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SYSTEMATIC CONFORMATIONAL ANALYSIS. TORSION CONSTRAINT EVALUATION IN CYCLIC SYSTEMS

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Abstract—In connection with a general procedure for manual systematic conformational analysis, a method for the evaluation of torsion constraint in cyclic systems is reported. Torsion constraining structural features presently include fusions and bridgings. Starting from the two-dimensional structure of the molecule, where stereocenters are indicated by the conventional wedged/hashed stereobond notation, the method allows for the ready determination of allowed endocyclic torsion angle magnitudes and signs at constrained bonds. The method rests on the analysis of the torsion angles related to a cyclic fragment. The limitations of the method are discussed and its scope is exemplified by the analysis of the required geometry of a key reaction in the total synthesis of quadrone.

The full description of molecular geometry requires the knowledge of bond distances, valency angles and torsion angles. Among those a chemist perceives only the latter as a sensitive parameter for the description of molecular shape, when using framework models. Indeed, molecular models merely consist of skeletal fragments, possessing, for a particular hybridization state, standard valency angles and bond distances. Different geometrical arrangements are then obtained by varying torsion angles. Within limits, the description of molecular geometry by torsion angles alone yields a fair approximation for the real three-dimensional picture of a molecule, and moreover, one that a chemist is familiar with.[1]

Using the very properties of molecular models (i.e. constant bond distances and valency angles) a method is presented which allows for the ready evaluation of torsion constraint in a cyclic system. The process is done through examination of the two-dimensional structure of the molecule, with stereocenters indicated by the conventional hashed/wedged bond notation. The torsion constraint is defined in terms of allowed signs and magnitudes of endocyclic torsion angles. Torsion constraint evaluation forms the base of a generalized procedure for systematic conformational analysis. This has recently been outlined with the focus on the seven-membered-ring system.[2] The procedure is based upon the derivation of a primary conformational set which includes every possible basic conformation[‡] that a system can adopt with respect to its intrinsic structural features and its torsion constraining structural features.[§] In the following paper in this series the basic conformations of five- and six-membered-ring models will be defined, and the importance of the torsion constraint evaluation in the derivation of a basic conformational set will be exemplified.

Basically, the method yields the same information as the one obtained *via* molecular model examination. However, at the same time it provides the reassuring confidence that every possible conformation of the system has been envisioned. Therefore, the procedure should find a broad range of applications in flexible systems,[¶] where molecular model examination alone cannot ascertain that every possible conformation of the system has in fact been examined. Moreover, the method allows for a useful approach to the description of transition-state geometries, as the analysis of the required geometry for a key reaction in the total synthesis of quadrone will further illustrate.[3]

In the first part of this paper the relationships between the torsion angles in a (substituted) four-atom fragment are analyzed and a stereoconvention for the unambiguous assignment of the orientation of substituents is presented. Further extension to torsion constraint evaluation in cyclic systems is given in the second part. Finally, the scope and limitations of the method are discussed.

Relationships between torsion angles in a four-atom fragment—the α,β-stereoconvention

Definition of torsion angle. In a fragment of attached atoms 1-2-3-4, where neither 1 nor 4 are collinear with 2 and 3, the torsion angle ω is defined as the smaller angle subtended by bonds 1-2 and 3–4 in a plane projection obtained by viewing the fragment along the axis 2–3; ω is considered positive or negative depending on whether a clockwise or anticlockwise rotation of the bond to the front atom (1 or 4) is required in order to coincide with the direction of the bond to the rear selected atom (4 or 1, respectively), respectively.[4–7] This definition implies that absolute values of torsion angles are equal to or smaller than 180°, and that it is immaterial whether the projection is viewed from the front or the rear.

The reference torsion angle Φ, the α,β stereodesignation. In order to allow for the unambiguous assignment of the orientation of substituents, located on the central atoms 2 and 3 of a given fragment 1–2–3–4, the following conventions are introduced: atoms 1 and 4 are defined as endo atoms, other atoms located on 2 and 3 as exo atoms, and the angle subtended by 1 and 4 along 2–3 as the reference torsion angle Φ; Φ will thus always imply the endo, endo-dihedral angle of a particular four-

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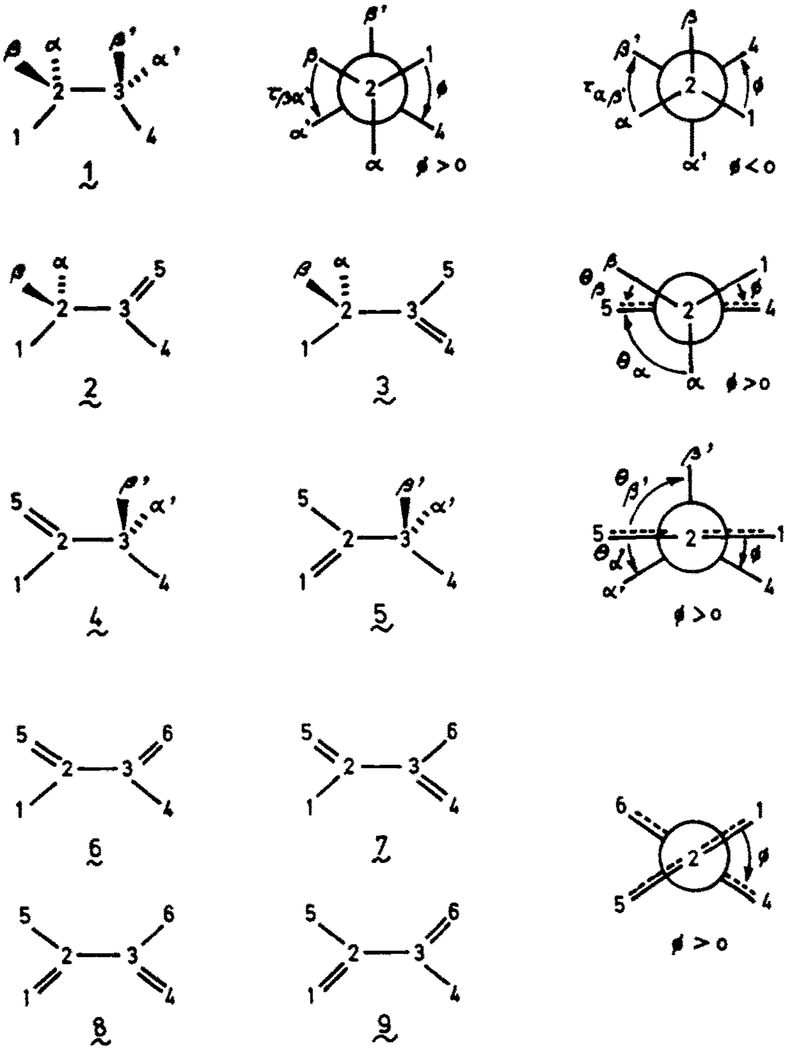
[‡] Basic or model conformation refers to a geometrically well-defined, usually symmetry-related form.

