JOC Article

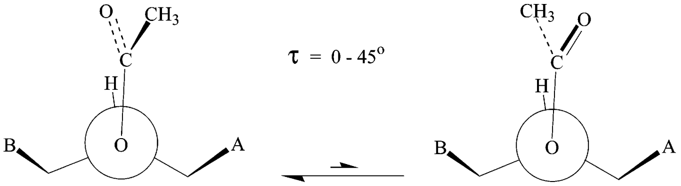
Conformation of Acetate Derivatives of Sugars and Other Cyclic Alcohols. Crystal Structures, NMR Studies, and Molecular Mechanics Calculations of Acetates. When Is the Exocyclic C−O Bond Eclipsed?[†]

Jorge González-Outeiriño,*[‡] Rima Nasser, and J. Edgar Anderson*

Chemistry Department, University College London, Gower Street, London WC1E 6BT, U.K.

j.e.anderson@ucl.ac.uk; uccajgo@ccrc.uga.edu

Received September 24, 2004



A study of published crystal structures (of O-acetylated sugars for the most part) suggests that the exocyclic C−O bond in acetate esters of cyclic alcohols intrinsically prefers a staggered conformation, although the eclipsed conformation is only slightly less stable. When the acetate is flanked by two equatorial substituents the preferred conformation is close to eclipsed. Over 1500 C−OAc bonds have been analyzed. Diagnostic NMR criteria for torsion angles and MM3 calculations are reported and confirm these conclusions.

Introduction

As a result of the extensive information available in the Cambridge Crystallographic Database,[1] much about the conformations of a given bond-type can be derived by examining a large number of crystal structures of molecules containing that bond.[2] If the number of examples is large enough, features generally observed can be concluded to be inherent to the bond rather than artifacts of the crystal lattice. This paper reviews an early example[3] of such an analysis and shows how a significantly refined generalization is arrived at by subdividing a now much larger set of examples into different subsets, on the basis of recent advances in conformational analysis.

In 1982, Dunitz[3] analyzed reports of crystal structures for about 170 secondary alkyl esters $R^1R^2CH{-}OC({=}O){-}R^3$, mainly acetates of structural type **1**, and found that for the alkyl-to-oxygen bond, henceforth the alkyl−O bond, the $H{-}C(R^1R^2){-}O{-}Ac$ torsion angle τ (see **2**), "invariably lies in the range 0−60° and mostly (actually 102 examples) in the range 0−30°, i.e., the C,H-bond is usually synperiplanar to (viz. eclipsing) the ester C,O-bond, as first noted by Mathieson". Neither Mathieson[4] nor Dunitz[3] gave more than a few sources for the data they studied, but undoubtedly many compounds were cyclic sugar derivatives with substituents adjacent to the ester group on the ring. Subsequently, it has often been concluded from Dunitz's work that in secondary alkyl acetates, etc., eclipsing of the alkyl−O bond $R^1R^2CH{-}OAc$ is to be expected, but this simplistically ignores almost 70 examples with $30° < \tau < 60°$.

Confusion may sometimes have arisen because the adjacent bond, from the oxygen to the unsaturated acyl

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[†] This paper is dedicated to Professor Stephen J. Angyal on his 90th birthday, November 21, 2004.

[‡] Present address: Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Road, Athens, GA 30602.

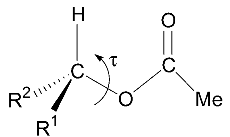
(1) (a) Allen, F. H.; Davies, J. E.; Galloy, J. J.; Johnson, O.; Kennard, O.; Maccrae, C. F.; Mitchell, E. M.; Mitchell, G. F.; Smith, J. M.; Watson, D. G. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 187−204. (b) Fletcher, D. A.; McMeeking, R. F.; Parkin, D. J. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746−749.

(2) Allen, F. H.; Kennard, O.; Taylor, R. *Acct. Chem. Res.* **1983**, *16*, 146−153.

(3) Schweizer, W. B.; Dunitz, J. D. *Helv. Chim. Acta* **1982**, *65*, 1547−1554.

(4) Mathieson, A. M. *Tetrahedron Lett.* **1965**, 4137−4144. It is helpful to recognize that the synperiplanar position Y_1 in Figure 1b in this paper, which is reported to be preferred by an equatorial acetate, is what is now called eclipsed, a word not used by the author. His Figure 4 refers to "esters attached to the ring by a polar oxygen" meaning what is now called an axial acetate, which likewise on the basis of "a few examples" prefers an eclipsed exocyclic bond. It is now little recalled that rather than "axial", "polar" was first suggested.

10.1021/jo048295c CCC: $30.25



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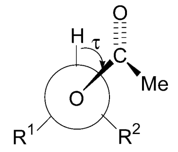

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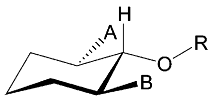

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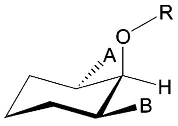
(**a**, R = Me; **b**, R = Acetyl)



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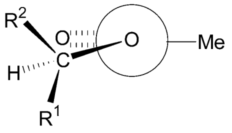
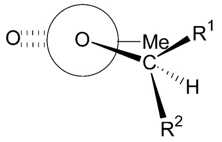
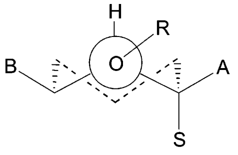


