Quantitative Correlation between Calculated Molecular Properties and Retention of a Series of Structurally Related Racemates on Cellulose Triacetate

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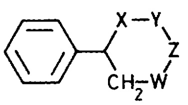
Racemic compounds consisting of an alicyclic six-membered ring with a phenyl group attached to the chiral carbon atom have been investigated. The chemical structure of the alicyclic part was varied systematically, in order to establish its influence on the separability of the racemates into their pure enantiomers on cellulose triacetate (CTA). Theoretical investigations, involving conformational analysis and charge distribution, have been undertaken to correlate structural features with chromatographic behaviour. For this class of compounds two major parameters governing the interaction with CTA are the rotational freedom of the bond to the phenyl group and thereby the relative ability to assume the flattest possible conformation, and a negatively charged neighbourhood of the chiral centre.

Cellulose triacetate (CTA) is a very powerful and versatile chiral sorbent for the chromatographic resolution of racemic compounds.[1a–i] The influence of the supramolecular structure of CTA on the chromatographic resolution power has been reported by Ishida *et al.*[1i] and by us.[1f] From our investigation it was deduced that only one crystallographic form of CTA, called CTA I, is able to separate a large variety of racemates. It has also become clear that both the absence of an ordered supramolecular structure and too pronounced crystallinity are detrimental to the resolution power. It has therefore been concluded that complexation of low molecular weight compounds with the polymer matrix must either take place at the boundary between domains of lower and higher order in the polymer or that the polymer must retain the necessary flexibility to accommodate intruding molecules. In any case, the obvious necessity of local order in the polymer matrix led to the assumption that chiral recognition on CTA I must be based on a highly enantioselective inclusion-type complex formation between the low molecular weight racemates and several monomer units of the polymeric sorbent spatially ordered in a well defined way. This has also been pointed out earlier by Hesse and Hagel[1a] and by Mannschreck and his co-workers.[1h]

In this work, we investigated the influence of the chemical structure of the racemates on the chromatographic resolution. For that purpose a class of compounds was chosen among which some are very well separated while small alterations in the chemical structure considerably reduce the effectiveness of the separation process. The first step in the elucidation of the interaction mechanism is undertaken by a theoretical investigation of structural features of the racemates in correlation with the experimental chromatographic data. At this stage, the chiral recognition itself is not modelled and the configuration on the chiral carbon atom is irrelevant for the molecular properties under investigation. We do *not* differentiate between the interaction possibilities of the two enantiomers of a racemic compound with the chiral sorbent CTA. Indeed, for both enantiomers the nature of possible interactions is the same and only the three-dimensional arrangement of the interacting groups is inverted. Because in a first step we are interested in the forces responsible for complexation with the sorbent, we will consider for every racemate the chromatographic data of the best retained antipode (without caring for its actual configuration).

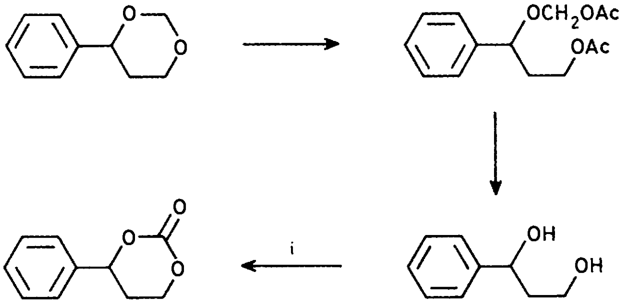
Chromatography

Model Compounds.—Starting from the observation that 4-phenyl-1,3-dioxane (**5**)[1f] and 2-phenylcyclohexanone (**1**)[1a] can be completely resolved into their enantiomers on CTA I, we defined a basis structure (**A**) of racemates consisting of two parts, a phenyl group and an alicyclic six-membered ring, the carbon chiral centre being directly bound to the aromatic moiety. The constitutional elements W—Z were varied independently and were chosen from among four possible diradicals, methylene (CH_2), oxygen (O), carbonyl ($>C=O$), or vinylidene ($>C=CH_2$). The model structures investigated in this work are in Table 1.



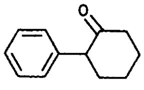
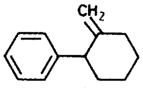
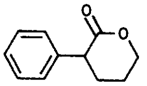
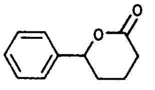
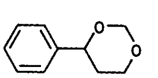
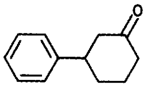
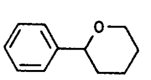
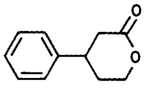
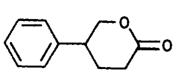
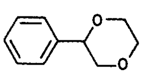
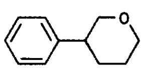
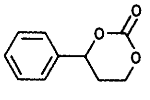
(A)

Most of the analysed compounds are commercially available or were prepared according to known procedures. 2-Phenyltetrahydropyran (**7**) and 2-phenyl-1,4-dioxane (**10**) were prepared by reaction of phenylmagnesium bromide on 2,4-dichlorophenoxy-2-tetrahydropyran[2] and 2-chloro-1,4-dioxane,[3] respectively. 3-Phenylcyclohexanone (**6**) was obtained by addition of phenylmercury chloride on cyclohexanone in the presence of palladium chloride.[4] The preparation of the lactones (**3**), (**4**), and (**8**) has been reported previously.[5–7] Starting from 1-phenylpropane-1,3-diol, the six-membered ring carbonate (**12**) was isolated in 30% yield after reaction with carbonyldi-imidazole, following the procedure of Kutney and Ratcliffe.[8] The reaction of the diol with phosgene or diethyl carbonate under various conditions led to the formation of a mixture of products with only traces of the desired carbonate. The starting diol is prepared in two steps from 4-phenyl-1,3-dioxane.[9]



Scheme. *Reagent:* i, carbonyldi-imidazole

Table 1. Chromatographic results: capacity factors k'_1 and k'_2 and separation factor α

	Racemate	k'_1	k'_2	α	Rotation*
(1)		1.2	2.6	2.2	+/−
(2)		0.8	0.8	1.0	+/−
(3)		1.3	4.2	3.3	+/−
(4)		1.3	29.7	23.3	+/−
(5)		2.4	11.1	4.6	+/−
(6)		1.2	1.6	1.4	+/−
(7)		1.0	3.3	3.3	−/+
(8)		1.7	1.7	1.0	†
(9)		1.5	1.5	1.0	†
(10)		2.2	12.0	5.4	−/+
(11)		0.8	0.8	1.0	+/−
(12)		1.4	9.5	6.8	+/−

* Sign of optical rotation at 365 nm of the first/second eluted enantiomer. † Resolution too poor to detect elution order.