[§] An illustrative chart is found in Ref. 2.

[¶] The notion of a ring being flexible is inherent is pseudorotating systems (e.g. cyclopentane, boat cyclohexane, chair and boat cycloheptane), where conformational interconversion is possible without bending bond angles.

atom fragment. When the central atoms are joined by a double bond, Φ is either 0° (Z geometry) or 180° (E geometry).† However, when 2 and 3 are joined by a single bond, nine different combinations corresponding to fragments **1–9** (Scheme I) can be considered depending on the hybridization state of the central atoms (i.e. sp^3 or sp^2). For the assignment of substituent orientation the fragment is disposed in a cisoid conformation,‡ so that, starting clockwise from atom 1, atom 4 is reached *via* 2 and 3 along the concave side of the fragment (eqn 1): depending on whether exo substituents are oriented above (wedged stereobond) or under the plane (hashed



^{a}Fragment **1**; endo-endo: $\omega(1,4) = \Phi$; exo-exo: $\omega(\beta,\beta') = \omega(\alpha,\alpha') = \Phi$, $\omega(\beta,\alpha') = \Phi - 120°$ (or $\Phi + 240°)^e = \tau_{\beta\alpha'}$, $\omega(\alpha,\beta') = \Phi + 120°$ (or $\Phi - 240°)^e = \tau_{\alpha\beta'}$; endo-exo: $\omega(\beta,4) = \omega(1,\alpha') = \Phi + 120°$ (or $\Phi - 240°)^e$, $\omega(\alpha,4) = \omega(1,\beta') = \Phi - 120°$ (or $\Phi + 240°)^e$.

^{b}Fragments **2–3**; endo-endo: $\omega(1,4) = \Phi$; exo-exo: $\omega(\beta,5) = \Phi - 60°$ (or $\Phi + 300°)^e = \theta_\beta$, $\omega(\alpha,5) = \Phi + 60°$ (or $\Phi - 300°)^e = \theta_\alpha$; endo-exo: $\omega(\beta,4) = \Phi + 120°$ (or $\Phi - 240°)^e$, $\omega(\alpha,4) = \Phi - 120°$ (or $\Phi + 240°)^e$, $\omega(1,5) = \Phi + 180°$ (or $\Phi - 180°)^e$.

^{c}Fragments **4–5**; endo-endo: $\omega(1,4) = \Phi$; exo-exo: $\omega(5,\beta') = \Phi + 60°$ (or $\Phi - 300°)^e = \theta_{\beta'}$, $\omega(5,\alpha') = \Phi - 60°$ (or $\Phi + 300°)^e = \theta_{\alpha'}$; endo-exo: $\omega(5,4) = \Phi + 180°$ (or $\Phi - 180°)^e$, $\omega(1,\beta') = \Phi - 120°$ (or $\Phi + 240°)^e$, $\omega(1,\alpha') = \Phi + 120°$ (or $\Phi - 240°)^e$.

^{d}Fragments **6–9**; endo-endo: $\omega(1,4) = \Phi$; exo-exo: $\omega(5,6) = \Phi$; endo-exo: $\omega(5,4) = \omega(1,6) = \Phi + 180°$ (or $\Phi - 180°)^e$.

^{e}For absolute values of ω larger than 180°.

Scheme I^{a,b,c,d}

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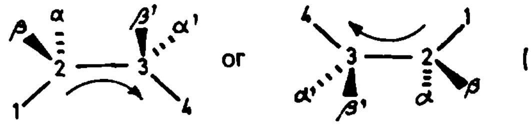
†Deviations from this ideal case are discussed in the second part.

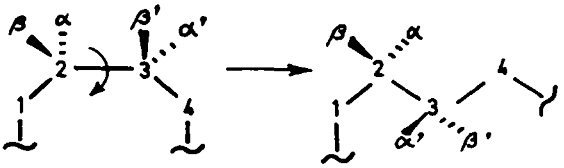
‡The plane formed by bonds 1-2 and 3-4, when Φ is set equal to 0°, coincides with the plane of the paper. The case of an E-double bond is discussed later in the text.



(1)

stereobond), they are designated by β (and β') or α (and α'), respectively, a prime indicating that the substituent is located on atom 3. When dealing further with cyclic systems, the atoms of the cyclic skeleton will always be considered clockwise and the endocyclic (or internal) torsion angles will be taken in turn as reference angles Φ.