3 *cis*

a $R^1 = R^2 = Me$
b $R^1 = R^2 = H$
c $R^1 = t\text{-Bu}, R^2 = H$
d $R^1 = R^2 = i\text{-Pr}$
e $R^1 = t\text{-Bu}, R^2 = Me$
f $R^1 = R^2 = t\text{-Bu}$



3 *trans*



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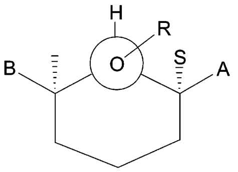

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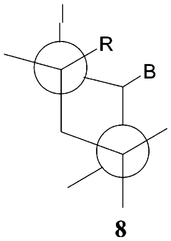


8

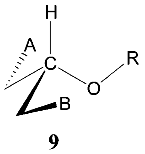
(**a**, R = Me; **b**, R = Acetyl)

carbon, the acyl–O bond, $R^1R^2CHO–Ac$, is always eclipsed with C=O and O–CHR^1R^2 in the same plane; see **3** *cis* and **3** *trans*.

It is the predominance of small torsion angles for the former, i.e., alkyl–O bond, that we want to reconsider, for it is striking that in primary and tertiary alkyl carboxylic esters this alkyl–O bond is conventional, that is, staggered,[3] with torsion angles close to 60° and 180°. Furthermore, in the simplest secondary alkyl acetate, isopropyl acetate[6] **1a**, the alkyl–O bond is again staggered, although due to interaction of methyl groups, the preferred H–C–O–C torsion angle τ is about 40°, that is, distorted toward eclipsing.

Our interest evolved from earlier studies[7] of the methyl ethers corresponding to these acetates, i.e., the exocyclic carbon–oxygen bonds in methoxy cyclohexanes, *O*-methylated sugars, and acyclic analogues. That work showed the not uncommon circumstances in which eclipsed conformations for the C–O bond are preferred. Thus, in BOTH equatorial and axial methoxycyclohexanes **4a** and **5a**, the exocyclic C–O bond is normally staggered in an unsubstituted ether (A,B = H), with $\tau = 40–45°$, but is eclipsed when there are *equatorial* substituents, e.g., A,B = methyl[7a] or methoxy[7d] at both the adjacent ring carbons.[8] This can be explained in terms of repulsive parallel-1,3-interactions of R with A and B, which are present in a perfectly staggered conformation; see **6a** for equatorial and **7a** for axial. These are quite analogous to *syn*-diaxial interactions in a 1,3-disubstituted cyclohexane, see **8** except that in **4** and **5**, O–R groups can rotate to reduce these interactions. If R rotates away from A or B to an eclipsed conformation, then it eclipses hydrogen, while the C1–C2 and C1–C6 bonds eclipse oxygen lone pairs; these eclipsing interactions are presumably smaller than the 1,3-interaction in **6** and **7**. The latter diagrams also show that a hypothetical adjacent *axial* substituent S is not in a position to affect the C–O bond conformation, as results[7a–f] confirm. Thus, the bond expected to be eclipsed may be equatorial or axial, but the adjacent substituents causing the eclipsing must be equatorial.

This model for eclipsing can be generalized to include acyclic systems[7a] for, if in a *sec*-alkyl ether A–C–CH(–OR)-C–B the A...B backbone adopts an *extended zigzag* conformation **9**, its structural similarity with **4** suggests that the C–OR bond should be eclipsed; see **10**. NMR observations and molecular mechanics calculations on methyl ethers confirm this.[7] Structural fragment **9** thus represents a stereotype for eclipsing, but this applies only as long as the extended A–C–C–C–B conformation is retained.[9] Thus, if the substitution A or B on a six-membered ring is axial as in the inverted chair conformation, it cannot form part of an extended zigzag system like **9**, and an eclipsed bond is not expected.



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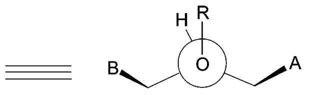

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From this work on methyl ethers, we suspected that the many examples of cyclic (and similar) acetates in the crystallographic literature which have small values of τ are not just secondary alkyl acetates but rather acetates whose backbone is restrained to an extended conformation like **9**, R = acetyl, A, B ≠ H. More tellingly, we expected to be able to show that secondary alkyl esters which do not fit the stereotype **9** usually have much larger torsion angles $\tau > 30°$ (if not quite 60°-staggered bonds) because one side of the acetate or the other lacks the substitution, and thus the parallel-1,3-interactions, that lead to eclipsing.

We now report our testing of these hypotheses on ester conformations by analyzing the torsion angle H–C–O–Ac found for the exocyclic C–O bond in *O*-acetylated

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[5] (a) Beckett, C. W.; Pitzer, K. S.; Spitzer, R. *J. Am. Chem. Soc.* **1947**, *69*, 2488. (b) Barton, D. H. R. *Experientia* **1950**, *6*, 316–320.

[6] Bredikhin, A. A.; Kirillovich, V. A.; Vereshchargin, A. N. *Izv. Akad. Nauk. SSSR Ser. Khim.* **1988**, 1067.

[7] (a) Anderson, J. E.; Ijeh, A. I. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1965–1967. (b) Anderson, J. E.; Watson, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 1517–1518. (c) Anderson, J. E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 441–443. (d) Anderson, J. E.; Angyal, S. J.; Craig, D. C. *Carbohydr. Res.* **1995**, *272*, 141–148. (e) Anderson, J. E. *J. Org. Chem.* **1996**, *61*, 3511–3513. (f) Anderson, J. E.; Angyal, S. J.; Craig, D. C. *J. Chem. Soc., Perkin Trans. 2* **1997**, 729–734. (g) Anderson, J. E. *J. Org. Chem.* **2000**, *65,* 748–754.