Results and Discussion.—The compounds in Table 1 resulting from various combinations of structural elements W—Z have been subjected to chromatography on an analytical column of CTA I. Table 1 lists the chromatography results, *i.e.* the capacity factors* k'_1 and k'_2 of the first and second eluted enantiomer, respectively, and the resulting separation factor $\alpha = k'_2/k'_1$. Figure 1 depicts some typical chromatograms [for (**3**), (**6**), (**7**), and (**12**)], obtained under the conditions described in the Experimental section.

The capacity factors k'_1 and k'_2 reflect the affinity of the sorbent for each enantiomer of a given compound. The separation factor α is the measure of the interaction energy difference $\Delta\Delta G$ of two compounds with the sorbent, since $\Delta\Delta G = -RT\ln\alpha$. In the chromatographic resolution of racemates, α expresses the chiral discrimination. Although a large value of k'_2 is often responsible for a large separation factor α, this is not stringent. There are examples in which k'_2 and k'_1 are large, *i.e.* where the affinity of both enantiomers for the chiral support is strong, resulting in a low chiral recognition. However, this is not the case for the 12 racemates of Table 1. The fact that, on CTA I, a large k'_2 value nearly always leads to a high α resides in the strong enantioselectivity of CTA I, which forms a tight complex with the 'good' enantiomer while the optical antipode displays much weaker interactions. Therefore we choose k'_2 as the important experimental parameter to be correlated in the subsequent sections with structural properties of the model compounds.

For both phenylcyclohexanones (**1**) and (**6**) which are resolved on CTA I, the (+)-enantiomers are eluted first and exhibit identical capacity factors. However, the (−)-antipode of 2-phenylcyclohexanone (**1**) is retained longer than that of 3-phenylcyclohexanone (**6**), indicating a stronger interaction with CTA I when the carbonyl group is adjacent to the chiral centre. The achiral 4-phenylcyclohexanone (not shown in Table 1), where the carbonyl group is still further away from the chiral centre has only a weak affinity for the stationary phase, as indicated by a small capacity factor of 0.73. A similar effect is observed for the lactone series (**3**), (**8**), and (**9**), where only tetrahydro-3-phenyl-2*H*-pyran-2-one (**3**) has a larger k'_2 value and is resolved into its enantiomers. By replacing the carbonyl group of 2-phenylcyclohexanone (**1**) with a carbon–carbon double bond, the capacity factor drops considerably and no separation occurs.

It is remarkable that all compounds possessing an oxygen atom adjacent to the chiral centre have rather high k'_2 values and are efficiently resolved: 2-phenyltetrahydropyran (**7**), both dioxane derivatives (**5**) and (**10**), the lactone (**4**), and the carbonate (**12**). The second eluted enantiomer of tetrahydro-6-phenyl-2*H*-pyran-2-one (**4**), which structurally is a combination of 3-phenylcyclohexanone (**6**) and 2-phenyltetrahydropyran (**7**), displays an exceptionally strong retention (k'_2 29.7) and the chiral discrimination in this case is very high (α 23.3, *i.e.* $\Delta\Delta G$ at 300 K is 1.88 kcal mol^{-1}). This enantiomer must fit particularly well into the chiral environment offered by the supramolecular structure of CTA I and is therefore an especially valuable model compound for further investigations of the interaction mechanism. The carbonate derivative (**12**) which is structurally closely related to the very well retained lactone (**4**) has a lower k'_2 value (9.53), resulting also in a lower chiral recognition (α 6.80). For compound (**12**), the negative influence of the oxygen *para* to the phenyl group conflicts with its positive influence in 4-phenyl-1,3-dioxane (**5**) where its introduction results in both a higher k'_2 and α compared with the structurally similar tetrahydropyran derivative (**7**). Interestingly, another isomer, 2-phenyl-1,4-dioxane (**10**) shows similar strong interactions with CTA I, whereas the achiral 2-phenyl-1,3-dioxane (not shown in Table 1) is only poorly retained (capacity factor 1.71). 3-Phenyltetrahydropyran (**11**) which has no oxygen in the vicinity of the chiral centres is poorly retained (k'_2 0.82) and not resolved. In summary, it can be stated that the presence of an electronegative atom close to the chiral centre favours the retention of one enantiomer and thereby may also enhance the chiral discrimination.

Finally, it is worth pointing out that structures, formally resulting from the combination of benzene with tetrahydropyran, cyclohexanone, dioxane, or δ-valerolactone, can in some cases interact very strongly with CTA I, exhibiting capacity factors which are higher than that of benzene alone (k' 4.65), although the four alicyclic structures as such are hardly retained on CTA I columns.

Theoretical Investigation

The crystal structure of the crystallographic form I of cellulose triacetate has been investigated in detail.[10] However, these data

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* The capacity factor k' is defined as $k' = V(V - V_0)/V_0$, where V is the elution volume of the eluate and V_0 is the elution volume of a non-retained compound.

