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# Syn Bromination of 2-Cyclohexen-1-ol Benzoates. Isolation of a *trans*-3-Bromocyclohexano-*cis*-1,2-(2'-anisyl-1',3'-dioxolan-2'-ylum) Intermediate<sup>†</sup>

Giuseppe Bellucci,\* Roberto Bianchini, and Sandra Vecchiani

Istituto di Chimica Organica della Facoltà di Farmacia, Università di Pisa, 56100 Pisa, Italy

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The addition of molecular bromine to 2-cyclohexen-1-ol benzoate, *p*-methylbenzoate, and *p*-methoxybenzoate in aprotic solvents of low to moderate dielectric constant gave, besides the expected vicinal *trans* diaxial and diequatorial dibromides, large amounts of two products of syn bromination, which have been identified by independent syntheses as *t*-2,3-dibromo-*r*-1-cyclohexanol and *t*-2,6-dibromo-*r*-1-cyclohexanol esters, 4 and 5. A product of type 5 was also formed in relevant amounts in the bromination of 2-cyclohexen-1-ol *p*-nitrobenzoate. The kinetic curves obtained with the stopped-flow technique for all the above reactions carried out in 1,2-dichloroethane at 25 °C showed in the early stages a fast increase in absorbance up to a maximum, followed by a slower decay to zero, pointing to the accumulation of intermediates of 2-phenyl-1,3-dioxolan-2-ylum-tribromide ion pair type. The ionic intermediate formed from 2-cyclohexen-1-ol anisoate was isolated as an orange-red oil by carrying out the bromination in carbon tetrachloride at –30 °C and was characterized as a stable crystalline *trans*-3-bromocyclohexano-*cis*-1,2-(2'-anisyl-1',3'-dioxolan-2'-ylum) tetrafluoroborate after reduction of the Br<sub>3</sub><sup>–</sup> anion to Br<sup>–</sup> and exchange with silver tetrafluoroborate. When dissolved in several different solvents this orange red salt intermediate collapsed to the two syn dibromo adducts 4 and 5 in ratios depending on the solvent polarity: 84.5% of 5 in carbon tetrachloride and 88% of 4 in nitromethane. The observed substituent and solvent effects on the product distributions of all these bromination reactions are discussed and rationalized on the basis of electronic and steric effects on the formation and opening of the ionic intermediates.

The addition of bromine to the carbon–carbon double bond is formally one of the simplest reactions typical of unsaturated compounds, but a detailed mechanistic picture is actually complex and in some respects still controversial.<sup>1</sup> Depending on the substrate structure, the intermediates can be open bromocarbonium ions, with free rotation about the carbon–carbon bond, or weakly bridged ions, with restricted rotation, or strongly bridged bromonium ions, with no rotation, each of these cationic species being paired to either a bromide or a tribromide counteranion, according to the polarity and the protic or aprotic nature of the solvent. As far as the stereochemistry is concerned, both anti and syn addition are obtained from 1-arylalkenes and 1,3-dienes, where syn addition may arise either by direct syn collapse<sup>2</sup> or, in the case of acyclic olefins, by rotation–translocation followed by anti collapse of bromocarbonium–bromide (or –tribromide) intermediates.<sup>3</sup> On the other hand, exclusive anti addition, resulting from an anti collapse of bridged ion pair intermediates, is a general rule for unconjugated olefins. With appropriately substituted cyclohexene derivatives this process leads to two diastereomeric anti dibromo adducts.<sup>4</sup>

However, in a recent kinetic and product investigation we found that mixtures of four isomeric dibromo derivatives were formed from benzoate esters of 2-cyclohexen-1-ol and molecular Br<sub>2</sub>.<sup>5</sup> In this paper we are reporting on the identification of these dibromo adducts, on the mechanism of their formation, and on the factors affecting their relative distribution.<sup>6</sup> The isolation of a 1,3-dioxolan-2-ylum salt intermediate, formed during the bromination reaction and shown to be the precursor of *cis* dibromides, is also reported.

## Results

**Products.** Four isomeric dibromo derivatives were isolated by preparative TLC from the reactions of Br<sub>2</sub> with the three olefin esters 1a–c. Only three products were

instead isolated in the case of 1d. Two of the components present in each a–d set were respectively identical with the vicinal *trans* diaxial and diequatorial adducts 2 and 3 obtained in the reactions of the same substrates with tetrabutylammonium tribromide.<sup>5</sup> The third component present in each set was easily identified as the *t*-2,6-dibromo-*r*-1-cyclohexanol ester 5 by its <sup>1</sup>H NMR spectrum, which always showed a triplet, due to an axial proton α to a benzoyloxy group coupled to two axial protons, and a six-line pattern appearing as a doublet of triplets, attributable to two chemically equivalent axial protons α to Br coupled to two axial and one equatorial H. The fourth isomer, isolated only from the reactions of 1a–c, always exhibited identical medium field NMR signals, which, however, did not provide unambiguous structural and stereochemical information. Its structure and relative configuration was thus deduced by preparing the benzoate esters 3a–5a through the reactions of known steric course shown in Scheme I. Acetyl hypobromite was added to