[8] For methyl ethers, substituents A and B should be not merely hydrogen atoms, but for *tert*-butyl *sec*-alkyl ethers the C–O bond is eclipsed,[7a] even for A = B = hydrogen. An example is the HC–O-*t*-Bu bond in isopropyl *tert*-butyl ether.[7a]

[9] The extended arrangement **9** is clearly present in the preferred conformation of many cyclic molecules. In all but a few acyclic molecules, however, rotation about the C2–C3 or C3–C4 bond will lead to a more stable molecular conformation where interactions of R with A or B are removed, and thus eclipsing of the C–O bond is not helpful.

cyclic alcohols, as shown by the now much more extensive crystal structure data. We also report MM3 molecular mechanics calculations of some simple model acetates, some of them acyclic, as indications of conformations in the gas phase, while measurements of NMR coupling constants of these acetates suggest criteria for determining the conformation in solution.

In crystal structures of 1546 secondary cycloalkyl acetates which we retrieved from the Cambridge Crystallographic Database,[1] only one[10] was found with the acetyl group *anti* to the methine hydrogen (**2**, $\tau \sim 180°$). Such *anti* conformations are calculated by molecular mechanics to be at least 2 kcal/mol less stable than the eclipsed or staggered conformations.

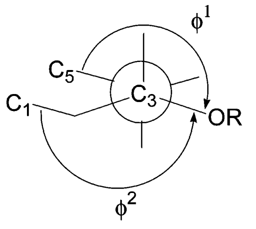
As for the adjacent acetyl−O bond, the conformation is normally *cis,* **3** *cis*. Crystal structures of almost 7000 acetates of all types yielded[11] only 13 with a *trans*-acetyl−O bond (C=O trans to O−C), **3** *trans*. Such *anti* and *trans* conformations will not be mentioned further.

We also carried out ab initio calculations of conformational energies (at the level MP2/6-311+g** level of theory) for the model molecules **1a**,**b**, **13**, and **15**−**17**. It is clear that the conclusions from molecular mechanics are confirmed by the quantum calculations with differences in detail that are unimportant in the context of this paper and the experimental results that we report. We therefore give no further account of these calculations here.

Results

There are two simplifying conventions we use here. Only the numerical size of the H−C−O−Ac torsion angles τ taken from a crystal structure is reported and is used to calculate mean torsion angles T, for each structural type. We thus make no distinction between two different flanking equatorial substituents. When there is equatorial substitution on only one side of the acetate, however, we will note whether the acetyl group is turned toward the substituent or toward the unsubstituted position. Rings with five or more atoms are considered, so we define the terms equatorial and axial, generalized for any ring size. A substituent OR at C3 in a ring is equatorial, see **11**, if both torsion angles C1−C2−C3−OR and C5−C4−C3−OR are greater than 120° (in a conventional six-membered ring chair these torsion angles are close to 180°). Substituent OR is axial, see **12**, if these two torsion angles are less than 120° (conventionally, in fact, close to 60°).[12]

Molecular Mechanics Calculations. Calculations for C−O bond rotation in a few typical *sec*-alkyl acetates are reported first since they illustrate points particularly relevant to the analysis of crystal structure results and to the NMR measurements. Allinger's MM3/94 program[13,14] was used, and a range of curve shapes has been found; see Figure 1. As might be expected for any 1,1,2-trisubstituted bond, there is a potential well for R^1R^2-CH−OAc that is about 240° wide, between acetyl-eclipsing-R^1 and acetyl-eclipsing-R^2. There are two staggered minima at 35−45° on either side of the acetyl-eclipsing-hydrogen with a small barrier to passing between them. Figure 1 shows significant parts of such potential energy diagrams for the CH−OAc bond in isopropyl acetate **1a**, $R^1 = R^2 = R^3 =$ Me, and for equatorial and axial epimers of 4-*tert*-butylcyclohexyl acetate **13**, **14**. These are typical examples of the structural stereotype **9** but with hydrogen atoms as both substituents A and B, so eclipsing is not expected.



equatorial $\phi^1, \phi^2 > 120^\circ$

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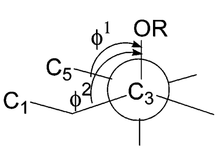

axial $\phi^1, \phi^2 < 120^\circ$

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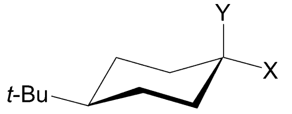
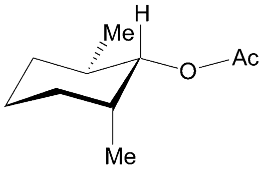


13 Y = H, X = O-Acetyl
14 Y = O-Acetyl, X = H



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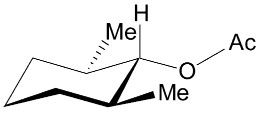

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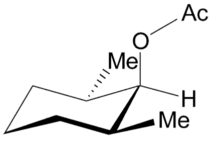

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We also calculated the potential for an equatorial acetate which has an equatorial methyl substituent on just one side, namely the conformation **15** of *cis,trans*-2,6-dimethylcylohexyl acetate; see Figure 1. There is still evidence of two minima, but one has become an inflection displaced by the methyl group toward a τ value of 0° and of higher energy than the other minimum where the acetate is rotated away from the methyl group. The potential well is narrower and steeper-sided. In primary esters methyl acetate **1b** and neopentyl acetate **1c**, minima, not illustrated, with conventional 60° and 180° torsion angles are obtained.

