ratio of 13:87 (1.849 g, 4.50 mmol, 45.0%) and silylfuran **5c** (1.185 g, 3.00 mmol, 30%). Their physical properties were identical to that of the already described compounds.

**Hydrogenation of 2-Butenolides.** To a suspension of 10% palladium on carbon (0.04 g) in anhydrous ethanol (20 mL) under $H_2$ was added 2-butenolide (3.982 mmol), and the whole was stirred overnight. After removal of the catalyst and concentration of the filtrate, the crude product was chromatographed to yield the desired butyrolactone. **(1′*S*,5*S*)-5-[1′-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]dihydro-2(3*H*)-furanone (*anti*-8c)**: yield 96%; bp 90–100 °C/0.6 mmHg; $[\alpha]^{28}_D$ −0.15° (*c* 1.09, MeOH), 96.1% ee; $R_f$ 0.31 (AcOEt:Hex = 1:5); $^1$H NMR δ 0.09 (3 H, s), 0.11 (3 H, s), 0.87 (9 H, s), 2.1–2.6 (4 H, m), 4.35 (1 H, dq, $J$ = 1.83, 7.14 Hz), 4.72 (1 H, dt, $J$ = 1.76, 7.29 Hz); $^{13}$C NMR δ −5.84, −5.25, 17.75, 20.13, 25.21, 28.01, 71.95 (q, $J$ = 30.1 Hz), 77.64, 123.65 (q, $J$ = 284.6 Hz), 176.41; $^{19}$F NMR δ 3.2 (d, $J$ = 8.1 Hz); IR (neat) ν 2950, 2875, 1790; HRMS calcd for $C_{12}H_{22}F_3O_3Si$ (M + H) 299.1290, found *m/e* 299.1283. **(1′*R*,5*S*)-5-[1′-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]-dihydro-2(3*H*)-furanone (*syn*-8c)**: yield 97%; $[\alpha]^{27}_D$ +24.32° (*c* 1.13, MeOH), 94.3% ee; $R_f$ 0.50 (AcOEt:Hex = 1:5); $^1$H NMR δ 0.11 (3 H, s), 0.13 (3 H, s), 0.89 (9 H, s), 2.0–2.7 (4 H, m), 3.97 (1 H, dq, $J$ = 5.02, 6.52 Hz), 4.62 (1 H, dt, $J$ = 4.91, 7.29 Hz); $^{13}$C NMR δ −5.46 (q, $J$ = 1.5 Hz), −5.13, 17.94, 23.66 (q, $J$ = 1.9 Hz), 25.32, 27.84, 73.19 (q, $J$ = 30.4 Hz), 77.95 (q, $J$ = 1.8 Hz), 123.78 (q, $J$ = 284.5 Hz), 176.17; $^{19}$F NMR δ 2.3 (d, $J$ = 6.5 Hz); IR (neat) ν 2950, 2875, 1780; HRMS calcd for $C_{12}H_{22}F_3O_3Si$ (M + H) 299.1290, found *m/e* 299.1311. **5-[1′-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]-3-(*tert*-butyldimethylsilyl)-dihydro-2(3*H*)-furanone (8a)**: inseparable diastereomer mixture between $C_1$ and $C_5$ (87:13); yield 99%; $R_f$ 0.43 (AcOEt:Hex = 1:7). **Major isomer**: $^1$H NMR δ 0.03 (3 H, s), 0.09 (3 H, s), 0.11 (3 H, s), 0.16 (3 H, s), 0.88 (9 H, s), 0.92 (9 H, s), 1.9–2.5 (3 H, m), 4.39 (1 H, dq, $J$ = 2.39, 7.11 Hz), 4.54 (1 H, dt, $J$ = 2.41, 5.68 Hz); $^{13}$C NMR δ −7.69, −7.10, −5.98, −4.57, 16.77, 17.92, 25.08, 27.17, 25.35, 26.59, 70.04 (q, $J$ = 30.2 Hz), 77.23 (q, $J$ = 1.6 Hz), 123.89 (q, $J$ = 284.2 Hz), 178.03; $^{19}$F NMR δ 2.7 (d, $J$ = 6.8 Hz). **Minor isomer**: $^1$H NMR δ 0.03 (3 H, s), 0.10 (3 H, s), 0.14 (3 H,

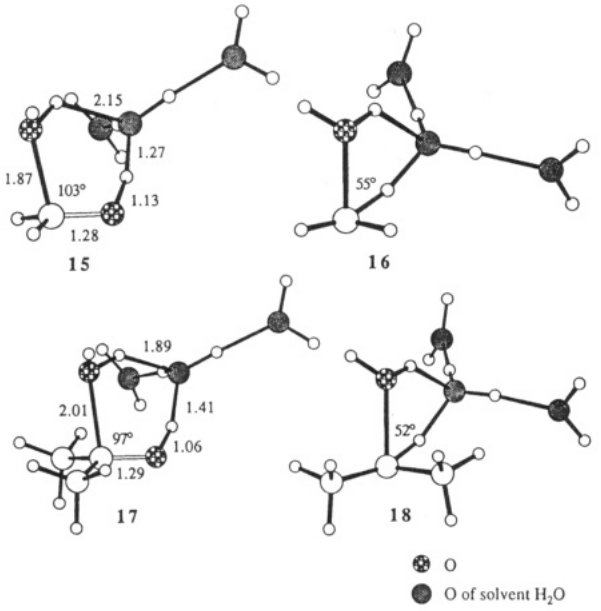



**Figure 5.** Front and side views of transition structures of reactions of water with formaldehyde (**15**, **16**) and acetone (**17**, **18**) catalyzed by $H_3O^+(H_2O)_2$ located with the 3-21G basis set.

in **12** raises the activation energy by 0.2 kcal/mol with respect to **1**.

In order to understand these results, information about the transition-state geometry as well as electronic and steric effects of substituents needs to be obtained. The theoretical approaches toward these are described in the following sections.