The above stereoconvention implies that every substituent lying above or underneath the plane of a ring will have its orientation defined by β or α, respectively, provided that the ring is considered in its most extended form (i.e. planar ring with all fragments in cisiod conformations), and that the corresponding two-dimensional structural diagram is drawn using the conventional wedged(β)/hashed(α) stereobond notation. The β, α designation used here is thus directly related to the *cis*, *trans*-stereoisomer distinction in cyclic compounds.[7] It should be stressed that the currently used β, α notation in steroids, designating substituents up and down at a given carbon when the ring is viewed from above, is maintained here, provided that the cycle does not present a reentrant angle in its structural diagram. Apart from an aesthetical point of view, the use of reentrant angles (e.g. in medium rings) is mostly not warranted. Often they are intended to provide additional information about a particular conformation of the molecule;[8] in some cases, however, this happens at the expense of clarity about the very structure of the molecule (i.e. its configuration, *vide infra*). Therefore, it is logical that a two-dimensional diagram should only be used to represent unambiguously the *configuration* of a molecule; any information regarding the *conformation* is best given by a drawing reflecting the three-dimensional situation. If one still wishes the use reentrant angles in a structural diagram, the following points should be kept in mind in order to avoid ambiguity when following the above outlined α, β stereodesignation. (1) The conventional wedged/hashed symbols are only used at tetrahedral ring atoms and are always drawn at the convex side of the concerned vertex. (2) At the vertex of a reentrant angle, wedged and hashed stereobonds indicate α and β substituents, respectively, as illustrated in eqn (2). (3) Since the presence of an E-double bond in a cycle necessarily implies that two four-atom fragments are disposed in a transoid conformation, the net result for the α, β stereodesignation is the same as if the double bond were not present.[†] In order to illustrate the problem, a case where ambiguity may arise is discussed below. The two-dimensional representation of tulirinol as **10** does not allow for the unambiguous assignment of the configuration at C-1, following the above convention, since it is not clear whether the substituent at C-1 would still be designated by a hashed stereobond if the ten-membered ring were considered in its most extended form. It was shown by X-ray diffraction that the three oxygen substituents at C-1, C-6 and C-10 are *cis*-oriented.[9] Following the proposed convention the three substituents are now defined as α substituents (relative configuration) and the structural diagram is drawn as **11**, when using a reentrant angle at C-1. It will be shown later that the contradiction apparent in **11** (i.e. an "α substituent" is indicated with a wedged stereobond) is in fact not real.[‡]



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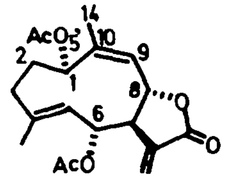

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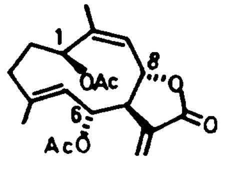

11

The Φ, Ψ, τ *and* θ *relations*. The dihedral angles subtended by the exo, exo atoms and exo, endo atoms in fragments **1**–**9** are directly related to the reference angle Φ (Scheme I). Assuming trigonal symmetry in the Newman projections, these dihedral angles correspond to Φ, Φ ± 180°, Φ ± 120°, or Φ ± 60°.[6b] The different relationships are further defined by eqns (3)–(7):

$$\Phi \pm 180° = \Psi \tag{3}$$

$$\Phi \pm 120° = \tau \qquad \begin{aligned} \Phi + 120° &= \tau_{\alpha\beta'} & (4)\\ \Phi - 120° &= \tau_{\beta\alpha'} & (5) \end{aligned}$$

$$\Phi \pm 60° = \theta \qquad \begin{aligned} \Phi + 60° &= \theta_{\alpha} = \theta_{\beta'} & (6)\\ \Phi - 60° &= \theta_{\beta} = \theta_{\alpha'} & (7) \end{aligned}$$

$$0 \leq |\tau|,\ |\theta|,\ |\Psi|, |\Phi| \leq 180°\S$$

A graphical representation is given in Fig. 1. Which relationship is followed by a dihedral angle around 2–3 depends on both the hybridization of the central atoms 2 and 3, and on the position (i.e. exo or endo) of the atoms subtending the angle (Table 1). Entries 3, 6, 8 and 9 in Table 1 need to be commented upon. (1) An exo, exo-dihedral angle in an sp^3, sp^3-hybridized fragment equals Φ when both exo substituents are *cis*-oriented, and follows the τ-type relation (i.e. Φ ± 120°) when *trans*-orien-

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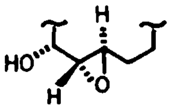
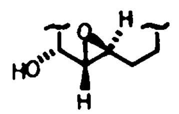
[†] A difficult case is the unambiguous representation of an epoxide originating from an E-double bond. Following the outlined conventions, an "α epoxide" should be represented either by i or ii (see also Ref. 8).



i



ii

[‡] Several of the above discussed points have been stressed before in connection with a proposed convention for describing germacranolide sesquiterpenes (Ref. 8).

[§] For values of τ and θ larger than 180°, the following equations are used: (4) Φ − 240°; (5) Φ + 240°; (6) Φ − 300°; (7) Φ + 300°.

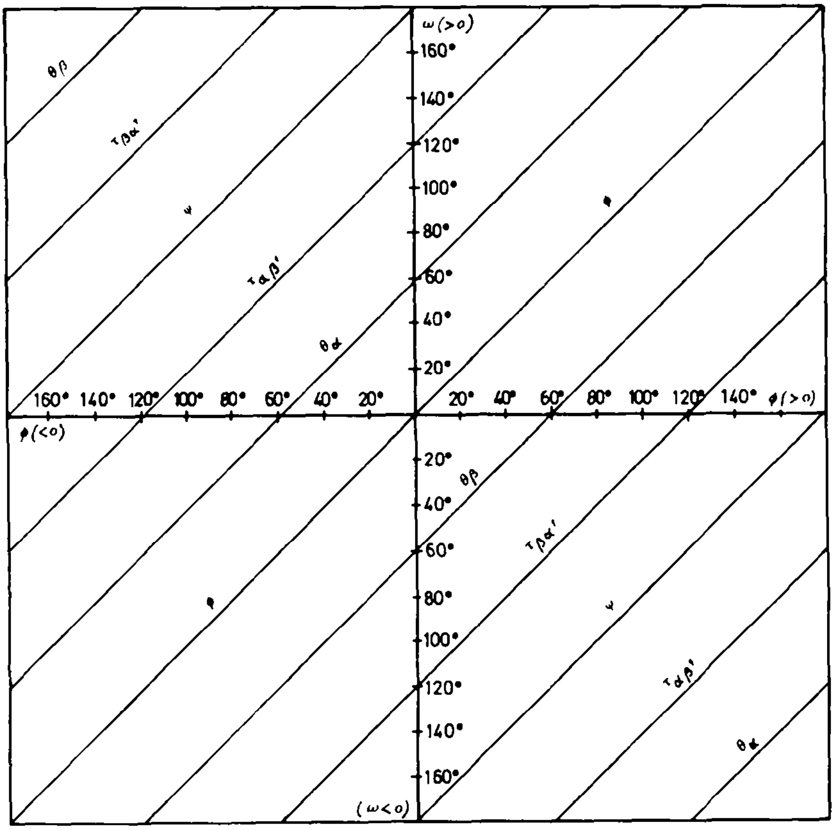
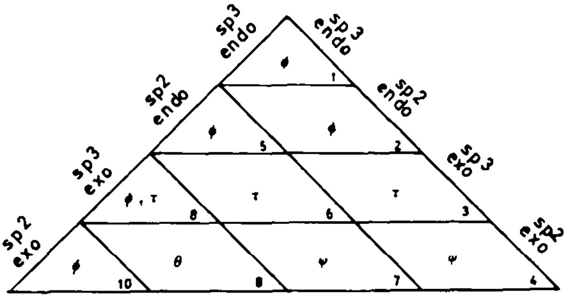