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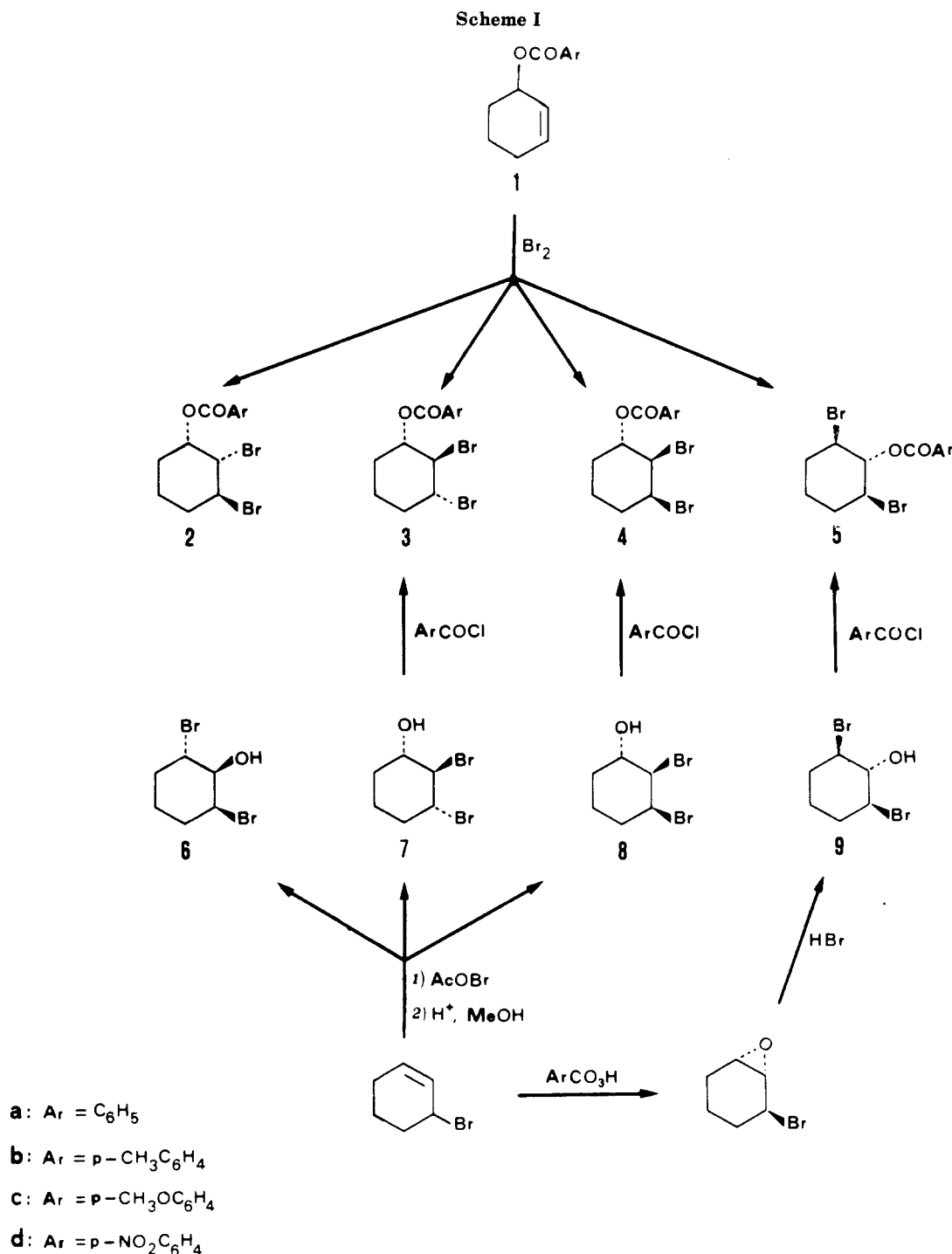
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(6) For a preliminary report, see: Bellucci, G.; Bianchini, R.; Vecchiani, S.; Fourth European Symposium on Organic Chemistry, 1985, Proceedings, PB 11.

<sup>†</sup>Chemical Abstracts would name the localized compound (3aα,4α,7aα)-4-bromo-3a,4,5,6,7,7a-hexahydro-2-(4-methoxyphenyl)-1,3-benzodioxol-1-ium.