## Transition Structures of Model Reactions

Transition structures of the hydration of formaldehyde and acetone catalyzed by $H_3O^+(H_2O)_2$, a model for acid catalysis, were located with the 3-21G basis set.[36] The front and side views of these structures are given in Figure 5. These are featured by having a six-membered cyclic structure. The cyclic structure is located on one side of the carbonyl plane. The forming C–O bond is 1.87 Å in **15** and increases to 2.01 Å in **17**. These forming bond lengths are similar to corresponding bond lengths for the transition structures involving lithium hydride as nucleophile.[37] The attack angle of the water on the carbonyl double bond is about 100°, similar to that in other nucleophilic addition transition structures.[11,38] The hydrated proton has largely transferred to the carbonyl oxygen. There have been arguments about whether the reaction is stepwise (formation of water adduct intermediate followed by proton transfer) or concerted.[39] About 0.2 unit of positive charge develops on the attacking water molecule. With partial "solvation" as in the present case, the concerted mechanism is favorable. However, this does not prove the mechanism, since full solvation can certainly change the situation.

(36) All calculations were performed with Pople's Gaussian 90, Revision 1, Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M.; Binkley, J. S.; Gonzalez, C.; Degrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melies, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. Gaussian Inc., Pittsburgh, PA, 1990.

(37) Wu, Y.-D.; Houk, K. N. Unpublished results.

(38) Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560–5562. Bachrach, S. M.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 3946–3951.

(39) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425–432.

**Table III. Calculated Total Energies (au) and Relative Energies (kcal/mol) of Transition Structures of Reactions of Water with Methyl Ethyl Ketone (R = Me), Chloroacetone (R = Cl), and Hydroxyacetone (R = OH) Catalyzed by $H_3O^+(H_2O)_2$**

| | inside | | anti | | outside | |
|---|---|---|---|---|---|---|
| basis set | $E$ | $E_{rel}$ | $E$ | $E_{rel}$ | $E$ | $E_{rel}$ |
| R = $CH_3$ | | | | | | |
| 3-21G | 532.54523 | 0.0 | 532.54457 | 0.4 | 532.54286 | 1.5 |
| 6-31G*// | 535.43283 | 0.5 | 535.43357 | 0.0 | 535.43280 | 0.5 |
| MP2/6-31*G// | 536.89472 | 0.0 | 536.894479 | 0.0 | 536.89468 | 0.1 |
| R = Cl | | | | | | |
| 3-21G | 950.53380 | 0.0 | 950.53020 | 2.3 | 950.53192 | 1.2 |
| 6-31G*// | 955.28057 | 0.0 | 955.28044 | 0.1 | 955.27986 | 0.4 |
| MP2/6-31G*// | 956.74448 | 0.0 | 956.74186 | 1.6 | 956.74190 | 1.6 |
| R = OH | | | | | | |
| 3-21G | 568.15424 | 1.3 | 568.14673 | 6.0 | 568.15625 | 0.0 |
| 6-31G*// | 571.23072 | 2.2 | 571.23430 | 0.0 | 571.23360 | 0.4 |
| MP2/6-31*// | 572.74556 | 0.0 | 572.74154 | 2.5 | 572.74169 | 2.4 |

*Inside*, *anti*, and *outside* transition structures for the reactions of water with methyl ethyl ketone, chloroacetone, and hydroxyacetone are shown in Figure 6. These structures were located with the 3-21G basis set and their energies were also evaluated with the MP2/6-31G* calculations. The allylic group was placed on the side away from the six-membered ring to minimize steric interactions. The hydroxyl group was restricted to be anti to the C–C bond (C–C–O–H = 180°) to model methoxy functionality. The calculated total energies and relative energies of these structures are collected in Table III.

The three transition structures for the reaction of methyl ethyl ketone (**19**–**21**) are similar to that of the acetone reaction (**17**). The MP2/6-31G* calculations gave nearly identical energies for the three structures. This is similar to our earlier calculations for the reaction of sodium hydride with propionaldehyde, where the *inside* transition structure is somewhat more stable than the other two.[11e]

The three transition structures for the reaction of chloroacetone (**22**–**24**) are similar in geometry. There is no hydrogen bonding between the chlorine and the attacking water. The *inside* transition structure (**22**) is calculated to be somewhat more stable than the *anti* (**23**) and *outside* (**24**) transition structures.

While the *anti* transition structure of hydroxyacetone reaction (**26**) still maintains the cyclic structure, the cyclic structure is disrupted in the *inside* (**25**) and *outside* (**27**) transition structures, because hydrogen bonding forms between the hydroxyl group and the attacking water in the latter structures. The calculated relative energies for the three structures are very basis set dependent. Geometrical optimizations at higher levels of theory (e.g., the 6-31G* basis set) will be necessary to get reasonable relative energies for this system. However, the calculations do indicate that participation of a methoxy by hydrogen bonding in the transition state can make a positive contribution to the rate of exchange of **12**.

The above results are qualitative. However, they suggest that, similar to nucleophilic additions by other nucleophiles, steric and electrostatic effects of substituents play significant roles in determining conformational preferences in these equilibrating rotameric transition structures.[11,12] Orbital antiperiplanar effects appear to play a minor role as indicated by the comparable energies for the *outside* and *anti* conformers. Further support for this interpretation will be provided in the discussion of experimental results which follows.