Figure 2 shows equivalent potential energy diagrams for two epimeric 2,6-dimethylcyclohexyl acetates with the acetate group equatorial **16**, or axial **17**, and for the

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[10] Schollmeyer, D.; Stadtler, R.; von Braunmuhl, V. *Z. Krystallogr. − New Cryst. Struct.* **1998**, *213*, 410−411. CCDB Refcode NUZRUV.

[11] CCDB Refcodes FEYDES, GELYOL, HOFTIF, KEBDUQ, LELNAR, MEFFOS, NIKKUN, PAZLIL, SEHFEQ, SUQREB, WIPRUI, ZINDEB, ZZZTUC01. If such a large number of crystal structures can serve as a model for the same number of molecules of a single acetate, the *cis*/*trans* equilibrium constant is 6840/13 = 526 and ΔG^0_{300} is 3.7 kcal/mol.

[12] Anet has given another general definition of axial and equatorial that is much less useful for the present study, since it is based on distances derived from experimental or calculated data rather than on directly reported torsion angles: Anet, F. A. L. *Tetrahedron Lett.* **1990**, *31*, 2125−2126

[13] (a) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551−8566. (b) Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8576−8582.

[14] Allinger, N. L.; Zhu, Z. S.; Chen, K. J. *J. Am. Chem. Soc.* **1992**, *114*, 6120−6133.

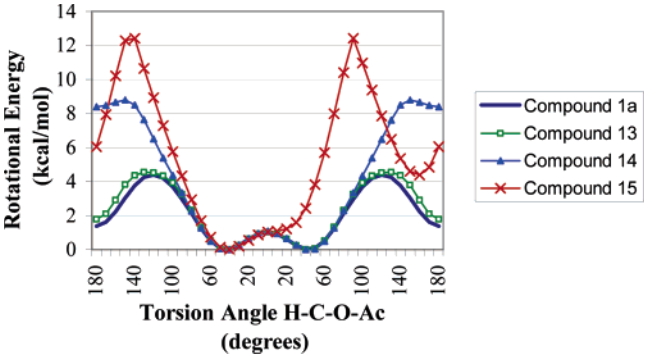


FIGURE 1. MM3-calculated potential energy diagrams for $R_2CH-OAc$ bond rotation in secondary alkyl acetates that prefer a staggered conformation.

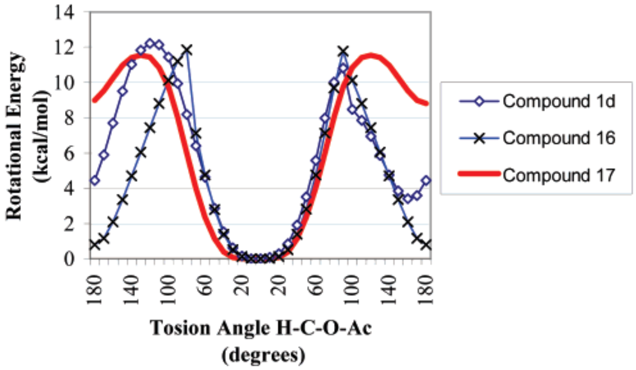
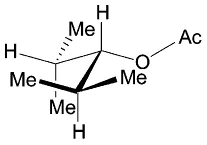


FIGURE 2. MM3-calculated potential energy diagrams for $R_2CH-OAc$ bond rotation in secondary alkyl acetates that prefer an eclipsed conformation.

acyclic 3-acetoxy-2,4-dimethylpentane **1d**, whose most stable conformation[15] is shown as **18**. All these fit the stereotype **9** for eclipsing where A = B = methyl.



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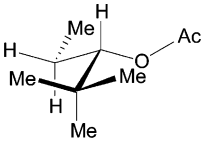

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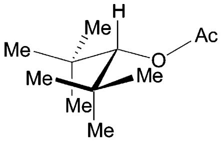

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Because of the two substituents flanking the acetate, both staggered minima of compounds in Figure 1 have been displaced and coincide as a single relatively steep-sided minimum at $\tau = 0°$. Little population of conformations much removed from eclipsed is expected.

Calculations thus suggest two distinct subsets of both cyclic and acyclic alkyl acetates in agreement with our hypothesis. Known crystal structures of cyclic acetates and proton−carbon vicinal coupling constant across the C−O bond in model acetates are now reported with these subsets in mind.

Crystal Structure Determinations. Following the Introduction, structures retrieved from the Cambridge Crystallographic Database have been divided into appropriate groups.

Cyclic Acetates with No Equatorial Flanking Substituents. We retrieved 402 examples from the database, of which 215 have an axial and 187 an equatorial acetate group. Figure 3 shows the distribution of values found for the H−C−O−Ac torsion angle τ in 10° divisions, with axial and equatorial acetates separated. The largest group of such acetates is the one with τ in the 30°−40° range.

The mean values T of the torsion angle τ, 30.9° for axial and 31.5° for equatorial, are deceptively small as can be understood by examining the rotational potentials and distributions of Figures 1 and 3, respectively. The potential curve between 30° and −30° is quite flat (with a barrier of only 1 kcal/mol), so crystal conformations with small torsion angles that tend to lower the mean value are not uncommon. On the other hand, the potential energy rises dramatically beyond 40° so there are few torsion angles greater than 40° to contribute to the mean.