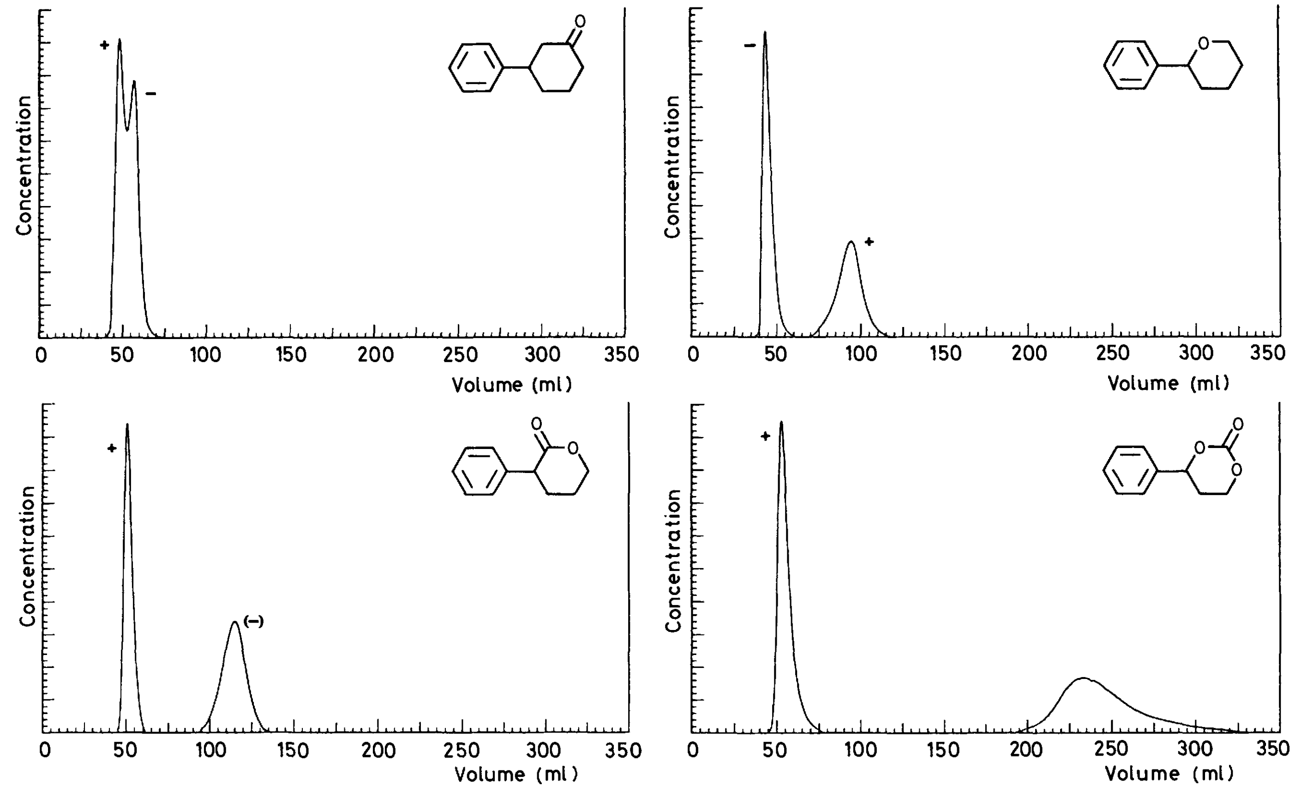

Figure 1. Chromatographic resolution of compounds (**3**), (**6**), (**7**), and (**12**) on CTA I (see Experimental section for chromatographic conditions)

are not suited for attempting directly the modelling of the interactions between low molecular weight compounds and CTA I since under optimum chromatographic conditions the polymer must be swollen[1] and the actual spatial configuration of the site or sites of complexation is not experimentally accessible.

On the other hand, the very sensitive dependence of the retention and eventual optical resolution on the supramolecular structure of the polymer[1f] and on the chemical structure of the racemates clearly indicates the presence of specific sites of complexation. Obviously, molecules which are well complexed must be some kind of casting (or negative) of such a site. It is therefore of interest to characterize these molecules from the viewpoint of interaction possibilities and thereby gain some insight into the topology of the chiral cavities in CTA I. Furthermore, a detailed knowledge of the factors governing the interaction with CTA I may turn out to be very useful since many racemates which cannot be resolved directly on CTA I, can be modified or derivatized[1g] in order to provide them with the structural features necessary for strong complexation and possibly optical resolution into their enantiomers.

We attempted to find quantitative descriptors for the structural properties of the model compounds (**1**)—(**12**) of Table 1 and to correlate them with experimental chromatographic data. It must be emphasized that the subsequent investigations deal with molecular properties which are independent of the absolute configuration, differences between two enantiomers resulting only from interactions with a chiral environment (*i.e.* by the formation of any kind of diastereoisomeric complex). Obviously, the stronger retention of the second eluted enantiomer in chromatography is due to a more favourable sum of interactions with the chiral sorbent and chiral discrimination by itself could only be modelled if based on interaction energy calculations with the polymeric stationary phase. However, in a series of model compounds like that of Table 1, the differences in the capacity factors k'_2 (*i.e.* for the better retained enantiomers) must reside in intrinsic structural properties and should be assessed regardless of the absolute configuration at the chiral carbon atom.

A qualitative comparison of the 12 model structures revealed that the interaction with CTA I is favoured for those compounds having a negative charge close to the carbon atom bearing the phenyl group. An sp^3 oxygen in the α-position of the chiral centre seems to be especially effective for strong complexation. This oxygen has two effects: it introduces a negative partial charge in the neighbourhood of the chiral carbon atom and it lowers the rotational energy barrier of the phenyl group, due to a lower van der Waals repulsion than, *e.g.*, methylene or carbonyl. Therefore we decided to proceed to a detailed analysis of the conformational freedom around the phenyl group and the charge distribution around the centre of chirality in all 12 model structures.

Three-dimensional Structures.—The three-dimensional structures of the substances (**1**)—(**12**) were computed with the help of Allinger's force field program MM2.[11] The following procedure was applied.

First, the alicyclic six-membered ring was built (see Figure 2a—g). In order to preserve the self-consistency of the force field, lone-pair electrons on sp^3 oxygens were introduced explicitly at this stage. The lone-pairs were then removed later for conformational energy evaluation and for CNDO calculations. In the case of the carbonate derivative (**12**), some force constants not included in MM2 had to be added. It was verified that the numerical values of these constants were not crucial for the final outcome, as long as they assumed values of the same order of magnitude as those for similar structural fragments. The energy for all structures converged rapidly to a minimum and the resulting geometries (bond lengths, bond angles, and dihedral angles) assumed values expected for such