3-bromocyclohexene and the resulting crude acetoxy bromo adducts were converted into a mixture of the three corresponding dibromo alcohols 6, 7, and 8 in ratios of 3:80:17. This crude mixture was reacted with benzoyl chloride and the two main products were separated by TLC. The more abundant one, 3a, was coincident with the vicinal trans diequatorial dibromo adduct, while the second, *t*-2,3-dibromo-*r*-1-cyclohexanol benzoate (4a), was identical with the fourth dibromo adduct obtained in the bromination of 1a. Furthermore, *trans*-3-bromo-1,2-epoxycyclohexane, obtained by epoxidation of 3-bromocyclohexene, was subjected to HBr ring opening to give *t*-2,6-dibromo-*r*-1-cyclohexanol (9). This was transformed into its benzoate ester 5a, which was identical with the 2,6-dibromide isolated from the bromination of 1a. The identification of the corresponding para-substituted derivatives followed from the strict similarity of their respective NMR spectra

with those of the unsubstituted compounds.

The product distributions determined by HPLC for the reactions of  $\text{Br}_2$  with olefin esters 1a-d in three aprotic solvents of low to moderate polarity are reported in Table I. Except for the case of 1d, appreciable amounts of all four products were always observed. With 1d only a very small peak, corresponding to 1% of the total products, was found in chloroform and 1,2-dichloroethane besides the main products 2d, 3d, and 5d. This peak was ascribed to product 4d by analogy with the reaction of all other olefin esters.

The relative amounts of products 2 changed little with changing both the para substituent and the solvent. More appreciable differences were observed instead in the distributions of products 3, 4, and 5, the most evident being the following. A *p*-nitro group increased the amount of 3d mainly at expense of 4d. The total yield of the syn

Table I. Product Distributions for the Reactions of Br<sub>2</sub> with Olefin Esters 1a-d in Carbon Tetrachloride, Chloroform, and 1,2-Dichloroethane<sup>a</sup>

olefin ester	2a-d			3a-d			4a-d			5a-d		
	CCl <sub>4</sub>	CHCl <sub>3</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	CCl <sub>4</sub>	CHCl <sub>3</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	CCl <sub>4</sub>	CHCl <sub>3</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	CCl <sub>4</sub>	CHCl <sub>3</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>
1a	44.5	48.0	46.5	5.0	9.5	15.0	10.0	12.0	12.5	40.5	30.5	26.0
1b	47.0	38.5	52.5	5.5	15.0	16.5	8.5	14.5	22.0	39.0	32.0	10.0
1c	43.5	39.5	54.0	4.0	13.0	19.5	7.0	14.5	17.0	45.5	33.0	9.5
1d	51.0	49.0	48.5	16.5	23.0	27.0	0	1.0	1.0	32.5	27.0	23.5

<sup>a</sup>The quoted values are averages of at least three experiments and were reproducible within  $\pm 0.5\%$ .

adducts 4 and 5 decreased, while that of 3 increased, with increasing solvent polarity. Moreover, the ratios of 4a-c to 5a-c were markedly affected by the solvent polarity, the least polar solvent favoring the formation of products 5.

**Kinetic Profiles.** In contrast with the reactions of tetrabutylammonium tribromide with compounds 1a-d, which exhibited regularly decreasing absorbance/time curves, the present reactions of Br<sub>2</sub> in 1,2-dichloroethane, followed with the stopped-flow technique, exhibited in the early stages a fast increase in absorbance followed by a slower decay to zero. Curves of this shape are typical for series reactions where the concentration of an intermediate goes through a maximum.<sup>7</sup> For reactions carried out under identical conditions, increasing electron donation by the para substituent on the benzoyl group shifted the position of the absorbance maximum at longer times and intensified it as well, indicating an increase of the rate of formation relative to that of collapse of the intermediate. Furthermore, a large increase in the value of absorbance at the maximum was observed when the same reaction was run under identical conditions but monitoring at decreasing wavelengths down to 300 nm. This change was parallel to that exhibited by the electronic spectrum of Br<sub>3</sub><sup>-</sup> salts in the same wavelength range.

All these spectrokinetic data indicated that tribromide ions were actually accumulated in all reactions of Br<sub>2</sub> with olefin esters 1a-d. Furthermore, since the bromonium-tribromide ion pairs are certainly short-lived species that collapse very fast to products, the accumulation of Br<sub>3</sub><sup>-</sup> ions suggested the involvement of cationic moieties more stable than bromonium ions. The latter species could be envisaged as 2-phenyl-1,3-dioxolan-2-ylum ions, arising by nucleophilic participation of the benzoate group in the opening of the first-formed *trans*-bromonium ions. The absorbing intermediates were therefore considered to consist of ion couples of type 10 and the obtainment of the two *cis* dibromides 4 and 5 was related to their intermediate formation.