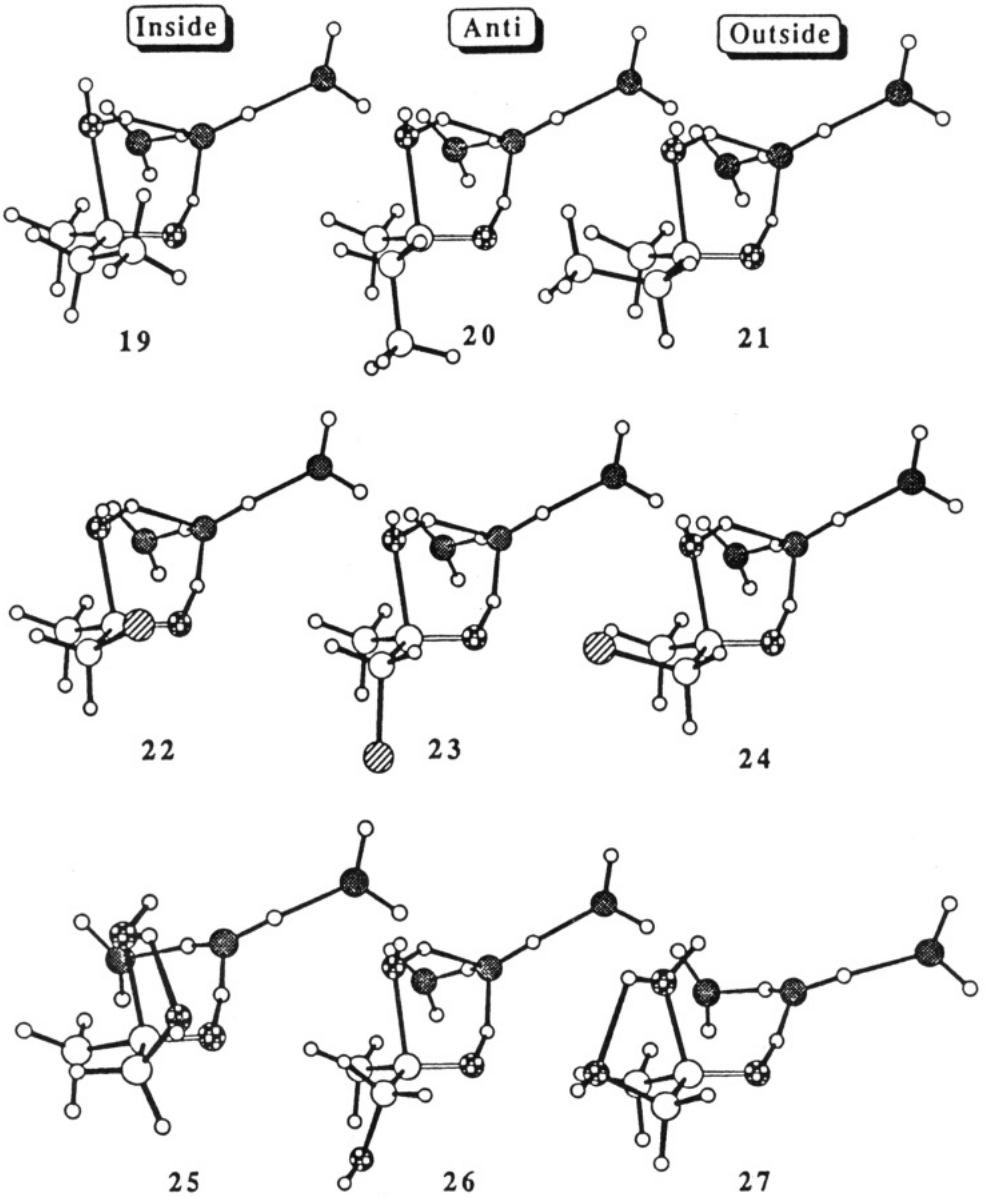



**Figure 6.** Transition structures of the reactions of water with methyl ethyl ketone, chloroacetone, and hydroxyacetone (∠H–O–C–C is restricted to 180°) catalyzed by $H_3O^+(H_2O)_2$.

### Rationalization of the Substituent Effects

Structure **28** is the transition structure for the reaction of **1** with a nucleophile (O atom) calculated with our MM2 transition-structure model for nucleophilic additions to ketones (Figure 7). We have previously applied the transition-structure force field model to the studies of stereoselectivities of nucleophilic additions to a variety of carbonyl compounds.[11] In the present case, an O atom was used as nucleophile. The forming O–C distance was 2.0 Å. Structures **29** and **30** are the Newman projections of **28** about the two C(O)–$C_\alpha$ bonds. Since the transition structure is unsymmetrical, the substituents at the four allylic positions are in quite different steric environments. While $R^1_{eq}$ and $R^1_{ax}$ are nearly ideally staggered with the carbonyl center, as shown in **29**, $R^2_{eq}$ and $R^2_{ax}$ are in eclipsed situations, as shown in **30** (note here that $R^1_{ax}$ is antiperiplanar and $R^2_{ax}$ is synperiplanar to the incoming nucleophile). As a result, the $R^2_{eq}$ and $R^2_{ax}$ positions are less favorable for a bulky substituent, and the observed reaction rates are determined by the transition structures with substituents at those positions.

For methyl substitutions, the observed relative rates of $^{18}O$ exchanges can be accounted for on the basis of structure **31**, assuming that substituent effects are additive. Thus, the activation energies of reactions of compounds **2** and **3** are determined by a methyl group in the $R^2_{eq}$ and $R^2_{ax}$ positions, respectively. A second axial methyl substituent (**4**) causes little increase in activation energy, because it assumes the $R^1_{ax}$ position. These deductions are strongly supported by the MM2 calculations based on the torsional strain transition-structure force field. For example, the MM2 calculations for the monoaxial methyl derivative gave a 1.7 kcal/mol preference for the transition structure with the $R^1_{ax}$ methyl as compared to the transition structure with the $R^2_{ax}$ methyl. This is quite favorable compared to the 1.9 kcal/mol experimental difference shown in **31**. For the monoequatorial derivative **2**, the calculations indicated that the methyl slightly favors the $R^1_{eq}$ position over the $R^2_{eq}$ position. The observed large increase in activation energy by a second equatorial methyl substituent (**5**) can be also easily explained. While the first equatorial methyl group can avoid steric interactions