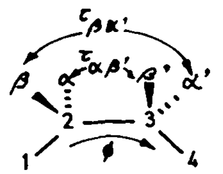
Fig. 1. Interrelationship between Ψ, $\tau_{\alpha\beta'}$, $\tau_{\beta\alpha'}$, θ_α and θ_β, and the reference torsion angle Φ, according to eqns (3)–(7).

Table 1. Effect of the hybridization of atoms 2 and 3 and of the exo/endo-position of substituents located on atoms 2 and 3 of a fragment 1-2-3-4 on the relationship between the torsion angle subtended by the substituents and the reference torsion angle Φ.[a]



[a] Φ, endo, endo-dihedral angle subtended by atoms 1 and 4. Ψ, defined by eqn (3). τ, defined by eqns (4) and (5), depending on the configuration; see text, notes 1 and 2. θ, defined by eqns (6) and (7), depending on the configuration; see text, note 3.

ted (cf. entry 8; fragment **1** in Scheme I); in the latter case, distinction is made between the $\tau_{\alpha\beta'}$ relation (eqn 4) and the $\tau_{\beta\alpha'}$ relation (eqn 5), depending on whether the substituent attached to atom 2 is α- or β-oriented, respectively. The case is exemplified in eqn 8. (2) The same distinction is made when dealing with an exo, endo-dihedral angle with the exo substituent attached to an sp^3-hybridized atom (entries 3 and 6; fragments **1–5**); however, in this case the $\tau_{\alpha\beta'}$ relation is followed when the exo substituent is β-oriented on 2 or α'-oriented on 3, and the $\tau_{\beta\alpha'}$ relation when α-oriented on 2 or β'-oriented

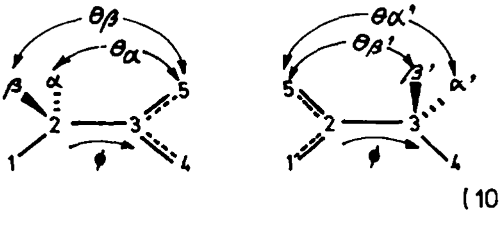


(8)

on 3 (eqn 9). (3) An exo, exo-dihedral angle in an sp^3, sp^2-hybridized fragment follows the θ relation (entry 9;

(9)

fragments **2–5**): θ_α (or the equivalent $\theta_{\beta'}$) if the exo substituent on the sp^3 atom is α-oriented on 2 or β' oriented on 3, and θ_β (or $\theta_{\alpha'}$) if β-oriented on 2 or α'-oriented on 3 (eqn 10). The use of these relationships is exemplified for product **12** in Scheme II.



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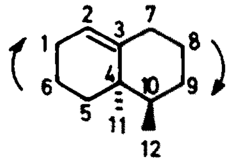

12

*When $\omega(10\text{-}4, 3\text{-}7)$ is set equal to Φ: $\omega\ (7\text{-}3, 4\text{-}5)$ corresponds to $\tau_{\alpha\beta'}$, $\omega(2\text{-}3, 4\text{-}10)$ to Ψ, and $\omega(5\text{-}4, 3\text{-}2)$ to θ_β, respectively.

When $\omega(9\text{-}10, 4\text{-}3)$ is set equal to Φ: $\omega(12\text{-}10, 4\text{-}11)$ corresponds to $\tau_{\beta\alpha'}$, $\omega(12\text{-}10, 4\text{-}3)$ to $\tau_{\alpha\beta'}$, and $\omega(11\text{-}4, 10\text{-}9)$ to $\tau_{\alpha\beta'}$, respectively.

Scheme II*.

For a particular fragment any dihedral angle can thus be related to an arbitrarily chosen reference angle Φ; in practice, the internal torsion angles of a cyclic system will be taken in turn as reference torsion angles since they are often restrained to a definite sign and a limited range of magnitudes (*vide infra*). The usefulness and consistency of the above introduced α, β stereodesignation is now fully apparent. For example the following dihedral angle values, related to the C(1)–C(10) fragment in tulirinol (**10**), were determined by X-ray diffraction:[9] $\omega(2\text{-}1, 10\text{-}9) = -123.1°$, $\omega(5'\text{-}1, 10\text{-}9) = +121.3°$, and $\omega(5'\text{-}1, 10\text{-}14) = -59.0°$. For Φ equal to $\omega(2\text{-}1, 10\text{-}9)$, one may readily deduce from Fig. 1 that $\omega(5'\text{-}1, 10\text{-}9)$ corresponds to $\tau_{\beta\alpha'}$ and $\omega(5'\text{-}1, 10\text{-}14)$ to θ_α, respectively; both equations 9 and 10 indicate the "absolute" α configuration for the 0-5' substituent at C-1.