**Isolation of *trans*-3-Bromocyclohexano-*cis*-1,2-(2'-anisyl-1',3'-dioxolan-2'-ylum) Salts.** A heavy orange-red oil precipitated immediately when Br<sub>2</sub> was added to 2-cyclohexen-1-ol anisoate (1c) in carbon tetrachloride at -30 °C. When this oil was stirred with cyclohexene in hexane at -30 °C the color slowly disappeared and a colorless solid remained, *trans*-1,2-dibromocyclohexane being formed. This product showed its strongest IR bands at 1250, 1160, and 1100 cm<sup>-1</sup>, very close to absorptions observed also for the orange-red oil. Since the red tribromide ion is known to brominate cyclohexene,<sup>8</sup> leaving the colorless bromide ion, the above transformation provided a further, although indirect, evidence for the Br<sub>3</sub><sup>-</sup> salt nature of the orange-red oil.

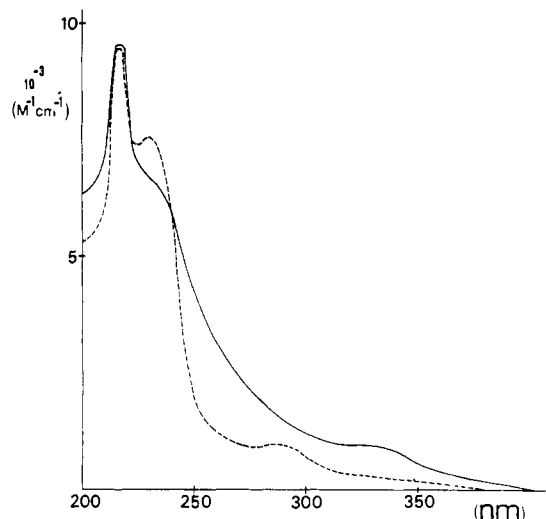
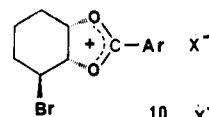


Figure 1. UV spectra of *trans*-3-bromocyclohexano-*cis*-1,2-(2'-anisyl-1',3'-dioxolan-2'-ylum)tetrafluoroborate (11c) (—) and of *t*-2,6-dibromo-*r*-1-cyclohexanol *p*-methoxybenzoate (5c) (---) in 1,2-dichloromethane.

Also the colorless bromide salt was very unstable in solution, collapsing fast to products 4 and 5. In order to obtain a stable salt, the Br<sup>-</sup> anion was exchanged with the nonnucleophilic BF<sub>4</sub><sup>-</sup> by reaction with AgBF<sub>4</sub>. A stable salt was thus obtained, which analyzed correctly for the *trans*-3-bromocyclohexano-*cis*-1,2-(2'-anisyl-1',3'-dioxolan-2'-ylum) tetrafluoroborate structure (11c). The IR spectrum of this salt had again its strongest bands at 1250, 1160, and 1090 cm<sup>-1</sup>. In our opinion these absorptions, and not the previously reported 1460 and 1435 cm<sup>-1</sup> bands,<sup>9</sup> are likely to be ascribed to the 2-anisyl-1,3-dioxolan-2-ylum O-C-O stretching modes, which therefore seem not to differ appreciably from the C-O stretchings of anisoate esters.



10  $X^- = Br_3^-$

11  $X^- = BF_4^-$

a: Ar = C<sub>6</sub>H<sub>5</sub>

b: Ar = *p*-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>

c: Ar = *p*-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>

d: Ar = *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>

The NMR spectrum of the tetrafluoroborate salt in CD<sub>3</sub>CN exhibited an unresolved multiplet at  $\delta$  5.0 attributable to the proton  $\alpha$  to Br and two overlapping multiplets around  $\delta$  5.8, as expected<sup>10</sup> for the two protons  $\alpha$  to