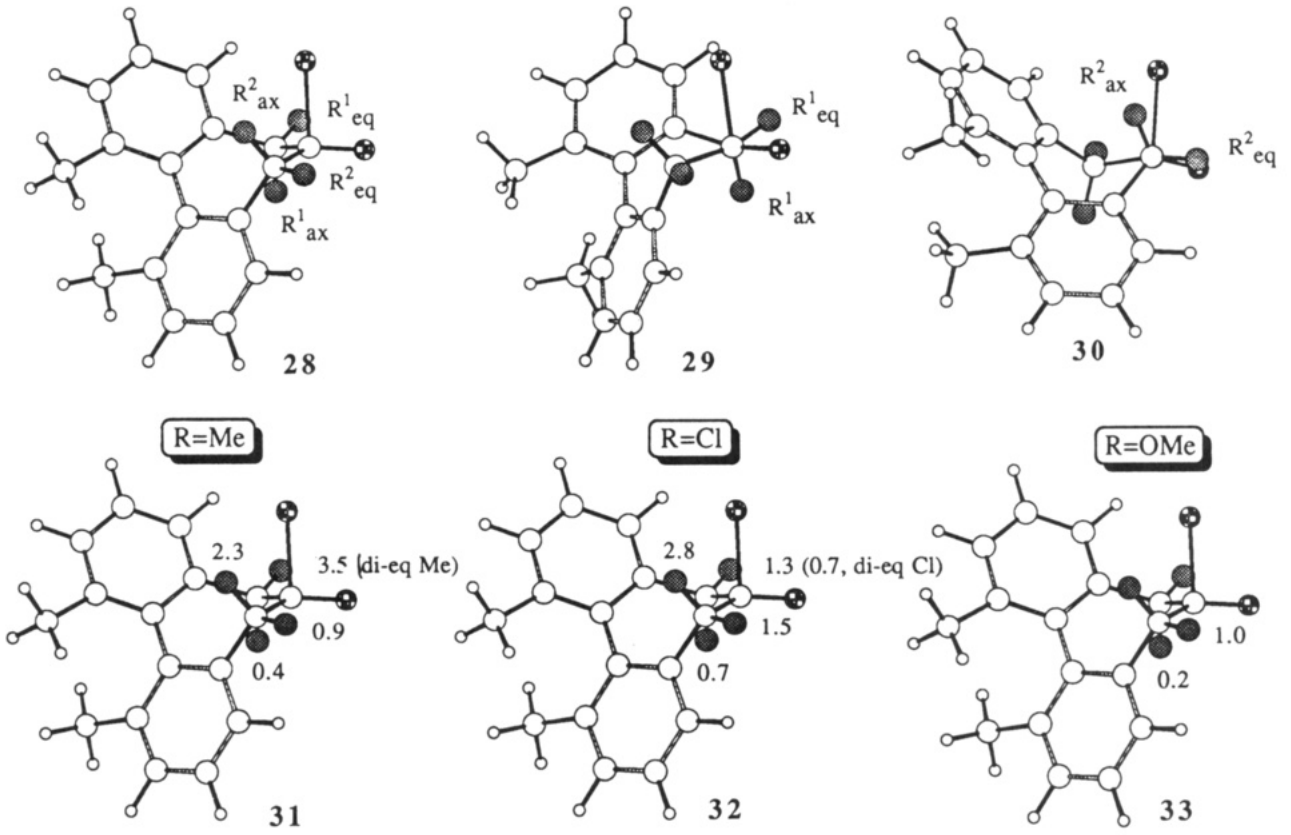



**Figure 7.** MM2 transition structure (**28**) for the addition of a nucleophile to compound **1**. Structures **29** and **30** are the Newman projections of **28** about the two C(O)–$C_\alpha$ bonds, which show the nonequivalency of the substituents in the transition structure. The $R_1$ and $R_2$ substituents in structures **31–33** are labeled to show their relative contributions to destabilizing the transition state for exchange.

with the transition-state ring structure, the second equatorial methyl group is forced to be in contact with the ring structure, as can be visualized in structures **17** and **18**.

The situation for the chloro substitutions can be deduced in a similar manner. Thus, a chloro substituent at the $R^1_{eq}$, $R^2_{eq}$, $R^1_{ax}$, and $R^2_{ax}$ positions causes 1.3, 1.5, 0.7, and 2.8 kcal/mol increases in activation energy, respectively. Contrary to the effect of a second equatorial methyl substituent, a second equatorial chlorine substituent causes significantly less rate retardation. This can be understood by assuming that the chlorine substituent at the $R^1_{eq}$ position can form hydrogen-bonds with the transition-state ring structure.

The observed relative rates of equatorial and axial methoxy substitutions can also be rationalized. According to the calculations, hydrogen bonding can form between the methoxy group and the attacking water if the methoxy group is at the $R^1_{eq}$ and $R^2_{ax}$ positions. It is likely that the relative rates are determined by substituents at the $R^2_{eq}$ and $R^1_{ax}$ positions where no hydrogen bonding is possible. Since the $R^1_{ax}$ is *anti* to the attacking water, it causes little steric interactions, just like an *anti* methyl or chlorine substituent. An equatorial methoxy group at the $R^2_{eq}$ position causes larger steric interactions, just like an equatorial methyl or an equatorial chlorine substituent.

There is not an easy way for the Cieplak theory to explain the observed substituent effects.[8,10] Since the formation of the C–O bond in the transition structure is proposed to be stabilized by an app electron-donating group and electron-donating ability is assumed to be in the order C–H > C–C > C–O > C–Cl, one would expect progressive increase in activation energy by an app hydrogen, methyl methoxy, and chlorine substituent. If the app electronic effect were dominating, one would expect the rates of the $^{18}O$ exchanges of monoaxial-substituted derivatives to be determined by the transition structure with the substituent antiperiplanar. The observed large rate retardation[40] by monoaxial methyl (**3**, 2.3 kcal/mol) and chlorine (**7**, 2.8 kcal/mol) seems to be in agreement with Cieplak's but not Anh's theory. However, Cieplak's theory fails to explain a 0.2 kcal/mol increase in free energy of activation for the monoaxial methoxy derivative (**12**). On the other hand, if one assumes that the steric effect of a synperiplanar substituent is dominating, the increase of activation energy by the second axial substituent[40] should correspond to the destabilization of the transition structure by the antiperiplanar substituent, as shown in **31–33** (although the value of 0.2 for the destabilization by an axial methoxy group may, in principle, represent the effect in either transition-state barrier (see Figure 4), it nevertheless provides a maximum value for the destabilization of the antiperiplanar transition state). From these increments of 0.4, 0.7, and 0.2, one can conclude that the app effect is not large, in contrast to the Cieplak proposal!

## Summary

We have shown that the first axial methyl and chlorine substituents cause large increases in activation energy of

(40) A referee has questioned our assumption, on the basis of the effects of the equatorial substituents, that their inductive influence is negligible. Since the effect of the electronegativity of the substituents would be destabilizing, consideration of this contribution would reduce that component of the observed retardation which we attribute to its app effect and would not alter our conclusions.

the $^{18}O$ exchange reaction, while the first axial methoxy substituent has no effect on the reaction rate. The second axial methyl and chlorine substituents cause small increases in activation energy. Calculations suggest that the transition structure is unsymmetrical, and the above results can be rationalized by large steric interactions (or torsional strain) in the transition structure with a substituent "synperiplanar" and small steric interactions in the transition structure with a substituent "antiperiplanar". Thus, any app electronic effect (hyperconjugation) is small, in agreement with Vedejs[41] and Meyers' assessments[42] but not with the Cieplak hypothesis.[8,10] The abnormal behavior of the monoaxial methoxy derivative is rationalized by the formation of hydrogen-bonding when the methoxy group is syn periplanar, which leaves the transition structure with an antiperiplanar methoxy as the rate-determining structure.