We conclude that the preferred conformation of the exocyclic C−O bond in an acetate ester of a cyclic alcohol without adjacent equatorial substitution is *staggered* but with a torsion angle usually between 30° and 40°.

Cyclic Acetates with Two Equatorial Flanking Substituents. When we specified an acetate attached to a ring in a monocyclic system with an equatorial flanking substituent on both sides, 493 equatorial acetates and 63 axial examples were recovered. Figure 4 shows the distribution of values found for H−C−O−Ac torsion angle τ. The two smallest τ-values ranges 0°−10° and 10°−20° are the most populated.

In these equatorial and axial acetate sets, the mean torsion angle T is 11.9° and 17.8°, respectively. Since most examples are not symmetrical, a torsion angle exactly 0° is not to be expected, so we conclude that for axial or equatorial acetate with an equatorial substituent on both sides the exocyclic bond is essentially eclipsed. The mean torsion angles reported are smaller than the unsubstituted case reported above, by 19° and 14°, much as found in the methoxycyclohexanes.

Cyclic Acetates with One Equatorial Flanking Substituent. We recovered 522 crystal structures of this type, of which 220 had the acetate group itself equatorial and 302 had an axial acetate. These do not fit the stereotype for eclipsing; however, they can be divided into subsets depending whether the acetate is found turned toward the equatorial substituent or away from it, in the crystal studied. We expect a substantial majority of the latter, but in the solid state, although 330 is a majority, 192 is a not-significant minority. Intermediate conformational behavior is expected on average, and in fact, the mean torsion angle τ is 18.8° in the 192 cases where the acetate is turned toward the equatorial flanking substituent and is 27.8° in the 330 cases when the acetate is turned toward the unsubstituted side.

Cyclic Acetates Adjacent to a Ring Oxygen Atom. We found 66 examples of cyclic acetates with a substituent on one side and an oxygen atom in the ring on the other side, which corresponds to an acetate at C1 ester in a pyranose or furanose sugar. In 28 of the 35 axial acetates found in the database, the acetyl group is turned toward the ring oxygen with a mean H−C−O−Ac torsion angle of 35.8°. The seven turned toward the substituent have a mean torsion angle τ of 15.0°. Of the 21 equatorial acetates, only six were turned toward the oxygen with

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[15] Conformations of compound **18** where an isopropyl group has rotated to place a hydrogen at position A or B, see **8**, are calculated to be at least 2.85 kcal/mol less stable than the conformation shown.

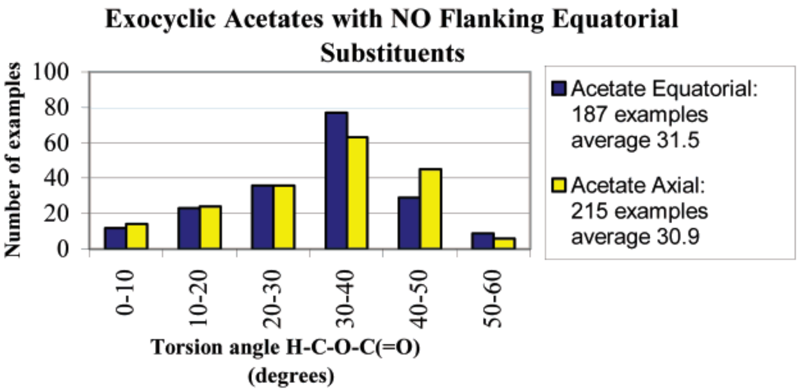

FIGURE 3. Statistical analysis of crystal structure torsion angles for cyclic acetates expected to show a staggered CH−OAc bond.

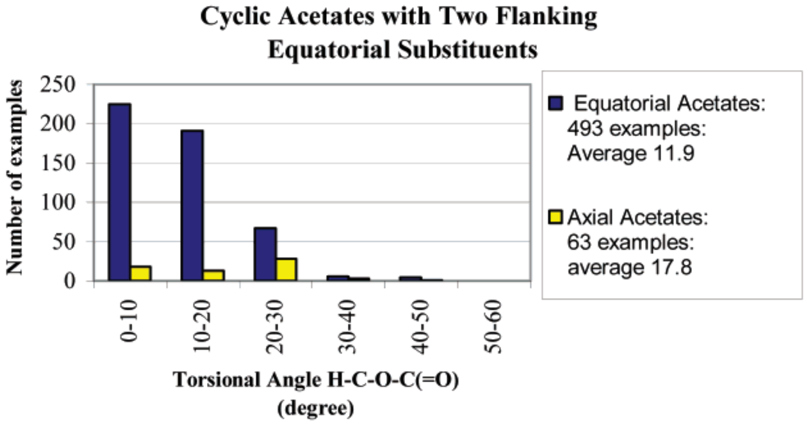

FIGURE 4. Statistical analysis of crystal structure torsion angles for cyclic acetates expected to show an eclipsed CH−OAc bond.

a mean $\tau = 26.7°$ while the remaining 15, all turned toward an adjacent equatorial substituent, had a mean $\tau = 7.0°$.

Both conformational types, with acetyl turned toward the ring oxygen, or more or less eclipsing the ring C−H bond, fit with the *exo*-anomeric effect,[16,17] since the exocyclic oxygen may be intermediate between sp^3 or sp^2 hybridized, and thus electron density is located more or less antiperiplanar to the ring C−O bond in both cases. Whatever the balance of forces or effects determining the conformation, the experimental observation fits with the eclipsing stereotype.