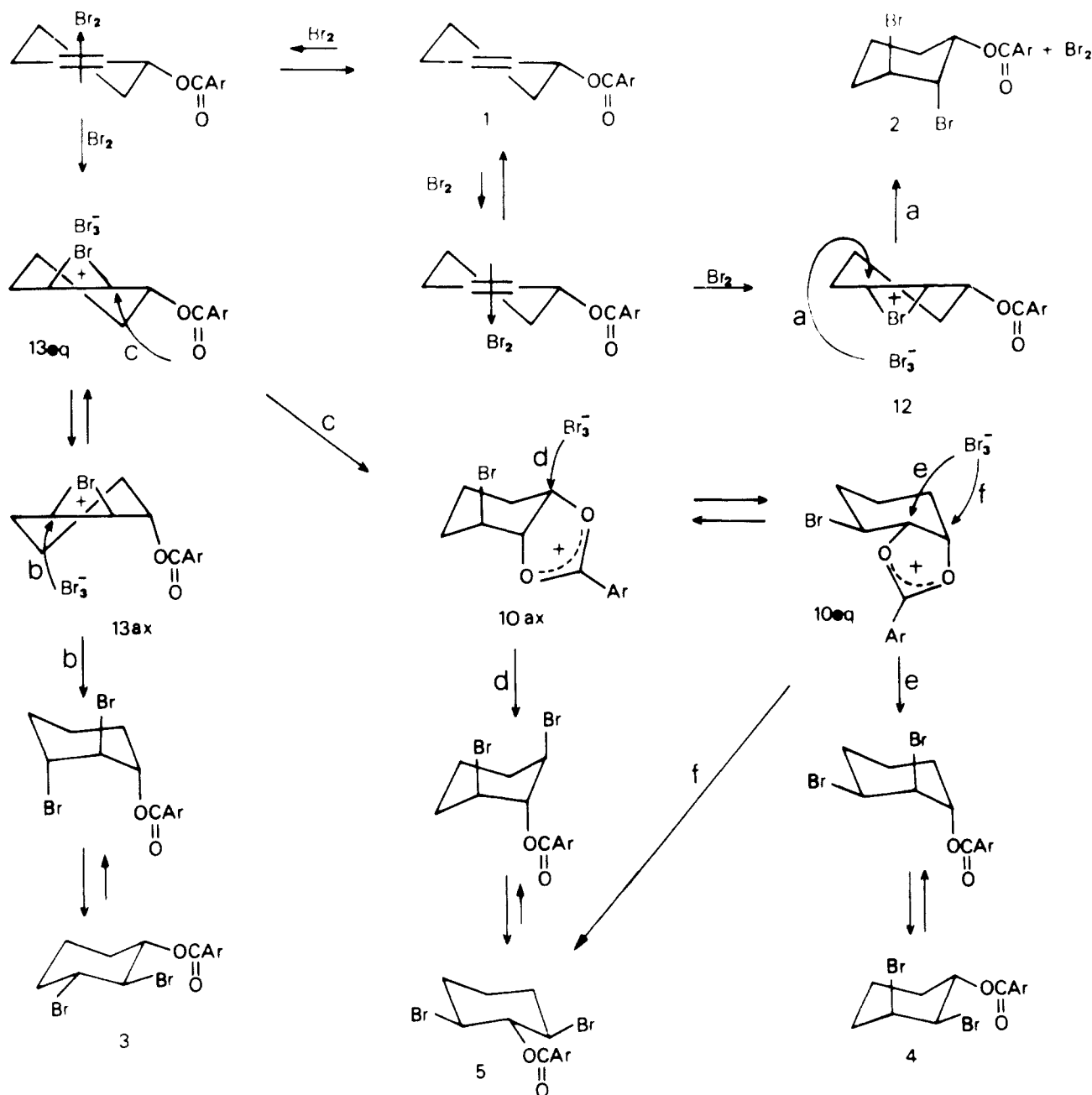
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Scheme II



the positively charged 1,3-dioxolenium oxygens of 11c.

The UV spectrum of 11c in dichloromethane is shown in Figure 1, together with that of the dibromide product of dioxolenium ring opening 5c. These spectra had similar shape and  $\lambda_{\max}$  (216–217 nm,  $\epsilon$  9500).<sup>11</sup> An important point is that the cationic moiety present in 11c, and therefore also in the orange-red oil 11c had been obtained from, did not absorb at 380 nm, the wavelength at which the kinetics of bromination of 1a–d had been monitored. This shows that only the anionic moiety of this salt was responsible for the increased absorption of the accumulated intermediate relative to  $\text{Br}_2$  and is consistent with the involvement of  $\text{Br}_3^-$  ions, having  $\lambda_{\max}$  270 nm, and a molar absorptivity at 380 nm higher than that of  $\text{Br}_2$ . The salt structure 10c appeared therefore to be rather firmly established for the orange-red oil.

When dissolved in several different solvents, salt 10c yielded the two syn dibromo adducts 4c and 5c, releasing

Table II. Distribution of the Products 4 and 5 Arising from the Collapse of *trans*-3-Bromocyclohexano-*cis*-1,2-(2'-anisyl-1',3'-dioxolan-2'-ylium) Tribromide (10c) in Several Solvents<sup>a</sup>

solvent	$\epsilon^b$	products, %	
		4c	5c
$\text{CCl}_4$	2.24	15.5	84.5
$\text{CHCl}_3$	4.80	27.5	72.5
$(\text{CH}_2\text{Cl})_2$	10.36	60.5	39.5
$\text{CH}_3\text{CN}$	37.5	71.5	28.5
$\text{CH}_3\text{NO}_2$	35.87	88.0	12.0

<sup>a</sup>The quoted values are averages of at least three experiments and were reproducible within  $\pm 0.5\%$ . <sup>b</sup>Taken from Riddick, J. A.; Toops, E. E. *Technique of Organic Chemistry*; Weissberger, A., Ed.; Interscience: New York, 1955; Vol. VII.