Torsion constraint evaluation in cyclic systems

Distinction is made between first and second order torsion constraint evaluation. During first order evaluation the *allowed signs and magnitudes* of the different endocyclic angles are defined. During second order evaluation the *preferred magnitudes* of torsion angles are evaluated. In order to allow for a semi-quantitative description, the magnitude (absolute values) of dihedral angles are further characterized by angle types.[2] These types are defined by a single capital letter (i.e. *O*, *A*, *B*, etc) or a double capital letter (i.e. *OO*, *OA*, etc.); they encompass ranges of 30° (but 20° for *O*) and 10°, respectively (Table 2).

Table 2. Dihedral angle types and their corresponding magnitude ranges (degrees)

OO	0-9	DE	90-99	O	0-19
OA	10-19	EE	100-109	A	10-39
AA	20-29	EF	110-119	B	30-59
AB	30-39	FF	120-129	C	50-79
BB	40-49	FG	130-139	D	70-99
BC	50-59	GG	140-149	E	90-119
CC	60-69	GH	150-159	F	110-139
CD	70-79	HH	160-169	G	130-159
DD	80-89	HI	170-180	H	150-180

With regard to the *allowed magnitude* of an endocyclic torsion angle Φ, two parameters are used: Φ_m and Σ_m. (1) Φ_m represents the largest torsion angle Φ of a particular cyclic fragment.† In the first instance, the magnitude of Φ_m is dicated by the ring size of the cycle and the hybridization of the fragment. Values for Φ_m in cycloalkanes (sp^3, sp^3 fragment) and cycloalkenes (sp^3, sp^2-endocyclic fragment) as a function of the ring size are given in Table 3; these values result from the preferred non-planar conformation of alicyclic compounds, and correspond to the largest torsion angle values encountered among the basic unsubstituted cycloalkane[10-12] and cycloalkene[13,14] conformations. Since the above Φ_m values can be increased significantly by the imposition of external strain on the system (*cf* fusions and bridgings) a $MA\Phi_m$ value (for Maximul Allowable) is further introduced. $MA\Phi_m$ indicates the largest possible torsion angle that the cycle can afford. As a measure for $MA\Phi_m$, Φ values in highly constrained model derivatives were considered. The $MA\Phi_m$ values for cycloalkanes smaller than nine-membered are given in Table 3.[15-19] Since the Φ_m values for sp^3, sp^2 fragments in cycloalkenes are already on the large side,[13,14] they will further merely be considered as $MA\Phi_m$ values. Nine- and larger membered rings are presently not considered.‡ A three-membered ring is merely identified with a double bond; types *OO* and *OA* (constrained case) are allowed for a Z-double bond, types *HH* and *HI* for an E-double bond.§ (2) Σ_m represents the largest sum of the torsion angles at two adjacent bonds in the cycloalkane series. Values given in Table 3 correspond to the largest sums encountered among the basic cycloalkane conformations.[11,12] A *ca.* 30% increase of these values is allowed for the corresponding $MA\Sigma_m$ values (Table 3).¶ It will further be shown how this parameter can effectively be used in the evaluation of possible conformations. It should be stressed here that the way both the $MA\Phi_m$ and $MA\Sigma_m$ values were deduced implies that any substantial larger value than the maximum allowable one should correspond to a situation where the ring is geometrically no longer viable.[∥] With regard to the ***sign*** of Φ, a torsion constraint is identified when a particular sign for Φ is imposed or rejected. Torsion constraining structural features include: fusions, bridgings and anchoring substituents located off the ring.[2]

Fusion. A fusion with a cycle may, depending on the ring size of both cycles and on the hybridization of the fusion atoms, impose a particular sign on the angle(s) at the fusion bond. This sign imposition depends critically on the configuration of the fusion atoms.

(1) In the case both fusion positions are sp^3-hybridized, one has to distinguish between *cis* fusions (i.e. exo, exo-dihedral angle of type $\alpha\alpha'$ or $\beta\beta'$) and *trans* fusions (i.e. exo, exo-dihedral angle of type $\alpha\beta'$ or $\beta\alpha'$). *Cis* fusions imply a Φ-type relation at both sides of the

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†Regardless of the preferred conformation of the cycle.

‡With regard to the Φ_m value of 152° calculated for the **BCB** of cyclodecane,[12] the corresponding $MA\Phi_m$ value probably corresponds to 180°.

§In view of the results obtained for E cyclooctene,[19] the minimum allowable Φ value for an E-double bond probably corresponds to type *FG*.

¶Comparison of Φ_m and Σ_m values in the cycloalkane series[12] reveals that for cyclopentane, $\Sigma_m = 0.62\ \Phi_m$, and that for larger-membered rings, $\Sigma_m \cong \Phi_m$.

[∥] In highly constrained systems one may expect important bond angle deviations rather than torsion angle values larger than the $MA\Phi_m$ value; see, e.g. Refs. 15, 16.

Table 3. Maximum values (absolute) of endocyclic torsion angles in cycloalkanes and cycloalkenes

	Cycloalkanes (sp^3-sp^3)				cycloalkenes
Ringsize	Φ_m[a]	$MA\Phi_m$[b]	Σ_m[c]	$MA\Sigma_m$[d]	(sp^3-sp^2) Φ_m[e]
4	AA	AB	0°	f	f
5	BB	BC	30°	40°	AB
6	CC	CD	60°	80°	BC
7	DD	EE	90°	120°	CD
8	FF	GG	110°	150°	DE

[a] Maximum torsion angle magnitudes encountered in basic cycloalkane conformations, according to references 10-12.

[b] Maximum Allowable Φ_m value in cycloalkanes, according to references 15-19.

[c] Maximum sum (rounded value) of torsion angle magnitudes at two adjacent bonds as found in basic cycloalkane conformations, according to references 11-12.

[d] Maximum Allowable Σ_m values (rounded values; see text).

[e] Maximum torsion angle magnitudes at C-2,C-3 bonds in $\Delta^{1,2}$-cycloalkenes, according to references 13-14.