NMR Studies. The obvious NMR indication of the mean torsion angle τ for an acetate in solution is the $^1H-C-O-^{13}C{=}O$ vicinal coupling constant ^3J. A similar coupling $^1H-C-O-^{13}CH_3$ has been used successfully in the case of methyl ethers[7a] where the $^1H-C-O-^{13}CH_3$ coupling is about 7.3 Hz when the bond is eclipsed, about 6.0 Hz when the bond is oscillating over a range of low energy conformations on either side of eclipsed,[7a,e,f] about 3.8 Hz for the normally adopted staggered torsion angle of about 43°, and about 2.65 Hz for a 60° staggered arrangement. This spread of values encourages a fairly specific interpretation of the conformation of any further methyl ether if the coupling constant can be observed (assuming that only a single conformation or two enantiomeric conformations are populated).

To find a comparable experimental measure for acetates, we determined the $^1H-C-O-^{13}C{=}O$ coupling constant in a range of acetates for which molecular mechanics calculations had already been used to suggest the minimum energy conformation. With gated decoupling of protons, the carbonyl carbon signal appears as a quartet of doublets, and Table 1 shows the three-bond coupling constant to the methine carbon. In neopentyl acetate **1c**, a single conformation where the torsion angle of the coupling nuclei is 60° is populated; see **2c**. The coupling constant is 2.5 Hz. The coupling ^3J in methyl acetate, 3.9 Hz, reflects the mean of two such 60° torsion angle values and one 180° value, see **2b**, whence the 180° coupling constant is derived as 6.7 Hz.

In the epimeric equatorial and axial 4-*tert*-butylcyclohexyl acetates the coupling constant is 2.9 and 3.3 Hz, respectively, although the torsion angles are calculated by molecular mechanics to be 44° in both cases. In isopropyl acetate, the torsion angle is calculated to be 38°, and the coupling constant is 2.8 Hz. In these last three examples, minima are very shallow, so conformations with quite a wide range of torsion angles may be contributing to the experimentally observed coupling constant.

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(16) Lemieux, R. U.; Koto, S.; Voisin, D. The Exo-Anomeric Effect. In *The Anomeric Effect, Its Origin and Consequences*; Szarek, W. A., Horton, D., Eds.; ACS Symposium Series 87; American Chemical Society: Washington, D.C., 1979.

(17) Wolfe, S.; Whangbo, M.-H.; Mitchell, D. J. *Carbohydr. Res.* **1979,** *69*, 1−26.

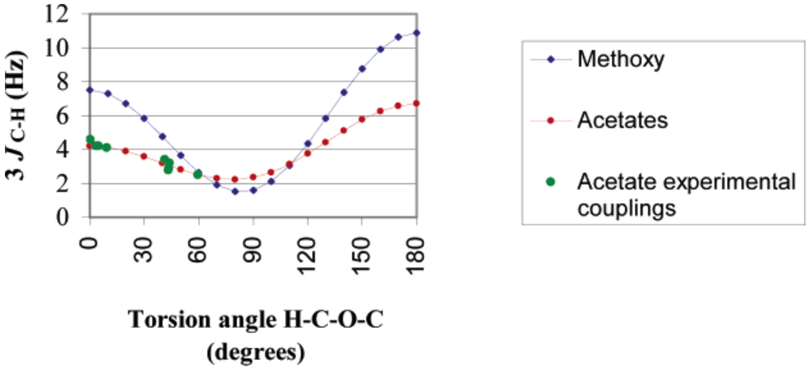
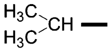
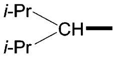
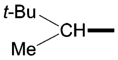
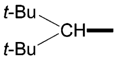
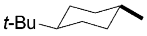
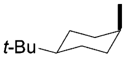
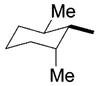
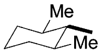
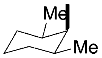


FIGURE 5. Karplus relationship of the $^1H-C-O-^{13}C$ coupling constant and the corresponding torsion angle for acetate and methyl ether[7a] derivatives of secondary alcohols. The curves are derived from 0°, 60°, and 180° values measured as described in the text. Individual points shown as green dots are for acetates taken from Table 1.

TABLE 1. MM3-Calculated Torsion Angle Minima τ and Experimental $^{13}C-^1H$ Coupling Constant ^3J $^1H-C-O-^{13}C(=O)$ for Acetates[a]

Acetate R— OAc R— =		Torsion angle τ H-C-O-Ac (°)	Coupling Constant $^3J_{1H-C-O-13C(=O)}$ (Hz)
	**1a**	43.3	2.8
CH_3—	**1b**	61.0, 179	3.9
t-Bu-CH_2 —	**1c**	59.7	2.5
	**1d**	1.6	4.2
	**1e**	0.3	4.2
	**1f**[19]	0.2	4.6
	**13**	43.6	2.9
	**14**	44.0	3.2
	**15**	41.3	3.4
	**16**	3.6	4.2
	**17**	9.6	4.1

[a] The carbonyl carbon also shows a coupling of 6.6−6.9 Hz with the methyl protons.