$\text{Br}_2$ . The distribution of these products in aprotic solvents of dielectric constant ranging between 2.2 and 37.5 is given in Table II. The 4c:5c ratio increased with increasing solvent polarity. Inverted product ratios were obtained in nitromethane and in carbon tetrachloride, thus pro-

(11) Beringer, F. M.; Galton, S. A. *J. Org. Chem.* 1967, 32, 2630.

viding an easy route to either of the cis dibromo adducts **4c** and **5c**.

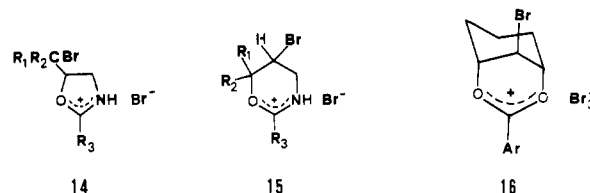
### Discussion

On the basis of the above-reported results, the course of the reaction of  $\text{Br}_2$  with 2-cyclohexen-1-ol benzoates can be depicted as shown in Scheme II. A  $\text{Br}_2$ -assisted heterolytic fission of the  $\text{Br}-\text{Br}$  bond of olefin- $\text{Br}_2$  charge-transfer complexes formed in a preequilibrium step at the two faces of the double bond leads to the cis and trans bromonium ion intermediates coupled to  $\text{Br}_3^-$  counteranions (**12** and **13**). While the cis ion pair **12** is only expected to undergo translocation followed by collapse to the diaxial dibromo adduct **2** (path a),<sup>5</sup> the trans ion pair **13** has two pathways available. One of them again consists in a translocation followed by nucleophilic attack by the counteranion at the bromonium carbons. It has been shown that a process of this type requires a transition state where C-Br bond breaking of the bromonium ring has preceded more than C-Br bond making to the nucleophile so that some positive charge is developed at the attacked carbon.<sup>4c,12,13</sup> It seems, therefore, reasonable to assume that this attack occurs at the position farther from the electron-withdrawing substituent (path b) to give **3**. This attack is likely to occur in a conformation of the six-membered ring with an axial benzyloxy group, **13ax**, as to conform to the requirement of diaxial opening of cyclohexene bromonium ions.<sup>14</sup> Ring inversion leads then to product **3** in its more stable triequatorial conformation. The alternative pathway (c) consists of a rearrangement of the cationic moiety not involving the counteranion. This can occur by an axial attack of the carbonyl oxygen at the adjacent bromonium carbon in conformation **13eq**, to give a 2-aryl-1,3-dioxolan-2-ylum ion, again paired with a  $\text{Br}_3^-$  ion (**10**). The cation of the latter ion pair can then undergo nucleophilic displacement by the anion at either of the uncharged dioxolenium carbons. Since these displacements take place with inversion of configuration, the net result is the formation of a cis 2,6- (**5**) and a cis 2,3-dibromide (**4**).<sup>15</sup>

After the pioneering work of Winstein<sup>16</sup> and Meerwein,<sup>17</sup> 1,3-dioxolan-2-ylum cations have become well-known species, which can be easily prepared and isolated as stable salts provided they are generated in media of low nucleophilicity and paired to nonnucleophilic anions.<sup>10</sup> Ions of this type have been invoked as intermediates of a variety

of reactions.<sup>10,18,19</sup> Their involvement in electrophilic halogenations has been suggested by the observation of 1,2-shifts accompanying bromination of allyl benzoates.<sup>20-22</sup> Exceptionally stable 2-aryl-1,3-dioxolan-2-ylum tri-bromides have also been isolated from the reaction of bromine with the *p*-nitrobenzylidene acetal of norbornane-2-*exo*,3-*exo*-diol<sup>23</sup> and with 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane.<sup>24</sup> Their unusual stability has been respectively attributed to steric hindrance to endo nucleophilic attack and to attack at the dimethyl-substituted C(4) and C(5) by the counteranion. However, we want to stress that the present one is, to our knowledge, the first report on the isolation of an 1,3-dioxolan-2-ylum tribromide salt as an intermediate of the electrophilic bromination of olefinic compounds. This isolation provides direct, conclusive evidence for the stepwise, ionic nature of the reaction of  $\text{Br}_2$  with olefins and it is particularly noteworthy that this feature has been established in a nonpolar solvent such as carbon tetrachloride.