[f] Not considered.

junction; consequently, both fusion torsion angles possess the same sign, but no sign is *a priori* imposed (e.g. **13** and **14** in Scheme III). On the contrary, *trans* fusions impose a sign on both angles provided that the cycles are smaller than eight-membered (e.g. **15** and **16** in Scheme III: n and n′ ≤ 7). Indeed, since the $MA\Phi_m$ values for rings smaller than eight-membered do not exceed 120° (i.e. smaller than type *FF*), The following can be readily deduced from Fig. 1: an $\alpha\beta'$ configuration of a cycle n′ fused at the reference cycle n (i.e. **15**) results in a positive torsion angle at the fusion position in n′ ($\tau_{\alpha\beta'} >$ 0) and a negative torsion angle in n ($\Phi < 0$); the inverse result is found for the alternative *trans* configuration (i.e. **16**).† In the case of *trans* fusions of cycles smaller than eight-membered it has been observed that the trigonal symmetry assumption is not always valid: the sum K of the absolute values of both angles depends on the substitution pattern at the junction.[20] In a first approximation equations 11 and 12 will be used, with two possible values for quaternary, tertiary substitution.‡

$$K = |\Phi| + |\tau_{\alpha\beta'}(\tau_{\beta\alpha'})| = \begin{matrix} 120° \text{ for quat./tert.-quat. subst.} & (11) \\ 110° \text{ for quat./tert.-tert. subst.} & (12) \end{matrix}$$

(ring size: 4–7).

If one of the cycles can adopt a conformation with a torsion angle larger than 120° (i.e. $MA\Phi_m$ corresponding to type *FF* or larger) a similar direct relationship between angle signs and fusion configuration is not compulsory: e.g. in the **BCB** conformation of the ten-membered ring[12] in **17**, both angles at the fusion are negative (e.g. $\Phi = -150°$ and $\tau_{\alpha\beta'} = -30°$, *cf* Fig. 1). Angle type correspondances for Φ and τ (K = 120° and 110°) in the case of *trans* fusions between 4-, 5-, 6- and 7-membered rings are given in Table 4. They were deduced from the

13 14 15 16

[a] ω(1-2, 3-4) is taken as Φ in **13**–**16**; ω(5-3, 2-6) corresponds to the β,β'-configuration in **13** (relative to cycle n), to α,α' in **14**, α,β' in **15** (thus $\tau_{\alpha\beta'}$) and β,α' in **16** (thus $\tau_{\beta\alpha'}$).

Scheme III[a].

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†The same conclusion is arrived at by Bucourt[6b] by considerring that the angular substituents are axially oriented to both rings. However, the present deduction is more general and takes into account that: (i) seven-membered rings may undergo *trans* fusions (e.g. with another cycloheptane) at bonds where one of the junction substituents is not axial (i.e. isoclinal in the twist-chair conformation);[12] (ii) when dealing with cycles larger than eight-membered, *trans* fusions with the same torsion angle sign at both sides of the junction may occur (see text).

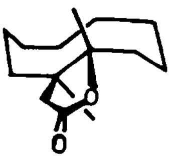
‡Important deviations may occur (K < 100°), especially in highly constrained systems (see Refs. 14 and 15).

Table 4. Effect of ring size and configuration on the sign and the magnitude of the endocyclic torsion angles at an sp^3-sp^3 trans fusion of cycles smaller than 8-membered[a]

$\tau_{\beta\alpha'}$ $(< 0) \rightarrow \Phi > 0$ $\tau_{\alpha\beta'}$ $(> 0) \rightarrow \Phi < 0$

Φ	OO	OA	AA	AE	BB	BC	CC	CD	DD	DE	EE	
4				a								6
4	a	a	a	a								7
5						a						5
5				a	a	a						6
5	a	a	a	a	a	a						7
6								a				4
6						a	a	a				5
6				a	a	a	a	a				6
6	a	a	a	a	a	a	a	a				7
7								a	a	a	a	4
7						a	a	a	a	a	a	5
7				a	a	a	a	a	a	a	a	6
7	a	a	a	a	a	a	a	a	a	a	a	7
K = 110°	EE	DE	DD	CD	CC	BC	BB	AB	AA	OA	OO	τ
K = 120°		EE	DE	DD	CD	CC	BC	BB	AB	AA	OA	

[a] For the reference cycle with torsion angle Φ (upper-left corner), torsion angle types are given in the first row and ring sizes in the left column; for the cycle fused at Φ with torsion angle τ ($\tau_{\alpha 3'}$, or $\tau_{3'\alpha'}$, depending on the configuration; lower-fight corner) torsion angle types are given in the last rows for K = 120° (eq 11) and K = 110° (eq 12); ring sizes are noted in the right column.



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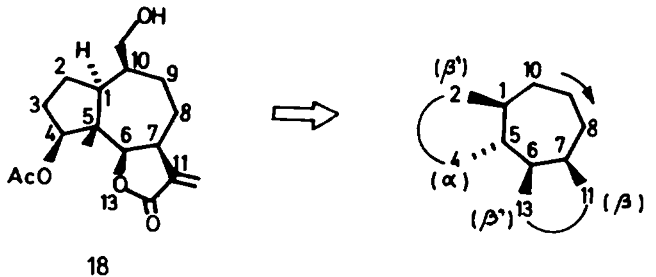
MAΦ_m values (Table 3) and eqns (4) and (5). Torsion constraint evaluation using these data is exemplified for the seven-membered ring of **18** in Scheme IV. One will further note that for K = 110° there is a direct correspondance between the symbols *O* and *E*, *A* and *D*, *B* and *C*, respectively; i.e. to a preferred type + *BB* at the fusion in the cyclopentane of **18** corresponds type − *CC* in the 7-membered ring.

(2) In the case one of the fusion atoms is sp^2-hybridized, the signs at the fusion bond are dependent on both the configuration of the fusion atom and on the ring



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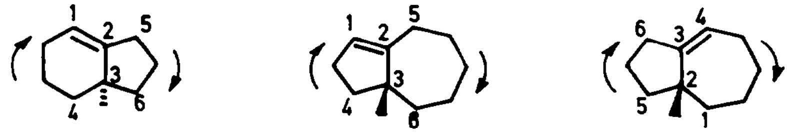
[a] ω(8-7, 6-5) = ω(13-6, 7-11) = Φ: possible types ±(*OO* to *BC*); *cf* MAΦ_m value for a 5-membered ring (Table 3). ω(6-5, 1-10) = Φ yields ω(2-1, 5-4) = $\tau_{\alpha\beta'}$; possible types for Φ: −(*BC* to *EE*), and for $\tau_{\alpha\beta'}$: +(*OO* to *BC*); *cf* Table 4.