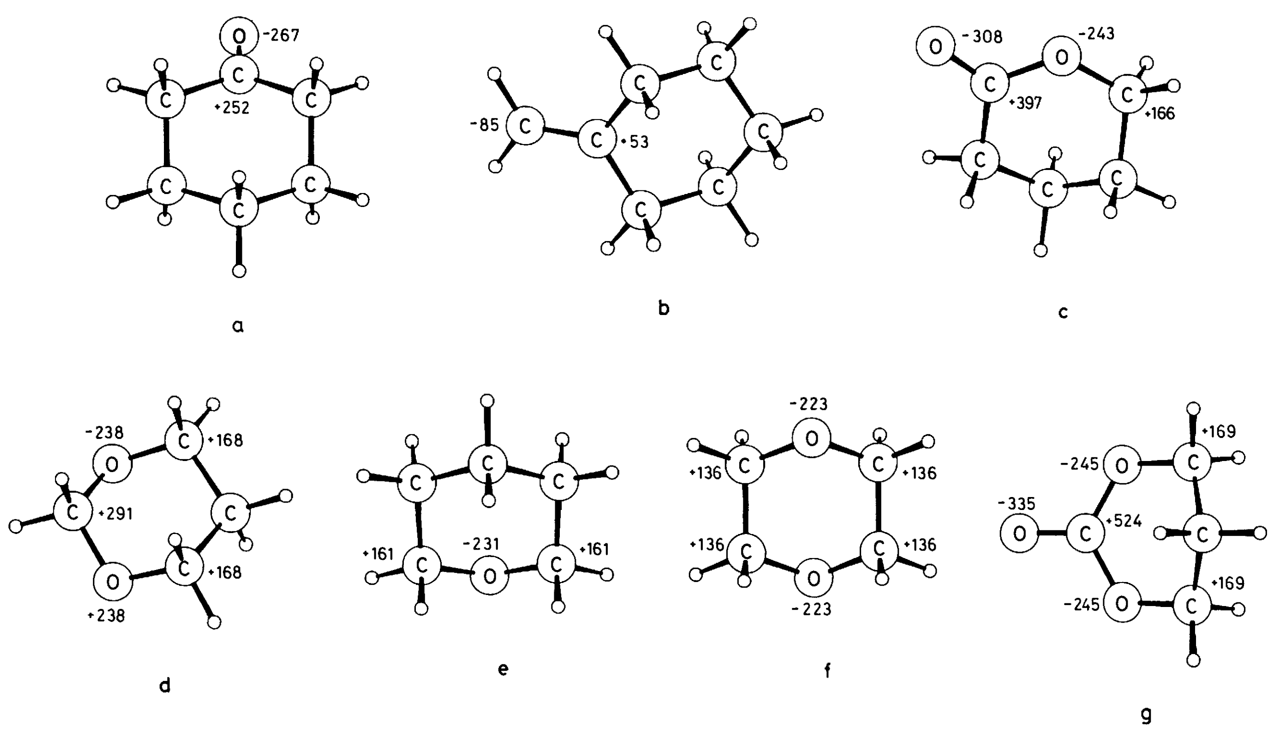

Figure 2. Structures (obtained with the force field MM2) of the alicyclic moieties of the twelve model structures of Table 1, with the partial charges computed by CNDO (in elementary charge units $\times 10^3$)

compounds. The phenyl group was then introduced by substituting the appropriate equatorial hydrogen atom. The bond length to the phenyl group was chosen as 1.53 Å,[12] which is slightly larger than the default value in MM2 (1.514 Å). The geometry of the alicyclic portion of the molecules was not further altered upon the introduction of the phenyl group.

Conformational Energy.—The only freely rotatable bond in all structures **(1)**—**(12)** is that to the phenyl group. For investigating its rotational freedom, the following approximations were made.

(*a*) Except for the torsion angle to the phenyl group, all angles and bond lengths were held constant, a procedure which can be termed 'rigid rotor' approximation.

(*b*) The only non-bonded energy terms were the van der Waals interactions between the atoms of the phenyl group and those of the alicyclic ring (excluding atom pairs being separated by less than three bonds). Coulombic energy terms were not involved because of the electroneutrality of the phenyl group.

(*c*) An intrinsic rotational potential was not included for the $C(sp^3)$–C(phenyl) bond.

This last approximation may lead to absolute values for the rotational barriers which are slightly underestimated. However there is evidence that this potential must be low since the total rotational barrier (including the van der Waals repulsions) of a methyl around a phenyl group is <0.5 kcal mol^{-1}.[13]

The 'rigid rotor' approximation obviously is an oversimplification for conformations in which the van der Waals repulsion between the atoms of the phenyl group and the alicyclic six-membered ring becomes severe. But such conformations are statistically insignificant anyway and thus do not have to be taken into account.

With the 'rigid rotor' approximation further use of the force field parameters of MM2 to evaluate the van der Waals interactions would not be appropriate, since those parameters are highly correlated and should only be used with the entire force field, *i.e.* when the relaxation of too much repulsion by bond angle or length variations is included. For calculating non-bonded interactions, we opted for the finite range modification of the standard Lennard-Jones function $U(r) = 4\varepsilon[(\sigma/r)^{12} - (\sigma/r)^6]$, as proposed by Theodorou and Suter,[14] applying range limits which well reproduce the full potential. The parameters ε and σ were calculated with the Slater–Kirkwood formula[15] from literature values for atomic polarizabilities α, effective number of electrons N_e, and van der Waals radii r_0, listed in Table 2.[16]

Table 2. Potential parameter values

Atom type	r_0/Å [a]	α/Å^3 [b]	N_e [c]
H	1.3	0.42	0.9
C (sp^3)	1.8	0.93	5.0
C (sp^2)	1.8	1.23	5.0
C (C=O)	1.8	1.23	5.0
C (aromatic)	1.95	1.23	5.0
O (–O–)	1.60	0.70	7.0
O (C=O)	1.60	0.84	7.0

[a] van der Waals radius. [b] Polarizability. [c] Effective number of electrons.[16]

The torsion angle φ around the phenyl group is defined as zero when the chiral centre carbon atom, the hydrogen atom bound to it, and the phenyl group are in one plane. The rotation is positive for a clockwise torsion of the phenyl group, when looking from the chiral centre towards the aromatic carbon atom connected to it. The conformational analysis of compounds **(1)**—**(12)** was performed with a step length of 1°. With the above definitions, the shortest dimension in all 12 model compounds is minimized for values of φ between 60 and 120°, *i.e.* the molecules adopt the flattest possible conformation for that φ range, referred to as [60°; 120°] from now on.

Table 3 summarizes the results of the conformational analysis: the statistical mechanical average rotation angle* $\langle\varphi\rangle$

Table 3. Results of theoretical analysis

	Conformational analysis			Electrostatic potential	Chromatographic data	
Model	$\langle\varphi\rangle$[a]	[D][b]	[Ω][b]	E_{00}[c]	k'_2[d] (exp.)	k'_2[e] (theor.)
(1)	-1.1	51	-35	-8.05	2.6	2.1
(2)	$+2.5$	39	-40	-1.68	0.8	0.9
(3)	-7.6	62	-20	-13.23	4.2	5.4
(4)	-17.7	133	51	-10.58	29.7	17.5
(5)	-18.7	145	60	-2.91	11.1	8.3
(6)	-0.5	59	-29	-1.77	1.6	1.1
(7)	-16.8	116	33	-5.53	3.3	6.5
(8)	-5.0	89	8	$+0.06$	1.7	1.9
(9)	$+4.2$	87	5	$+1.53$	1.5	1.5
(10)	$+16.2$	152	60	-4.50	12.0	10.1
(11)	$+1.5$	60	-34	-0.83	0.8	0.9
(12)	-18.4	146	60	-7.05	9.5	13.8

[a] In degrees (for the *R* enantiomer in all cases, with the definition of the sense of rotation of φ in the text; the sign inverts for the respective antipodes). [b] In degrees, see text for details. [c] In kcal mol^{-1} (normalized for the interaction with a charge of +1). [d] Experimental k'_2 values. [e] Corresponding k'_2 values evaluated by equation (2).

for the conformation domain [D] having a conformational energy <5 kcal mol^{-1}, the size of [D] in degrees and the overlap [Ω] of [D] for φ 60—120° in degrees, *i.e.* $[\Omega] = [D] \cap [60°; 120°]$. For those model compounds for which the conformational energy $E(\varphi)$ does not exceed 5 kcal mol^{-1} in the range [60°; 120°], [Ω] becomes 60°. For molecules with $[\Omega] = \phi$, the negative distance between the nearest 5 kcal mol^{-1} boundary of [D] and [60°; 120°] in degrees was introduced as a penalty.