The formation of bromocyclization products of 1,3-oxazolium and 5,6-dihydro-4*H*-1,3-oxazinium type, **14** and **15**, besides the normal dibromo adducts, has been reported in the bromination of allylic benzamides.<sup>25</sup> In spite of the fact that 1,3-dioxan-2-ylum ions analogous to **15** can be prepared and isolated as stable salts with nonnucleophilic anions,<sup>10</sup> no evidence for the formation of salt **16**, which could have arisen by attack of the carbonyl oxygen at C(3) of **13ax**, has been obtained in the present study. Ap-



parently, **13ax** is attacked at C(3) only by the better  $\text{Br}_3^-$  nucleophile, while axial attack at C(2) of **13eq** is more easily carried out by the neighbouring carbonyl, because this process does not require translocation of  $\text{Br}_3^-$  and, moreover,  $\text{Br}_3^-$  attack is hindered by the benzyloxy group.

A solvent dependence of the relative contributions of the two pathways b and c is shown by the data of Table I, where the ratios of the percentages of **3** to (**4** + **5**) always increase on passing from carbon tetrachloride to chloroform to 1,2-dichloroethane. This can be related to an increase in the lifetime of the ion pairs with increasing solvent polarity, which may allow a more extensive  $\text{Br}_3^-$  translocation and therefore collapse through pathway b.

Table I also shows for all three solvents a remarkable constancy of the sum of the amounts of products **3**, **4**, and **5**, which, moreover, is always comparable to that of **2**.

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(15) The obtainment of a cis dibromide in the bromination of a non-conjugated cyclic alkene, 3-thiabicyclo[3.2.0]hept-6-ene 3,3-dioxide, has been recently reported and attributed to a syn attack by  $\text{Br}^-$  at an open carbocation, stabilized by a long-range Coulomb interaction with the  $\text{SO}_2$  group (Cadogan, J. C. G.; Cameron, D. K.; Gosney, I.; Highcock, R. M.; Newlands, S. F. *J. Chem. Soc., Chem. Commun.* 1985, 1751). However, the results of the present investigation allow us to exclude a similar possibility for the reaction discussed in this work.

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Assuming, on the basis of the above-discussed arguments, that **2** is formed from the *cis* ion pair **12** while **3**, **4**, and **5** arise from the *trans* ion pair **13**, the data reveal the lack of any relevant stereoselectivity in the bromonium ions formation. This is at variance with the considerable syn stereoselectivity inferred for the electrophilic step of the bromination of the free alcohol, 2-cyclohexen-1-ol, and of its methyl ether.<sup>26</sup> This stereoselectivity was ascribed to the formation of a charge-transfer complex of Br<sub>2</sub> to the hydroxyl or methoxyl oxygen, allowing a syn intramolecular transfer of the halogen to the carbon-carbon double bond. As expected, esterification reduces the availability of the oxygen lone pairs, making complex formation at this site unimportant.

Apart from the case of the *p*-nitro derivative **1d**, a considerable solvent effect on the formation of the two *cis* dibromides **4** and **5** is apparent from the data of Tables I and II. These indicate a remarkable susceptibility to solvent polarity of the mode of ring opening of the intermediate **10** by the Br<sub>3</sub><sup>-</sup> anion.

The steric course of the ring opening of 1,3-dioxolan-2-ylum ions fused to a six-membered ring has been elucidated by using conformationally rigid *trans*-decalin and steroid derivatives.<sup>9</sup> In the absence of steric interactions, *trans* diaxial products have been found to be greatly predominant, as in the ring opening of epoxides and structurally related three-membered cyclic ions. This preference has been rationalized by a reduction in the puckering of the 1,3-dioxolan-2-ylum ring, with a consequent lessening of angle strain, in the transition state for diaxial opening, opposed to an increased puckering, involving a considerable increase in angle strain and decrease in resonance stabilization, in that for diequatorial opening. However, axial attack at the 1,3-dioxolan-2-ylum ring was shown to be much more sensitive to syn-diaxial steric repulsions by axial substituents on the six-membered ring than in the epoxide ring opening, so that in these circumstances equatorial attack competes favorably. Also the stereo- and regiochemistry of the nucleophilic attack by bromide ions on 1,3-dioxolan-2-ylum species supposed to be the intermediates of the bromination of 3,4-*O*-benzylidenepyranosides has been rationalized on the basis of these principles.<sup>27</sup>

In the case of **10**, axial attack at C(2) on conformation **10eq** (path e) is free from 1,3-diaxial repulsive interactions. However, this attack should be disfavored by the inductive effect of the electron-withdrawing bromine atom, which is expected to decrease the rate of the nucleophilic attack at the nearer carbon if bond breaking is far more advanced than bond making in the transition state, as found for the ring opening of the corresponding protonated bromo epoxide.<sup>4c</sup> This inductive effect should be most important in the least polar carbon tetrachloride solvent, where stabilization of the incipient charge at carbon by solvation is impossible. Under this condition the 1,3-dioxolan-2-ylum ring opening will be forced to occur mostly either by equatorial attack on conformation **10eq** (path f) or by axial attack on conformation **10ax** (path d), leading to product **5**. As the solvent polarity is increased, the inductive effect of bromine becomes less and less important as a consequence of incipient charge solvation. The 1,3-diaxial repulsion experienced by the attacking nucleophile in the transition state of pathway d, and the unfavorable

puckering effect of the 1,3-dioxolan-2-ylum ring in that of pathway f, become therefore decisive in directing the reaction mainly through pathway e to give product **4**. Specific solvation effects can also play a significant role in the most polar solvents, as suggested by the different values of the **4c**:**5c** ratio in two solvents, acetonitrile and nitromethane, of very similar dielectric constant (Table II).