The epimeric 2,6-dimethylcyclohexyl acetates **16** and **17** with equatorial methyl groups are calculated to have torsion angles of 0° and found to have coupling constants of 4.2 and 4.1 Hz, respectively. Two further, acyclic, acetates, 2,4-dimethyl-3-acetoxypentane **1d**, see **18**, and 2,2-dimethyl-3-acetoxypentane **1e**, see **19**, are calculated to have eclipsed C−O bonds with torsion angles of 2° and 0°, respectively. In both these compounds the coupling constant is 4.2 Hz. Finally, the vicinal coupling constant in 2,2,4,4-tetramethyl-3-acetoxypentane **1f**, see **20**, which is also calculated to have the alkyl-oxygen bond eclipsed, has already been reported by Karabatsos and coworkers[18a] to be 4.6 Hz. These authors suggested an eclipsed conformation for the alkyl bond, an isolated early recognition −1966−of preferred eclipsing of a single bond.

Thus, for a secondary alkyl acetate, the range of coupling constants 4.6−2.5 Hz for torsion angles τ from 0° to 60° is not very large. However, as reported above, torsion angles greater than 50° have seldom been encountered in 1546 crystal structures and there is only one example[19] with a 180° value, so an $^1H-C-O-^{13}C=O$ coupling constant of 4 Hz or greater indicates a near to eclipsed conformation. Using coupling constant values of 4.2, 2.5, and 6.7 Hz to represent torsion angles of 0°, 60°, and 180°, respectively, and assuming that a Karplus-type relationship holds, the following equations relate the mean torsion angle τ to the coupling constant: $^3J = 3.1 \cos 2\tau - 1.25 \cos \tau + 2.35$; otherwise, $^3J = 1.55 \cos 2\tau - 1.25 \cos \tau + 3.9$. This Karplus relationship is shown in Figure 5 along with the corresponding curve for methyl ethers.[7a]

Discussion

The results presented here bear out the extension of the model structure **9** for bond-eclipsing to acetates, i.e., R = acetyl. Acyclic examples, e.g., **18**−**20**, can be found, but most commonly, eclipsing is a feature of the exocyclic C−O bond in cyclic acetates, either axial or equatorial, when there are equatorial substituents on both sides. Repulsion between the carbonyl oxygen atom of the acetyl group in a *cis*-arrangement **3** *cis*, and substituents A and B is plausibly the cause of eclipsing.

When there are no equatorial substituents on either side of the acetate **9**, A = B = H, the H−C−O−Ac torsion angle is likely to be in the 30°−40° range. The rotational potential is flat; however, the barrier to rotation from −43° to +43° through the eclipsed conformation in cyclohexyl acetate is calculated to be only1.15 kcal/mol, for example, so smaller torsion angle values may be encountered and smaller than maximum coupling constants measured. When there is an equatorial substituent on only one side, various kinds of intermediate behavior that may occur have been indicated, the most interesting

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[18] (a) Karabatsos, G. J.; His, N.; Orzech, C. E., Jr. *Tetrahedron Lett.* **1966**, 4639−4643. (b) Dorman, D. E.; Bauer, D.; Roberts, J. D. *J. Org. Chem.* **1975**, *40*, 3729−3735.

[19] Zefirov, N. S.; Samoshin, V. V.; Subbotin, O. A.; Baranenkov, V. I.; Wolfe, S. *Tetrahedron* **1978**, *34*, 2953−2959.

being that in crystal structures with the acetate turned toward the substituted side, the torsion angle is on average small; that is, the bond is eclipsed.

In this paper, no attempt has been made to link the *nature* of adjacent substituents A and B to a particular conformational behavior. Many crystal structures are of polyacetylated sugars so the substituents flanking one acetate group are often other acetate groups whose steric compression is less than that of the methyl groups in the model compounds used for NMR measurements and in calculations.

With neighboring acetate groups, the "gauche effect" of adjacent vicinal polar groups along the C−C bond of a ring is substantial,[19] disfavoring the *antiperiplanar* diaxial arrangement of two acetate groups. This inevitably favors a diequatorial arrangement which is apt for eclipsing conformations. This and other effects may merit closer study elsewhere but need not complicate the present broad analysis.

The sample size of the original studies of Mathieson[4a] and Dunitz[3] has been extended 10-fold, and H−C−O−Ac torsion angles found cover the range from 0° to just over 50°. We have shown that such acetates can be divided into the two sets with an eclipsed or a 30−40° staggered alkyl−O bond. The more general model **9**, (A−C−C(−OAc)−C−B with A, B $\neq$ H), which includes acyclic systems, seems to hold so that the C−O bond is eclipsed provided the A−C−C−C−B system adopts an extended *zigzag* conformation. There is some overlap of the sets which reflects the relative shallowness of rotational potential when A = B = H.

The Karplus curve for the C−O bond in secondary alkyl acetates reported above has the usual shortcomings. Coupling constants are measures quite precisely, but the expression of the one bond conformation as a single torsion angle is less certain. The 0°, 60°, and 180° values used to derive the equation represent as well defined minima as are available. The intermediate experimental points shown on the graph in Figure 5 should have substantial error bars for the torsion angle which is derived from MM3 calculations. Such a Karplus curve will occasionally be useful for confirming experimentally some expectation of the bond conformation. A coupling constant of 4−4.6 Hz suggests an eclipsed bond, values approaching 4 Hz most likely reflect population of a range of conformations centered on eclipsed, while a value about 3 Hz represents a torsion angle of 30−40°, as near as such a C−O bond gets to staggered (see Figure 5).

If the methyl of the acetyl group is replaced by larger groups R to give other esters, similar conformational effects should be encountered. Since the group R is *trans* to the exocyclic bond as in **3** *cis*, eclipsing result from repulsive interactions of C=O with adjacent equatorial positions. Thus when R is larger, these repulsions may not be greatly enhanced, but we present no evidence for this here. The case of formate esters with R = H is special, and we shall report on that elsewhere.