## Experimental Section

**General Procedure.** Melting points were taken on a Mel-Temp apparatus and are uncorrected. A Varian XL-300 NMR spectrometer was used to record the 300-MHz $^1H$ NMR spectra and 75-MHz $^{13}C$ NMR spectra. A Varian EM-360 NMR spectrometer was also used for recording $^1H$ NMR spectra of the biaryl ketone derivatives and their synthetic intermediates. Spectra were recorded in $CDCl_3$, and chemical shifts are given in ppm relative to $Me_4Si$ (0 ppm, $^1H$), or $CDCl_3$ (77 ppm, $^{13}C$) unless otherwise specified. Mass spectra were recorded on a VG-7070-E mass spectrometer using the direct insertion technique. Infrared spectra were recorded using a Perkin-Elmer Model 783 spectrometer. For monitoring reactions by TLC, a commercial preparation (DC-Alufolien kieselgel 60 $F_{254}$ EM SCIENCE) was used with 5% ether–hexanes as developing solvent. For purification of the biaryl ketone derivatives, column chromatography was used with silica gel (70–230 mesh, Terochem) as packing material and ether–hexanes as eluent. Flash chromatography was also used with silica gel (equivalent to Merck 9385, pH 7.1, 20–45 μm, Terochem), and ethyl acetate–hexanes as eluent. Isomerization of the diaxial dichloro biaryl ketone was performed on a Chromatotron (Harrison Research Inc. CA) with silica gel (7749 kieselgel 60 $PF_{254}$ gipshaltig, Merck) and 2–4% ethyl acetate–hexanes (gradient) as eluent. Deuteriochloroform (99.98%), dioxane-$d_8$ (99%), and $H_2{}^{18}O$ (98.3%) were obtained from MSD ISOTOPES (Montreal, Canada).

**Determination of the Relative Rates of Isotopic Exchange.** All the rate constants were measured by the following general procedure. To a solution in a 10-mm NMR tube of each (0.7 mmol) of two ketones in 3 mL of dioxane containing 20% of dioxane-$d_8$ as the source of a signal for the deuterium lock was added 140 mg (7.5 mmol) of $H_2{}^{18}O$. A predetermined[43] quantity of trifluoroacetic acid was added to catalyze exchange of $^{18}O$ for $^{16}O$ at the carbonyl group, and the time was noted. The tube was shaken vigorously, inserted into a spinner turbine, and placed in the pretuned probe[44] of the NMR. When the spinning rate was constant at 20 rps, the homogeneity in the $Z$ axis was optimized and the time noted as the accumulation of spectra began. At the end of 128 acquisitions (transients) the time was again noted, the accumulated free induction decay's (fid's) were filed, and then a new set of acquisitions was started. The spectrum from transformation of the first 128 fid's was examined to estimate the half-life for the more rapidly exchanging carbonyl group. Subsequent sets of acquisitions were increased to 256 fid's if the exchange rate was slow enough to permit two such sets to be acquired by the expiration of the first half-life. Two more sets were acquired and then the number of transients increased to the maximum permissible in order to obtain at least four sets of fid's in which the exchange of the less reactive carbonyl would lie in the 30–70% region. Accumulation and storage of the remaining data were programmed for the evening or overnight.

**Table IV**

| time, s | $^{16}O$, % | $B$ | $I/I+B$ | $\ln[A_0-A_e]/[A_t-A_e]$ | $10^4k$, $s^{-1}$ | $10^4\bar{k}$, $s^{-1}$ |
|---|---|---|---|---|---|---|
| Exchange Data for 1 (0.6 mmol) in the Presence of 2 (0.4 mmol) | | | | | | |
| 10 803 | 60.9 | 4.40 | 0.96 | 0.589 | 0.52 | |
| 16 333 | 41.6 | 5.77 | 0.94 | 0.976 | 0.56 | |
| 19 493 | 35.0 | 6.34 | 0.94 | 1.184 | 0.57 | 0.55 ± 0.02 |
| 22 653 | 30.7 | 6.76 | 0.94 | 1.36 | 0.56 | |
| 27 393 | 27.0 | 7.20 | 0.93 | 1.59 | 0.54 | |
| Exchange Data for 2 (0.4 mmol) in the Presence of 1 (0.6 mmol) | | | | | | |
| 19 493 | 80.3 | 6.34 | 0.94 | 0.236 | 0.114 | |
| 22 653 | 76.9 | 6.76 | 0.94 | 0.284 | 0.117 | |
| 27 393 | 73.7 | 7.20 | 0.93 | 0.334 | 0.113 | 0.115 ± 0.002 |
| 30 553 | 70.2 | 7.66 | 0.93 | 0.389 | 0.118 | |

**NOE Difference Measurements.**[45] All measurements on the ketones 2–12 were made on solutions of the ketone (1 mg) in 0.5 mL of $CDCl_3$. It proved unnecessary to degas the samples prior to measurement. The acquisition parameters used to obtain the data in Table II were $D$ = 15 s, SS (steady state) = 6, BS (block size) = 4, IL = $Y$, DLP = 18 to 22, pulse angle = 90°, NT = 32. The frequency of the irradiation was chosen at the chemical shift of the methine proton and alternated with a 2000-Hz offset after each block of four transients.

**Determination of the Rate Constants for Isotopic Exchange.** The rate of exchange at the carbonyl group can be assumed to be rate = $k$[ketone][$H_2{}^{18}O$][$H^+$]. Being acid catalyzed, and involving a 10-fold excess of $H_2{}^{18}O$, the exchange proceeds as a pseudo-first-order reaction. Allowance for a small dilution in the isotope pool is made using the equation described by Sachs;[25] $I/(I+B)\ln(A_0-A_e)/[A_t-A_e]) = kt$, in which $I$ = the isotopic enrichment in $^{18}O$, B = the percent of $H_2{}^{18}O$ in the reaction medium at time $t$, $A_0$ = the initial concentration of $^{16}O$ in the carbonyl group, $A_e$ = the concentration of $^{16}O$ in the solvent at time $t$, and $A_t$ = the concentration of $^{16}O$ in the carbonyl group at time $t$. The data for the exchange of 1 vs 2, taken from six sets of spectral acquisitions, appear in Table IV along with the calculations of $k$, using the equation of Sachs (note that the spectra taken at $t$ = 19493 s and 27393 s are those which appear in Figure 3).