Thus the magnitude of [D] reflects the conformational freedom of the molecule, whereas [Ω] is a measure of its ability to assume the flattest possible conformation within the energy limits of 5 kcal mol^{-1}.

According to their conformational freedom, the 12 model structures investigated here can be divided into three major classes: (i) compounds **(1)**—**(3)**, **(6)**, and **(11)** have a small torsion freedom ([D] $\leqslant$ 60°) and a flat conformation is highly improbable ([Ω] $\leqslant -20°$), steric hindrance arising from van der Waals repulsion between the carbonyl oxygen, the vinylidene group, or the methylene hydrogens and the nearest hydrogen atoms of the phenyl group; (ii) model structures **(8)** and **(9)** display intermediate values for [D] of *ca.* 90° and a slightly positive value for [Ω], the higher conformational freedom being due to the distortion of the lactone ring resulting in a larger interatomic distance between the methylene hydrogens and the hydrogens of the phenyl group; (iii) all five compounds with an oxygen atom α to the carbon atom bearing the phenyl group [**(4)**, **(5)**, **(7)**, **(10)**, and **(12)**] have a large conformational freedom ([D] > 115°) and can readily adopt a flat conformation ([Ω] > 30°).

In Figure 3 are represented the Boltzman distributions† at 300 K of the conformational states for a representative of each of the three classes above.

Partial Charges.—The partial charges on all atoms were evaluated by CNDO calculations[17] using the atomic coordinates obtained from the force field calculations reported above. It was verified that the orientation of the phenyl group has no sizeable influence on the values of the partial charges. In Figure 2a—g are represented the alicyclic moieties of structures **(1)**—**(12)**, with partial charges indicated when larger than ±0.05 elementary charge units. The small influences of the position of the phenyl substituent on the alicyclic substructures are averaged out. Of course, the subsequent calculations were performed with the actual partial charges, as derived from CNDO.

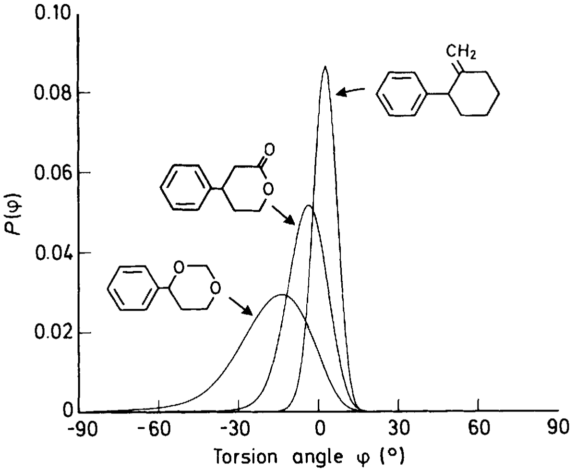

Figure 3. Boltzman distribution of the conformational states of the three compounds **(2)**, **(8)**, and **(5)** displaying, respectively, very restricted, intermediate, and high conformational freedom

Electrostatic Potentials.—The two major types of intermolecular interactions are van der Waals and electrostatic

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* The statistical mechanical average $\langle\varphi\rangle$ is evaluated as

$$\langle\varphi\rangle = \frac{\int_{\varphi_A}^{\varphi_B} \varphi \exp\{-E(\varphi)/RT\}\, d\varphi}{\int_{\varphi_A}^{\varphi_B} \exp\{-E(\varphi)/RT\}\, d\varphi}$$

where φ_A and φ_B are the two rotation angles corresponding to the 5 kcal mol^{-1} boundaries.

† The probability $P(\varphi)$ of a given conformation is $P(\varphi) = \exp\{-E(\varphi)/RT\}/Z$, where $E(\varphi)$ is the conformational energy associated with the torsion angle φ and Z the partition function of the entire conformational domain, *i.e.* $0° \leqslant \varphi < 180°$ (because of the symmetry of the phenyl group, the range $180° \leqslant \varphi < 360°$ does not have to be considered):

$$Z = \int_0^{180°} \exp\{-E(\varphi)/RT\}\, d\varphi$$

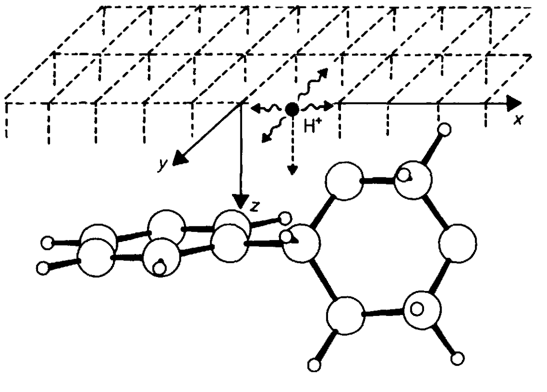

Figure 4. Schematic representation of the procedure used to calculate electrostatic potentials by taking into account the van der Waals repulsion. A probe (H^+) scans over the molecule in the x–y plane. Normalized electrostatic energy is evaluated at regular intervals in the x and y direction for the value of z, at which the van der Waals repulsion of a hydrogen atom would start

forces. The electrostatic interaction energy E between two point charges δ_i and δ_j, separated by a distance r (in Å), is given by $E = 332\delta_i\delta_j/(\varepsilon r)$ kcal mol^{-1}, where δ_i and δ_j are expressed in elementary charge units, ε being the effective dielectric constant of the medium.

In an overall neutral molecule, positive and negative partial charges are mostly alternating over the space occupied by the molecule, so that at some distance the effects of their interaction with an external partial charge are smeared out. This is especially the case when they are buried deep in the van der Waals volume of the molecule and thereby are less accessible.

Therefore we developed a method to represent the effect of partial charges on their surroundings by considering simultaneously the van der Waals repulsion. The procedure is in some respects comparable to methods described by Cohen[18] and is represented schematically in Figure 4.

A molecule is positioned in a defined orientation (see below) in a three-dimensional grid. A proton (elementary charge $+1$) is chosen as a probe and scanned over the x–y plane in steps of 0.5 Å in the x- and y-direction. The third dimension is introduced by the approach towards the molecule in the z-direction. The closest approach (± 0.05 Å) is defined at the point where the van der Waals repulsion between a hydrogen atom and the molecule would start. The onset of van der Waals repulsion is evaluated with the above mentioned Suter–Theodorou modification of the 6-12 Lennard-Jones potential,[14] this time applying the range limits which neglect the attractive part of the potential and consider only the repulsive effects (termed 'soft-sphere' potential).