We have also investigated the tendency for eclipsing of C−OR bonds in other alcohol derivatives, namely silyl ethers[21] $C{-}OSiR^1R^2R^3$ and diethyl phosphate esters[22] $C{-}OP({=}O)(OEt)_2$. In these series, the O−R bond is longer than in acetates, thus reducing the steric interaction with adjacent positions, but there is still a marked tendency for eclipsing of the C−O bond when there is appropriate neighboring substitution, in sugars, for example. Molecular mechanics calculations agree with such eclipsed conformations, and vicinal coupling across the C−OR bond show a correlation with the bond conformation of the type described above for acetates. For silyl ethers,[21b] the Karplus equation derived as above is $^3J = 3.4\cos^2\tau - 2.1\cos\tau + 2.5$, while for phosphate esters[22] it is $^3J = 5.8\cos^2\tau - 2.1\cos\tau + 6.1$.

The point has already been made[7a] that carbon−oxygen bonds are particularly likely to be eclipsed compared with analogously substituted carbon−carbon bonds, since the former are shorter. Interactions of R with A or B as in structure **9** are larger since, with two intervening carbon−oxygen bonds, the two groups are closer than when on a hydrocarbon backbone. Furthermore, the barrier to rotation for carbon−oxygen bonds (i.e. the relative instability of the eclipsed conformation), is inherently lower than for carbon−carbon bonds. We confirmed this from the MM3 calculated barrier to isopropyl group rotation in isopropyl acetate **1a** of 1.06 kcal/mol, while in isobutylmethyl ketone (**1a** with $-CH_2-$ replacing −O−) it is 2.84 kcal/mol. The low barrier at $\tau = 0°$ in esters such as 1a means that there may be significant population of conformations between −43° and +43°.

The effect of flanking equatorial substituents is to displace the minima at $\tau \sim \pm 43°$ in isopropyl acetate or cyclohexyl acetate, toward $\tau = 0°$, and coincidentally lower or eliminate the barrier to eclipsing. The substituents do not need to be as large as methyl groups for the two minima to coincide at $\tau = 0°$. The eclipsing we demonstrate from the NMR of compounds **1d**−**f** and **16** and **17** is thus only an enhancement of a distortion that is inherent in the simplest secondary alkyl acetate. The essence of this paper is to show when eclipsing is particularly marked.

Conclusion

For the most simple secondary alkyl acetates $R^1CH_2(R^2CH_2)CH{-}OAc$ including cyclohexyl acetates, there is a very shallow potential energy well for torsion about the C−O bond, with overall minima where the H−C−O−Ac torsion angle is about ±43°. There is a small barrier of little more than 1 kcal/mol to rotation between these.

A substantial number of substituted secondary alkyl acetates are found to adopt an eclipsed conformation about the C−O bond. Many of these examples are cyclic with either axial or equatorial acetate, where there are equatorial substituents flanking the acetate group on both sides. More generally eclipsing is to be expected when an acetate, cyclic or acyclic, is part of a fragment A−C−CH(OAc)−C−B whose framework A−C−C−C−B takes up an extended conformation as in **9**.

Experimental Section

All the acetates in the NMR study are either commercially available or known compounds.[23−26] The isomeric 2,6-dimeth-

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[20] The strain-free C−O bond length used in MM3 calculations[12] is 143.5 pm whereas the C−C bond length is 151.5pm.

[21] (a) Marzabadi, C. H.; Anderson, J. E.; Gonzalez-Outeiriño, J.; Gaffney P. R. J.; White, C. G. H.; Tocher, D. A.; Todaro, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 15163−15173. (b) Gonzalez-Outeiriño, J. Ph.D. Thesis, University of London, 2001.

[22] Anderson, J. E.; Nasser, R. Unpublished results reported in Nasser R., M.Sc. Thesis, University of London, 1997.

ylcyclohexyl acetates **15**−**17** have been described.[24] We prepared them from the commercially available mixture of isomers of 2,6-dimethylcyclohexanol, and determined NMR coupling constants from the spectrum of the reaction product after workup and for **1a**−**c** agree well with previously recorded values.[18a,b] Isomers were not separated but were identified from other coupling features which are characteristic of configuration and from NMR correlation experiments. Compounds **1d**[25] and **1e**[26] were synthesized from similarly available alcohols.

The molecular mechanics calculations used the 1994 version of Allinger's MM3 program[13,14] run on a Silicon Graphics workstation. Coupling constants were determined from the natural abundance ^{13}C spectrum of the carbonyl carbon with gated irradiation at the proton frequency. They are accurate to ±0.2 Hz.

Acknowledgment. J.G.-O. acknowledges financial support from the Bogue Research Fellowship.

Supporting Information Available: Tables S1−S11 include Cartesian coordinates for the compounds displayed in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048295C

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(23) Rosado-Lojo, O.; Hancock, C. K.; Danti, A. *J. Org. Chem.* **1966**, *31*, 1899−1902.

(24) Cornubert, R.; Anzani, P.; Aubrey, A.; Hartmann, P.; Lemoine, M. *Bull. Soc. Chim. Fr.* **1950**, 631.

(25) Wibaut, J. P.; van Pelt, A. J. *Recl. Trav. Chim. Pays-Bas* **1941**, *60*, 55−61.

(26) Foley, W. M.; Welch, F. J.; La Combe, E. M.; Mosher, H. S. *J. Am. Chem. Soc.* **1959**, *81*, 2779−2784.