All subsequent spectral measurements were analyzed by the same procedure and the resultant rate constants and the average deviation are recorded in Table I.

**Synthesis. 5,7-Dihydro-1,5,11-trimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one (2, Equatorial).** A solution of biaryl ketone 1 (1.25 g, 5.29 mmol) in 1,1-dimethylhydrazine (2 mL) was heated under reflux (62–64 °C) for 6 h, after which time TLC (1:3 ethyl acetate–petroleum ether) indicated that the reaction was complete. After evaporation of the excess hydrazine, the dimethylhydrazone of the biaryl ketone was obtained quantitatively. It

(41) Vedejs, E.; Dent, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 6861–6862.

(42) Meyers, A. I.; Wallace, R. H. *J. Org. Chem.* **1989**, *54*, 2509–2510. A theoretical calculation for this stereoselective reaction revealed no evidence for an app effect, concluding the probable influence to be solvation; Durkin, K. A.; Liotta, D. *J. Am. Chem. Soc.* **1990**, *112*, 8162–8163.

(43) Predetermined means that every pair of rate constants reported in Table I represent a second or third set of kinetic measurements. In the initial trial run, a 5% solution of trifluoroacetic acid in dioxane was prepared and a 2-μL aliquot was added to the solution of ketones, and the spectra for 128 transients were obtained as described above. If no exchange could be detected, a second aliquot was added and the process repeated. For run 1 exchange was observed, but an additional microliter was required to give an acceptable half-life of 30 to 60 min. The exchange was then monitored as in the above description. Although the initial rate data for each pair of ketones were less accurate, there was always agreement with the final experimental values, within the limits of error. For subsequent runs involving less reactive pairs of ketones, increasing amounts of catalyst were required to produce the same desired half-life for the more rapidly exchanging ketone.

(44) Pretuning the probe refers to checking all aspects of the performance of the 10-mm probe including capacitor tuning and homogeneity optimization. The signal for the carbonyl group of the experimental solution was then examined to ensure the line width to be less than 0.75 Hz and the shape to be normal, particularly to be symmetrical. The acquisition parameters used for the spectral measurements were sweep width 2000 Hz, acquisition time 3.0 s, pulse angle 22°.

(45) For a detailed discussion of the effect of various acquisition parameters on the success of this method, see: Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703–5711.

was placed in a flask under argon and subjected to further reaction directly without purification: $^1H$ NMR 2.19 (s, 6H), 2.44 (s, 6H), 2.87, 4.27 (dd, 2H), 3.30 (AB q, 2H), 7.12–7.25 (m, 6H); $^{13}C$ NMR (THF-$d_8$, 75 MHz) 171.46, 137.91, 137.05, 136.46, 136.28, 136.04, 135.82, 128.93, 128.91, 127.26, 126.30, 125.91, 47.28, 42.15, 35.45, 19.80, 19.78; IR 1635 $cm^{-1}$ (C=N); MS $m/z$ 278 ($M^+$), 263 ($M^+ - CH_3$), 234 ($M^+ - Me_2N$).

To a solution of LDA (5.8 mmol, prepared from *n*-butyllithium and diisopropylamine) in THF (13 mL) was added dropwise a solution of the hydrazone (1.47 g, 5.28 mmol, in 2 mL of THF) within 10 min under an argon atmosphere at −78 °C with stirring. Then the temperature of the solution was raised to 0 °C. After 1 h the solution was recooled to −78 °C and methyl iodide (0.8 mL, 13.3 mmol) was added. After 3 h at −78 °C, the temperature of the solution was raised to ambient temperature within 0.5 h. Dilute hydrochloric acid (0.05 N) was added, and the solution was extracted with ether. The organic phase was evaporated and a syrupy product (1.35 g, 88%) obtained. Column chromatography with ethyl acetate–petroleum ether, 1:9, as the eluent afforded pure methylated hydrazone (1.25 g, 81%): $^1H$ NMR 0.72 (d, 3H), 2.18 (s, 6H), 2.43, 2.45 (s,s, 6H), 3.30 (AB q, 2H), 4.70 (q, 1H), 7.12–7.25 (m, 6H); MS $m/z$ 292 ($M^+$), 232, 207, 58, 30.

The hydrazone of the methylated ketone (1.05 g, 3.6 mmol) was dissolved in dry DMF (40 mL) and the solution was cooled to −63 °C. *m*-Chloroperbenzoic acid (1.5 g) was slowly added while the solution was being stirred and the temperature maintained. After 0.5 h, the cold solution was poured into $NaHCO_3$ solution (50 mL) and the mixture was immediately extracted twice with hexanes. The hexane extracts were washed with cold sodium bisulfite, $NaHCO_3$, and water, the solution was filtered through $Na_2SO_4$ and evaporated. The crude product (0.80 g, 89%) thus obtained was purified by flash chromatography with ethyl acetate–petroleum ether, 1:24, as the eluent. Compound **2** was obtained from the fraction with less polarity than the unsubstituted ketone, mp 85 °C: $^1H$ NMR 1.34 (d, 3H), 2.13 (s, 6H), 3.34, 3.44 (AB q, 2H), 3.64 (q, 1H), 7.06–7.21 (m, 6H); $^{13}C$ NMR 209.60, 138.57, 137.98, 137.82, 137.20, 136.99, 136.28, 129.59, 129.40, and 128.23, 128.10, 126.83, 122.40 48.15, 46.92 19.82, 19.78, 19.60; MS $m/z$ 250 ($M^+$), 222 ($M^+ - C{=}O$), 207 ($M^+ - C{=}O - CH_3$). Anal. Calcd for $C_{18}H_{18}O$: C, 86.40; H, 7.20. Found: C, 86.22; H, 7.12.