At every closest approach point $z(x,y)$, a *normalized* electrostatic interaction energy E_n (in kcal mol^{-1}) is calculated [equation (1)] where N is the number of atoms in the molecule,

$$E_n(x,y,z) = 332 \sum_{i=1}^{N} \delta_i/r_i \qquad (1)$$

δ_i is the partial charge on the ith atom, and r_i is the distance between the ith atom and the probe. By definition, $E_n(x,y,z)$ is negative in regions where the probe H^+ senses an overall attractive (*i.e.* negative) interaction energy and positive elsewhere. The effective electrostatic interaction energy E_{eff} felt by a partial charge δ at a point (x,y,z) may be calculated according to $E_{eff} = E_n\delta/\varepsilon$, ε being the effective dielectric constant of the medium.

By connecting all points with the same values of E_n, equipotential lines are obtained on the 'van der Waals envelope' of the molecule and thus represent the global effect of the individual partial charges around the molecule by taking into account the van der Waals volume.

It had been deduced from the experimental chromatographic results that a negative environment around the chiral carbon atom might favour the complexation with CTA I. Figure 5 shows the electrostatic potential contour maps of the 12 model structures, computed by the procedure outlined above. All molecules were positioned so that the chiral centre was located at the origin of the co-ordinate system, the atom opposite to the chiral carbon atom (*i.e.* in γ-position to the phenyl group) in the alicyclic six-ring on the x-axis and the carbon atom of the phenyl group bound to the chiral centre in the x–y plane. The torsion angle φ was set to $\langle\varphi\rangle$, the statistical mechanical average as listed in Table 3. The direction of the approach of the probe H^+ parallel to the z-axis (see Figure 4) was chosen so that the proton scanned over that face of the molecule that presents the most negative surrounding for the chiral centre. The numbers annotating the contour lines represent the electrostatic interaction energy of the proton serving as a probe with the molecule calculated by equation (1) in kcal mol^{-1}. Negative regions are represented by dashed lines, positive ones by continuous lines.

As a quantitative parameter for the negative charge distribution around the chiral centre was chosen the value of the potential calculated by equation (1) at the location of the chiral carbon atom ($x = y = 0$). These values, termed E_{00}, are given in Table 3.

Correlation between Experimental Data and Theoretical Structural Parameters.—As reflected by their high values for $[\Omega]$, the five compounds having an oxygen α to the chiral centre [(**4**), (**5**), (**7**), (**10**), and (**12**)] can easily adopt the flattest possible conformation within the 5 kcal mol^{-1} boundaries. The experimental capacity factors k'_2 for the more strongly retained enantiomer of these molecules are high and all five are resolved on CTA I. The model structures for which X in the schematic structure above is $-CH_2-$, $>C=O$, or $>C=CH_2$ display small (or even negative) values for $[\Omega]$, steric hindrance resulting from the van der Waals repulsion between the methylene hydrogens, the carbonyl oxygen, or the vinylidene group and the nearest hydrogen atoms of the phenyl group. However, (**1**) and especially (**3**) have quite high experimental capacity factors k'_2, suggesting that the flatness reflected by $[\Omega]$ cannot be the only important factor for a good complexation with CTA I.

A qualitative analysis of Figure 5 and Table 1 immediately reveals that all model structures for which the chiral carbon atom in the above defined projection falls within negative electrostatic potential contours [(**1**), (**3**)—(**5**), (**7**), (**10**), and (**12**)] have rather high capacity factors k'_2 for the best retained enantiomer (all >2.60), which in all seven cases also leads to an optical resolution on CTA I. For the model compound (**6**), the negatively charged region in the contour map barely touches the chiral centre. The capacity factor k'_2 of this structure is low (1.59) and the resulting resolution leads to a relatively small α value of 1.35, rather due to the small k'_1 value of the first eluted enantiomer than to a good complexation of the best retained antipode. The other four structures (**2**), (**8**), (**9**), and (**11**) have small k'_2 values and none of them is resolved into its enantiomers.

The influence of the two quantities $[\Omega]$ and E_{00}, extracted from the conformational analysis and charge distribution calculations, on the capacity factors k'_2 has been discussed qualitatively. In the following an attempt will be made to find a quantitative correlation. The goal of such a correlation is not to predict accurately k'_2 values prior to an experiment, but rather to prove that indeed $[\Omega]$ and E_{00} are two major parameters governing the complexation between CTA I and chemical compounds *structurally similar* to the 12 models investigated here.