Scheme IV[a].



19 20 21

[a] ω(1-2, 3-4) = Φ in products **19**, **20** and **21**; ω(6-3, 2-5) in **19**, **20** and **21** correspond to $\theta_{\beta'}$, $\theta_{\alpha'}$ and θ_{α}, respectively. Allowed types (*cf* Table 5) in **19**: $\Phi = -(OO \text{ to } BC)$, $\theta_{\beta'}(=\theta_{\alpha}) = +(OO \text{ to } BC)$; in **20**: $\Phi = \pm(OO \text{ to } AB)$, $\theta_{\alpha'}(=\theta_{\beta}) = -(AA \text{ to } DE)$; in **21**: $\Phi = -(OO \text{ to } CD)$, $\theta_{\alpha} = +(OO \text{ to } BC)$ and $-(OO, OA)$.

Scheme V[a]

size of both cycles (*cf* Fig. 1 and Φ_m values in Table 3). Table 5 allows for the direct deduction of type and sign correspondances at the fusion of 5-, 6- and 7-membered rings. Here Φ is taken as the endocyclic torsion angle in the cycloalkene. Examples are given in Scheme V. Cyclobutenes being essentially planar, they are not considered in Table 3.

Fused systems that cannot be treated by the present procedure: (1) *trans* fusions between 5- and 4-membered rings, and between 7- and 3-membered rings (*cf* Table 4); (2) *cis* fusions between small rings (i.e. 3- and 4-membered).

Bridging. Torsion constraint originating from bridging is in the first instance restricted at the cyclic bonds that are directly attached to the bridgehead atoms; these bonds are further defined as CB bonds (for Constrained Bridged). Endocyclic torsion angles at CB bonds follow the $\tau_{\alpha\beta'}$ or $\tau_{\beta\alpha'}$ relation depending on the configuration of the bridgehead atoms (*cf* endo, exo-dihedral angle, equation 9). This is exemplified in Scheme VI. Consequently, bridgings can be treated as *trans* fusions involving sp^3-hybridized fusion atoms;[6b] Table 4 is used for determining possible angle types and signs of torsion angles at CB bonds. Provided that two cycles which have a CB bond in common are both smaller that 8-membered, a direct sign relationship between the angles at the CB bond is found (*vide supra*).

Bicyclo[2.1.1]hexanes and bicyclo[1.1.1]pentanes cannot be treated by the present procedure since *trans* fusions between 4- and 4- or 5-membered rings are not considered (*cf* Table 4). Several examples dealing with bridged systems will be discussed in the following paper in this series. Bridging with sp^2 hybridization at the bridgehead position necessarily involves the incorporation of an E-double bond in a cycle. The smallest ring which can afford this, and still can yield an isolable compound is suggested to be the 8-membered ring (*cf* bicyclo[3.3.1]non-1-ene);[21] this is in accord with type *FG* for the minimum allowable torsion angle of an E-double bond (*vide supra*).

22 23

[a] ω(1-2, 3-4) in cycle ab of **22** and **23** is taken as Φ; ω(4-3, 2-5) in cycle bc then corresponds to $\tau_{\beta\alpha'}$ in **22** and to $\tau_{\alpha\beta'}$ in **23**, respectively (see eqn 9).

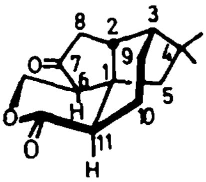
Scheme VI[a].

Scope and limitations

The above outlined procedure allows for the assessment of torsion constraint in a cyclic compound in terms of allowed torsion angle signs and magnitudes. The obtained data serve as a stringent criterion for the deduction of the possible conformations of a cyclic system.[2] The importance of configurational constraints in the assignment of conformation has already been stressed before.[6b] The recognition of constraining structural features is an essential part in the recently reported computer method for semiquantitative assignment of conformation of 6-membered ring systems.[22] Preliminary fragment approach in computerized molecular modeling has also been used before.[23] However, these methods for conformer generation are inconvenient for manual use, since they were primarily developed for automatic treatment by machine. The primary aim in the development of the present procedure has been the possibility of using it manually in a rapid and reliable way for the solution of day-to-day problems encountered in synthetic organic chemistry. The conceptually unifying approach used in the development of the method should in principle allow for future computer treatment as well. Since the method is based on a geometrical analysis of framework models, without being restricted by their physical limitations, one may expect its most interesting applications in cases where molecular model examination does not yield satisfactory results: (1) in flexible systems, where molecular model examination alone cannot guarantee that every possible form of the system has been examined; (2) in the description of the geometry of a transition state (*vide infra*).

It should be stressed here that the essential relationships (eqns 3–7) upon which rest the deduction of the method were derived assuming standard valency angles (i.e. *ca* 109° and 120° for sp^3- and sp^2-hybridized atoms). Consequently; the procedure should not be applied to systems where bond angles depart considerably (*ca* 20° and more) from their ideal values. With this respect, caution should be taken when considering four-membered rings. The few systems, that are too constrained to be considered here, show such important angle deviations: bicyclo[1.1.1]pentanes,[24,25] bicyclo[2.1.1]hexanes,[24] *trans*-bicyclo[5.1.0]octanes,[26] cyclopropenes and cyclobutenes.[27]

One of the possible applications of the method is illustrated with the analysis of a particular strategy for the construction of the cyclic carbon skeleton of quadrone (**24**).[3] An attractive approach could involve bond formation between C-1 and C-11 in **25** *via* an intramolecular reaction. Depending on the proposed reaction—which obviously must also involve participation of the enone system—C-11(Z) could stand for a