**5,7-Dihydro-1,5,11-trimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one (3, Axial).** To a solution of LDA (1.8 mmol, prepared from methyllithium and diisopropylamine) in THF (15 mL) was added dropwise a solution of compound **1** (354 mg, 1.5 mmol) in THF (3 mL) at 0 °C with stirring. After 0.5 h at 0 °C, methyl iodide (0.46 mL, 7.35 mmol) was added and the reaction was continued at 0 °C for 0.5 h and then at room temperature for 0.5 h. The reaction mixture was washed with water and extracted with ether. The combined extracts were evaporated to a syrupy mixture. Separation of the product by repeated column chromatography with ether–hexanes, 2%, as the eluent afforded pure **3** (220 mg, 59% yield) that crystallized upon standing in refrigerator, mp 58.0 °C: $^1H$ NMR 0.80 (d, 3H), 2.12 (s, 6H), 3.36, 3.69, (dd, 2H), 3.46 (q, 1H), 6.95–7.02 and 7.12–7.20 (m, 6H); $^{13}C$ NMR 210.74, 141.48, 131.75, 137.63, 137.34, 136.79, 132.14, 129.74, 129.64, 128.64, 126.81, 55.07, 49.63, 19.85, 19.77, 19.51; MS $m/z$ 250 ($M^+$), 222 ($M^+ - C{=}O$), 207 ($M^+ - C{=}O - CH_3$). Anal. Calcd for $C_{18}H_{18}O$: C, 86.40; H, 7.20. Found: C, 86.24; H, 7.21.

**5,7-Dihydro-1,5,7,11-tetramethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one (4, Diaxial).** Compound **4** was obtained from **3** (250 mg, 1 mmol) by the same procedure used for the preparation of **3** from **1**. Purification of the crude product was performed by column chromatography with ether–hexanes, 2%, as the eluent, and crystalline **4**, mp 84 °C, was obtained (158 mg, 60% yield): $^1H$ NMR 0.82 (d, 6H), 2.16 (s, 6H), 3.64 (q, 2H), 6.99–7.07 and 7.18–7.24 (m, 6H); $^{13}C$ NMR 215.58, 137.47, 136.95, 129.46, 127.58, 126.69, 56.07, 19.53, 18.22; MS $m/z$ 264 ($M^+$), 236 ($M^+ - C{=}O$), 221 ($M^+ - C{=}O - CH_3$), 206, 43, 28. Anal. Calcd for $C_{19}H_{10}O$: C, 86.37; H, 7.58. Found: C, 86.43; H, 7.78.

**5,7-Dihydro-1,5,7,11-tetramethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one (5, Diequatorial).** A solution of compound **4** (264 mg, 1 mmol) and sodium methoxide, 4:1, in methanol was stirred at room temperature for several days, and the reaction was monitored by TLC. After evaporation of methanol, the reaction mixture was separated by column chromatography with 2% ether–petroleum ether as the eluent. Compound **5** (mp 103 °C, 172 mg, 65% yield) was obtained as the less polar fraction along with a more polar compound identified (MS and NMR) as the α-axial, α′-equatorial isomer (78 mg, 30%): $^1H$ NMR 1.38 (d, 6H), 2.20 (s, 6H), 3.49 (q, 2H), 7.12–7.34 (m, 6H); $^{13}C$ NMR 211.18, 140.50, 138.60, 137.16, 129.55, 128.40, 122.55, 47.20, 20.33, 12.18; MS $m/z$ 264 ($M^+$), 236 ($M^+ - C{=}O$), 221 ($M^+ - C{=}O - CH_3$), 206, 43, 28. Anal. Calcd for $C_{19}H_{20}O$: C, 86.37; H, 7.58. Found: C, 86.20; H, 7.62.

**5-Chloro-5,7-dihydro-1,11-dimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one (6, Equatorial).** To a solution of tetrabutylammonium bromide (192 mg, 0.6 mmol) in dry acetonitrile (5 mL) was added trimethylchlorosilane (1.14 mL, 9 mmol) under stirring. After 10 min the biaryl ketone **1** (708 mg, 3 mmol) and then dimethyl sulfoxide (0.63 mL, 9 mmol) were added dropwise. The reaction was left at room temperature for 24 h and then was partitioned between water (80 mL) and dichloromethane (3 × 5 mL). The organic layer was dried over anhydrous sodium sulfate and then evaporated to dryness. The $^1H$ NMR spectrum of the crude product showed a 60% yield of monochlorination with **6** and **7** in a ratio of 5.5:1. Purification of the crude product was carried out by silica gel column chromatography with hexanes–ether (0–2% gradient) as eluant at a flow rate of 2 mL/min. Compound **6** (460 mg, 57%) was obtained as crystals (mp 90–100 °C) from appropriate fractions. Recrystallization from ether–hexanes afforded pure equatorial isomer, **6**. Compound **6** was also prepared by chlorination with sulfuryl chloride (1.1 equiv) and then separation by column chromatography (see below). Compound **6** was hygroscopic, as indicated by its elemental analysis showing the presence of water, mp 112 °C: $^1H$ NMR 2.19, 2.20 (s,s, 6H), 3.50 (AB q, 2H), 5.57 (s, 1H), 7.10–7.62 (m, 6H); $^{13}C$ NMR 200.14, 137.21, 136.68, 136.09, 135.14, 133.63, 132.96, 130.53, 129.88, 128.19, 128.09, 126.5, 122.6, 66.38, 46.91, 19.82, 19.71; MS $m/z$ 270, 272 ($M^+$), 207 ($M^+ - C{=}O - Cl$), 192 ($M^+ - C{=}O - Cl - CH_3$). Anal. Calcd for $C_{17}H_{15}ClO \cdot 0.2H_2O$: C, 74.42; H, 5.65. Found: C, 74.14; H, 5.82.

**5-Chloro-5,7-dihydro-1,11-dimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one (7, Axial).** To a solution of **1** (1.44 g, 6.1 mmol) in carbon tetrachloride (2.4 mL) was added sulfuryl chloride (0.54 mL, 6.7 mmol) slowly, dropwise, with stirring at 45–50 °C, and stirring was continued for 1.5 h. The reaction mixture was evaporated under vacuum and a light orange syrupy product was obtained. The $^1H$ NMR of the crude product showed monoequatorial and monoaxial chloride together with dichlorides and starting material in a ratio of 3:4:2:1. Separation by column chromatography with 1–2% ether–hexanes (gradient) at a flow rate of 6 mL/min gave a 3:2 mixture (920 mg, 56%) of **7** and **6** from appropriate fractions. An attempt to obtain pure **7** by recrystallization in ether–hexanes failed since only equatorial isomer **6** was obtained because of the isomerization during the recrystallization. Compound **7** was slowly isomerized to **6** during long-term storage. The spectral data for **7** in the presence of **6** are as follows: $^1H$ NMR 2.02, 2.12 (s, s, 6H), 3.51 (AB q, 2H), 4.94 (s, 1H), 7.15–7.60 (m, 6H); $^{13}C$ NMR 202.4, 138.31, 137.41, 136.79, 134.29, 132.69, 132.21, 131.01, 130.79, 129.49, 127.82, 127.61, 126.09, 61.40, 48.14, 19.72, 19.54; MS $m/z$ 270, 272 ($M^+$), 207 ($M^+ - C{=}O - Cl$), 192 ($M^+ - C{=}O - Cl - CH_3$).