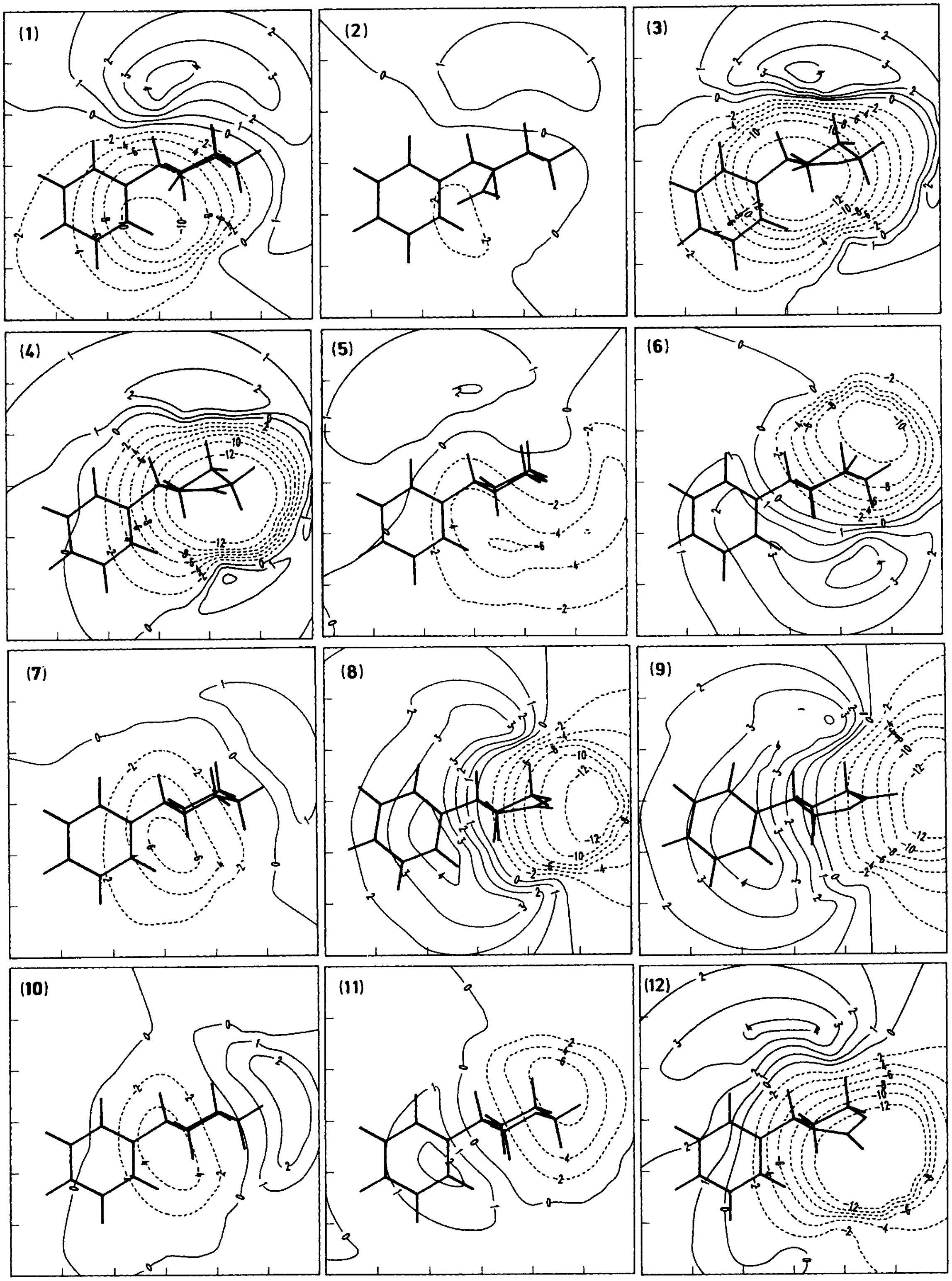

Figure 5. Electrostatic potential contour maps of the model structures (**1**)—(**12**), obtained with the procedure represented schematically in Figure 4. The annotations of the contour lines are in kcal mol^{-1}. Positive regions are encompassed by continuous lines, negative ones by dashed lines (see text for details about the exact orientation of the molecules)

If [Ω] and E_{00} are two predominant properties determining the interaction with CTA I, there must be a function f([Ω], E_{00}) which reproduces more or less accurately the experimental capacity factors k'_2. Since $-RT\ln k'_2$ represents an energy term,[19] it seems natural to correlate the logarithm of the capacity factors with the terms [Ω] and E_{00}. The simplest function f([Ω], E_{00}) is a linear combination of both terms so that equation (2) holds, *A*—*C* being constants evaluated by

$$\ln k'_2(i) = AE_{00}(i) + B[\Omega](i) + C \quad (i = 1\text{—}12) \quad (2)$$

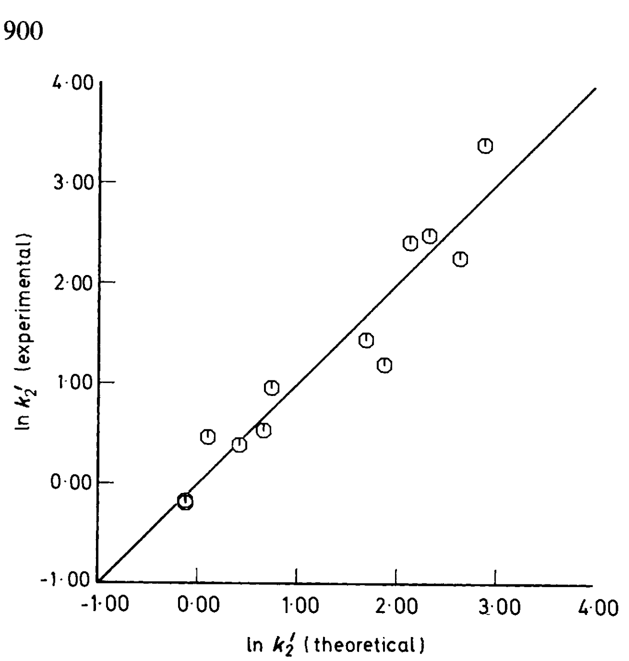

Figure 6. Experimental $\ln k'_2$ values *versus* those calculated by equation (2), using for the constants *A*—*C* the values which minimize the sum of squares of residuals for the set of 12 equations (2)

solving the overdetermined system of the 12 equations (2). The sum of squares of residuals was minimized for *A* −0.122, *B* 0.0211, and *C* 0.497. The last two columns of Table 3 list the experimental values of k'_2 and the k'_2 values calculated with the respective $[\Omega]$ and E_{00} and the constants *A*—*C* above. In Figure 6 the experimental $\ln k'_2$ values are plotted against the calculated ones; the correlation coefficient is 0.96, a fair value.

Discussion.—The good quantitative agreement between experimental and calculated k'_2 values indicates, that both the magnitude of the overlap $[\Omega]$ (*i.e.* the possibility of assuming a flat conformation), and the negative electrostatic potential around the chiral centre, are important factors for the interaction between the model compounds (**1**)—(**12**) and CTA I. The linear combination of the two quantities $[\Omega]$ and E_{00} in equation (2) has no immediate physical meaning although it resembles the chromatographic relation[19] $-RT \ln k' = \Delta H - T\Delta S + \ln \beta$, ΔH being the enthalpy of the transfer of a solute from the solvent to the stationary phase, ΔS the associated change in entropy, and β the phase ratio of the column.

The term E_{00} is comparable to enthalpy. It is proportional to the interaction energy of a positively charged atom or group of atoms with the negatively charged surrounding of the chiral centre, if approaching the molecule from the *same* side as the probe H^+ used to calculate E_{00} and it can be regarded as a contribution to the overall ΔH value. The fact that E_{00} contributes only (or at least to a larger extent) to the retention of one enantiomer is easily explained by considering that in the optical antipode, the three-dimensional charge distribution is also mirrored, thus leading to a different interaction scheme for both enantiomers with the optically active polymer. Assuming that the (chiral) site of complexation for a given configuration requires the molecule to be negatively charged on one face and positively (or neutrally) on the opposite side, it is not surprising that two enantiomers form diastereoisomeric complexes of very different strength with the chiral sorbent. Such a requirement would also explain the finding that the achiral 2-phenyl-1,3-dioxane (not modelled here), negatively charged on *both* sides of the carbon atom bearing the phenyl group, is poorly retained on CTA I, although it could assume a flat conformation like all other compounds where X = O.