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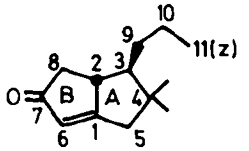

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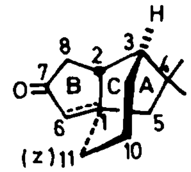

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diene (i.e. Diels–Alder reaction),[28] an olefin (i.e. ene reaction),[29] an allene (i.e. photocycloaddition).[29] In every one of these cases, a transition state depicted as in **26** can be formulated, taking into account the formation of the new bond and the concomitant change in hybridization at C-1. The structure of **26** implies that the 5-membered ring A, originally only fused at B, now also becomes part of a bicyclo[3.2.1]octane system (*cf* rings A and C). At this point the question arises, whether the constraints imposed on the system in the starting material **25** are compatible with the constraints that will be induced in the system *upon reaching* the required transition state geometry **26**. More specifically, one should consider the constraints at a bond that is part of both cycles A and C, and that is not directly involved in the reaction, i.e. bond C-2, C-3. Constraint evaluation at this bond in **26** leads to possible types $+AB$, $+BB$ or $+BC$ for Φ (1-2, 3-4); a *trans* fusion of type $\beta\alpha'$ between a 5(A)- and 6(C)-membered ring in a bridged system is involved (eqn 9; Table 4). On the other hand, the fusion between two 5-membered rings in **25**, involving the sp^2-hybridized C-1 and a β-oriented hydrogen at C-2, results in allowed types for the torsion angles (8-2, 1-6)/(5-1, 2-3): $-AB/+AA$, $-AA/+AB$, $-OA/+BB$, $-OO/+BC$, respectively (Table 5). Thus, in approaching the transition state geometry **26**, ring A must accomodate a situation where $\Phi(1,2)$ and $\Phi(2,3)$ correspond to $+(AA-BC)$ and $+(AB-BC)$, respectively; the sum of the torsion angles at these adjacent endocyclic bonds equals 50° or more, whereas the $MA\Sigma_m$ value in a 5-membered ring is 40° (Table 3). Consequently, a reasonable geometry for ring A cannot be obtained without introducing too much strain in either the B or the C ring;† this should effectively preclude the transformation of **25**, *via* **26**, into

Table 5. Effect of ring size and configuration on the sign and magnitude of the endocyclic torsion angles at an sp^3-sp^2 fusion of cycles smaller than 8-membered[a]

Φ	-CD	-CC	-BC	-BB	-AB	-AA	-OA	-OO	+OO	+OA	+AA	+AB	+BB	+BC	+CC	+CD	
5					α	α	α	α	β	β	β	β					5
5					α	α	αβ	αβ	αβ	αβ	β	β					6
5					αβ	αβ	αβ	αβ	αβ	αβ	αβ	αβ					7
6			α	α	α	α	α	α	β	β	β	β	β	β			5
6			α	α	α	α	αβ	αβ	αβ	αβ	β	β	β	β			6
6			α	αβ	αβ	αβ	αβ	αβ	αβ	αβ	αβ	αβ	αβ	β			7
7	α	α	α	α	α	α	α	α	β	β	β	β	β	β	β	β	5
7	α	α	α	α	α	α	αβ	αβ	αβ	αβ	β	β	β	β	β	β	6
7	α	α	α	αβ	αβ	αβ	αβ	αβ	αβ	αβ	αβ	αβ	αβ	β	β	β	7
				-EE	-DE	-DD	-CD	-CC	-BC	-BB	-AB	-AA	-OA	-OO	+OO	+OA	Θ_β
	-OA	-OO	+OO	+OA	+AA	+AB	+BB	+BC	+CC	+CD	+DD	+DE	+EE				Θ_α

[a] α and β designate the configuration at the junction; α corresponds to Θ_α (= $\Theta_{\beta'}$), and β to Θ_β (= $\Theta_{\alpha'}$), respectively. The cycle containing the double bond at the junction is the reference cycle and the corresponding torsion angle at the juction the reference angle Φ (upper-left corner); allowed torsion angle types and signs for Φ are given in the first row; ring sizes for the unsaturated cycle in the left column. For the cycle fused at Φ with torsion angle Θ (Θ_β or Θ_α depending on the configuration; lower-right corner) angle types are given in the last rows and ring sizes in the right column.

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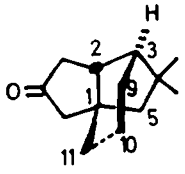
†An indication for the raise in strain energy which occurs upon increasing the dihedral angle magnitude in a 5-membered ring is found in the work of Hendrickson:[11] for a cyclopentane in the twist conformation, $\Phi_m/\Sigma_m/E$(kJ/mole): 45°/28.1°/0; 50°/31°/2.2; 55°/34°/6.4; 60°/37°/14.2; 65°/39.3°/26.2.



27

a quadrone precursor.[29] It is interesting to note that the recent successful route to quadrone involved the closure of the propanobridge on the convex face of the bicyclo[3.3.0]octanone system *via* **27**.[30] The absence of sp^2 hybridization at C-1 now allows for a negative torsion angle (e.g. $-BB$) at bond C-1, C-2 in the A ring; while proceeding from the starting material to the transition state **27**, a conformation is now available to ring A where both C-11 and C-9 are axially oriented, thus allowing for a successful ring closure. This lengthy analysis could in principle be abbreviated if one could approach directly the transition-state geometry **26**, i.e. determine the allowed torsion angle signs and magnitudes at the C-1, C-2 bond during the change in hybridization at C-1. An approach, based on the description of transient geometries using intermediate hybridization states, is under study and will be reported shortly.

In summary, this paper has detailed a manual method for the ready evaluation of torsion constraint in a cyclic system, starting from the two-dimensional structure of the molecule. In order to allow for an unambiguous configurational assignment, a consistent α, β stereodesignation of substituents located off a ring has been implemented. Torsion constraint is expressed in terms of allowed torsion angle signs and magnitudes. These data can be used in the determination of possible conformations of a cyclic system[2] and in the assessment of pre-transition-state geometries, as has been shown for a key reaction in the total synthesis of quadrone.

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