**5,7-Dichloro-5,7-dihydro-1,11-dimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one (8, Diaxial).** To a solution of **1** (2 g, 8.5 mmol) in carbon tetrachloride (3 mL) was added sulfuryl chloride (1.5 mL, 18.7 mmol) slowly, dropwise, at 45–50 °C under stirring. After 1.5 h at 45–50 °C, another 0.9 mL of sulfuryl chloride was added and the reaction was continued for another 1.5 h. The reaction mixture was evaporated to a light orange syrup that was subjected to column chromatograph with hexanes–ether (1–2% gradient) as eluent at a flow rate of 6 mL/min. Compound **8** was obtained as crystals from the first fraction. Recrystallization from ether–hexanes afforded pure **8** (950 mg, yield 37%), mp 134 °C. A mixture (1.35 g) of **6**, **7**, diequatorial dichloro **9**, and α-equatorial, α′-axial dichloro derivative **10** was obtained in a ratio of 3:1:0.3:1.5 from the rest of the fractions in the separation. Pure **8** gave the following: $^1H$ NMR 2.14 (s, 6H), 5.13 (s, 2H), 7.18–7.37 (m, 6H); $^{13}C$ NMR 195.52, 138.51, 137.29, 132.02, 130.91, 127.69, 127.41, 61.02, 19.61; MS $m/z$ 304, 306, 308 ($M^+$), 276 ($M^+$

– C=O), 241 ($M^+$ – Cl – C=O), 206 ($M^+$ – 2Cl – C=O). Anal. Calcd for $C_{17}H_{14}Cl_2O$: C, 66.89; H, 4.59. Found: C, 66.86; H, 4.62.

**5,7-Dichloro-5,7-dihydro-1,11-dimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one (9, Diequatorial, and 10, α-Equatorial, α′-Axial Dichloro).** Pure compound 8 (600 mg) was subjected to isomerization of a chromatotron with hexanes–ethyl acetate (2–4% gradient) as eluent. A 5:4 mixture (370 mg) of 9 and 10 was obtained from the major fraction. Recrystallization from dichloromethane–hexanes gave pure 10 (202 mg, yield 34%), mp 161 °C, and a residue rich in 9. Repeated recrystallization of the residue gave pure 9 (150 mg, 25%), mp 142 °C. The spectral data for 9 are as follows: $^1$H NMR 2.20 (s, 6H), 5.47 (s, 2H), 7.17–7.60 (m, 6H); $^{13}$C NMR 193.81, 137.02, 134.03, 133.49, 131.02, 128.63, 122.89, 64.92, 19.70; MS *m*/*z* 304, 306, 308 ($M^+$), 276 ($M^+$ – CO=O), 241 ($M^+$ – Cl – C=O), 206 ($M^+$ – 2Cl – C=O). Anal. Calcd for $C_{17}H_{14}Cl_2O$: C, 66.89; H, 4.59. Found: C, 67.14; H, 4.44. The spectra data for 10 are as follows: $^1$H NMR 2.14, 2.20 (s, s, 6H), 5.10 (s, 1H), 5.75 (s, 1H), 7.10–7.60 (m, 6H); $^{13}$C NMR 194.38, 138.46, 137.54, 136.27, 134.93, 134.39, 132.65, 130.83, 129.39, 128.70, 128.23, 127.81, 122.78, 65.37, 59.42, 19.71, 19.47; MS *m*/*z* 304, 306, 308 ($M^+$), 276 ($M^+$ – C=O), 241 ($M^+$ – Cl – C=O), 206 ($M^+$ – 2Cl – C=O). Anal. Calcd for $C_{17}H_{14}Cl_2O$: C, 66.89; H, 4.59. Found: C, 67.24; H, 4.51.

**5-Methoxy-5,7-dihydro-1,11-dimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one (11, Equatorial).** Pure 11 was obtained by the isomerization of 12 (270 mg, 1 mmol) in methanol (4 mL) containing 2,6-lutidine (0.24 mL, 2 mmol) by heating under reflux for 18 h. The solution was cooled, concentrated under vacuum, and partitioned between dichloromethane (3 × 3 mL) and hydrochloric acid (0.5 N, 20 mL). The organic extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to a syrup. Purification by chromatography on silica gel using 4% ether–hexanes as eluant gave 145 mg (55%) of a syrup, which decomposed slowly on storage under argon: $^1$H NMR 2.19, 2.22 (2s, 2 $CH_3$), 3.44 (AB q, 2H), 3.45 (s, 3H), 4.71 (1H), 7.06–7.56 (m, 6H); $^{13}$C NMR 205.4, 136.5–120.9, 85.0, 58.3, 47.0, 19.9, 19.7; MS *m*/*z* 266 ($M^+$), 238 ($M^+$ – CO), 223, 207, 192. Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.20; H, 6.69. Found: C, 80.86; H, 6.43.

**5-Methoxy-5,7-dihydro-1,11-dimethyl-6*H*-dibenzo[*a*,*c*]cyclohepten-6-one (12, Axial).** A solution of equatorial chloro derivative 6 (540 mg, 2 mmol) in methanol (10 mL) containing 2,6-lutidine (0.47 mL, 4 mmol) was heated under reflux for 16 h. Workup as described above for 11, gave, after chromatography, 270 mg (52%) of a syrup, which decomposed slowly on storage under argon: $^1$H NMR 2.12, 2.14 (2s, 2 $CH_3$), 2.95 (s, 3H), 3.58 (AB q, 2H), 4.36 (s, 1H), 7.08–7.52 (m, 6H); $^{13}$C NMR 204.9, 137.6–125.8, 89.8, 56.7, 47.7, 19.8, 19.6; MS *m*/*z* 266 ($M^+$), 238 ($M^+$ – CO), 223, 207, 192. Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.20, H, 6.69. Found: C, 80.90; H, 6.78.

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