The term $[\Omega]$ is a measure of flatness. By assuming that the low molecular weight compounds (**1**)—(**12**) interact with CTA I by being included between the sheet-like arranged polymer chains,[1f,20] it is conceivable that flat molecules more easily penetrate the polymer matrix than bulky ones. Thus, the model structures with broader torsional potential wells are submitted to less intramolecular 'stress' when complexing with CTA I. Our decision to use $[\Omega]$ in the functional form displayed in equation (2) is admittedly completely arbitrary, however.

Conclusions.—It can be stated that both the electrostatic potential in the neighbourhood of the chiral centre (E_{00}) and the ability to assume the flattest possible conformation (characterized by the term $[\Omega]$) are two dominant factors differentiating the interaction of the molecules of Table 1 with the crystallographic form I of cellulose triacetate.

From the necessity of a negative electrostatic potential on one side of the chiral centre it might be concluded that a positively charged atom (or group of atoms) in the polymer matrix specifically attaches from one face of the molecule to the neighbourhood of the carbon atom bearing the phenyl group.

These conclusions are based on the comparison of the capacity factors for the better retained enantiomer of each model compound in Table 1. The interaction of the respective first eluted enantiomers with CTA I, reflected by the capacity factors k'_1, cannot be related to the above molecular properties in the same way. The k'_1 values in Table 1 do not differ dramatically for the 12 structures, indicating that the interaction mechanism between the first eluted enantiomers and CTA I is much less sensitive to the chemical structure.

Neither $[\Omega]$ nor E_{00} contain chiral information. However, the three-dimensional charge distribution in two optical antipodes are mirror images. The procedure of evaluation of E_{00} outlined above implies that in molecules *like those* of Table 1, a large negative value of E_{00} also reflects a large dissymmetry in the partioning of charges which of course must favour the chiral recognition.

The logarithm of the separation factor, $\ln \alpha = \ln k'_2 - \ln k'_1$, can be correlated with E_{00} and $[\Omega]$ in the same way as $\ln k'_2$, the correlation being equally good in both cases. However this is not surprising, since all k'_1 values are of the same order of magnitude for the 12 compounds. It merely underlines the statement, that the high optical resolution power of CTA I resides in its capability to form, with one enantiomer, a strong inclusion complex, which is very sensitive both to the supramolecular structure of the polymer[1f] and to the chemical structure of the racemate, while the retention of the optical antipode is much less selective.

Although the correlation was established with 12 compounds which are structurally closely related, it should be noted that the alicyclic moiety has not to be a six-membered ring. In fact, several five-membered ring analogues and even related non-cyclic compounds have been analysed and the findings of this investigation can easily be extended to a larger number of molecules in which a phenyl group is attached to a chiral carbon atom with a negatively charged group in the proximity. Furthermore, the relevance for the complexation with CTA I of the structural property referred to as flatness in this work has already been recognized empirically before.[21]

Experimental

Chromatography on CTA I.—The sorbent CTA I was prepared by heterogeneous acetylation of native cellulose (Merck no. 2331) according to the Schering process,[22] as described by Hesse and Hagel.[23] A particle size of 25—32 μm was adjusted by brief milling and sifting. A glass column (30 × 1.25 cm ID) was slurry-packed with CTA I swollen in

95% ethanol. The pressure at the column top was 0.4 bar for a flow rate of 0.5 ml min^{-1}. Toluene-*p*-sulphonic acid served as a chromatographic reference (V_0) and eluted after 22 ml. The racemates were injected as a solution of 2—5 mg in 0.3 ml of the eluent, ethanol–water 95:5, in all cases. Chromatography was performed using an Altex 110 A pump, a Chromatix injector with a 0.3 ml loop, and a variable-wavelength Shimadzu 120-02 u.v. detector in series with a Perkin-Elmer 241 MC polarimeter equipped with a flow cell (length 10 cm), with the wavelength set at 365 nm. Both signals (u.v. absorption and optical rotation) were recorded and processed by a Hewlett–Packard HP-85B calculator through a Hewlett–Packard 3421A data aquisition-control unit.

Model Compounds.—Compounds (**1**) and (**5**) are commercially available (Aldrich). Compounds (**2**),[24] (**3**),[5] (**4**),[6] (**6**),[4] (**7**),[2] (**8**),[7] (**10**),[3] and (**11**)[25] (obtained from 2-phenylpentane-1,5-diol[26]) were prepared by literature methods.

4-*Phenyl*-1,3-*dioxan*-2-*one* (**12**). The general method of Kutney and Ratcliffe[8] was applied. To a solution of 1-phenylpropane-1,3-diol[9a] (2 g, 13.1 mmol) in toluene (20 ml) at room temperature was added *NN'*-carbonyldi-imidazole (3.2 g, 19.7 mmol). The resulting clear solution was stirred at room temperature for 16 h (a precipitate appeared after *ca.* 1 h). Neutral work-up (H_2O–CH_2Cl_2) yielded a yellow oil which was purified by chromatography on silica gel (eluant, dichloromethane). On standing, the oil crystallized slowly to give a solid (0.68 g), m.p. 56—58 °C; $\nu_{max.}$($CHCl_3$) 3 005, 1 750, 1 405, 1 245, 1 190, and 1 125 cm^{-1}; δ_H (250 MHz; $CDCl_3$; Me_4Si) 7.32—7.5 (5 H, m, Ph), 5.53 (1 H, dd), 4.42—4.60 (2 H, m, CH_2), and 2.16—2.44 (2 H, m, CH_2) (Found: C, 67.2; H, 5.7. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.7%).

Tetrahydro-5-*phenyl*-2H-*pyran*-2-*one* (**9**). To a suspension of sodium borohydride (0.9 g, 24.4 mmol) in dimethylformamide (25 ml) at 10 °C was added dropwise 2-phenylglutaric anhydride (4.56 g, 24.4 mmol) dissolved in dimethylformamide (30 ml). The mixture was stirred for 1.5 h at room temperature and then 6N-HCl (20 ml) was slowly added. The solution was diluted with water and extracted twice with ether. After evaporation of the organic phase the residue was distilled (0.01 mmHg) and yielded a first fraction (135—138 °C) which was purified by chromatography on silica gel (eluant, chloroform–ethyl acetate 5:1). As indicated by n.m.r., a *ca.* 1:1 mixture of (**9**) and (**3**) (1.23 g) was isolated and used without further purification for the chromatography on CTA.* The spectral data were in agreement with published values.[27]

Calculations.—All calculations (force field, CNDO, electrostatic potential maps, and correlations) were performed on an IBM PC XT equipped with an Accelerator PC (Titan Technologies). The contour maps were drawn on a Hewlett-Packard plotter 7475A by a program written in IBM Professional FORTRAN using several subroutines of the PLOT88 library of Plotworks.

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* Peaks corresponding to the enantiomers of (**3**) can easily be assigned based on the chromatogram of pure (**3**).