On the other hand, the formation of the *cis* 2,6-dibromide **5**, but not of the 2,3-isomer **4**, from the *p*-nitrobenzoate ester **1d** in all three solvents can be ascribed to the electron-withdrawing effect of the *p*-nitro group, increasing the localization of positive charge at carbon in the transition state for the dioxolenium ring opening so much that the inductive effect of bromine always prevails in directing the opening at C(1) through paths d and/or f.

In conclusion, the present investigation has provided for the first time direct, conclusive evidence for the involvement of 1,3-dioxolan-2-ylum tribromide intermediates in the bromination of allylic alcohols esters. Of particular interest is the finding that the regiochemistry of the nucleophilic opening of *trans*-3-bromocyclohexano-*cis*-1,2-(2'-aryl-1',3'-dioxolan-2'-ylum) tribromides, which can be easily isolated from the bromination of the corresponding 2-cyclohexen-1-ol esters, can be simply determined by an appropriate choice of the solvent in which the reaction is carried out. This provides a simple, one-step common route to *cis* dibromides of type **4** and **5**.

## Experimental Section

**Materials and Methods.** Melting points were determined on a Kofler block and are uncorrected. IR spectra were registered on a Pye-Unicam SP3-300 spectrophotometer. UV spectra were recorded on a Pye-Unicam SP8-400 UV-vis spectrophotometer. <sup>1</sup>H NMR spectra were taken on a CFT 20 Varian instrument from CDCl<sub>3</sub> solutions (unless otherwise stated) using Me<sub>4</sub>Si as internal standard. Kinetic measurements were performed on a Durrum D-110 stopped-flow apparatus equipped with a 2-cm observation cell. HPLC analyses were carried out on a Pye-Unicam 4000 chromatograph using a Lichrosorb Si 60-10 column (25 cm, Chrompack) and monitoring at 254 nm. Preparative chromatographic separations were performed by TLC on 20 × 20 cm glass-supported silica gel 60 plates (1-mm layer, F-254, Merck). GC analyses were carried out on a Dani 2800 instrument, equipped with a 1.8-m glass column, 2.5-mm i.d., packed with 3% OV 17 and a flame-ionization detector.

1,2-Dichloroethane and chloroform were treated as previously reported.<sup>5,28</sup> Carbon tetrachloride was refluxed over P<sub>2</sub>O<sub>5</sub> and distilled. Anhydrous acetonitrile (C. Erba, >99.8%) was used without further purification. Nitromethane (Fluka, >99%) was simply distilled before use. The best quality commercial bromine (C. Erba, >99.5%) was employed without further purification. Silver tetrafluoroborate and 2-cyclohexen-1-ol were purchased from Aldrich Co. 2-Cyclohexen-1-ol benzoate (**1a**), *p*-methylbenzoate (**1b**), *p*-methoxybenzoate (**1c**), and *p*-nitrobenzoate (**1d**) were prepared as reported.<sup>5</sup>

**Bromination Procedure.** In a typical experiment 10 mL of a 0.22 M solution of olefin **1a-d** (10% excess) in 1,2-dichloroethane, chloroform, or carbon tetrachloride were added dropwise to 20 mL of a freshly prepared 0.1 M solution of Br<sub>2</sub> in the same solvent at 25 °C. The mixture was allowed to react in the dark until the color disappeared. The solvent was removed under reduced pressure, and the residue was subjected to HPLC analysis under the conditions reported below and to separation of the products by preparative TLC.

**Bromination Products. A. From 1a.** Four products were separated by preparative TLC using 85:15 hexane-ethyl ether (relative R<sub>f</sub> on analytical plate: **2a**, 1.7; **4a**, 1.4; **3a**, 1.2; **5a**, 1.0).

**2a** and **3a** were identical with those prepared by bromination of **1a** with tetrabutylammonium tribromide.<sup>5</sup>

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(27) Reference 18, pp 102-103.

(28) Bellucci, G.; Berti, G.; Bianchini, R.; Ingrosso, G.; Ambrosetti, R. *J. Am. Chem. Soc.* **1980**, *25*, 7480.

**4a:** oil;  $^1\text{H}$  NMR  $\delta$  8.05, 7.50 (m, 2 and 3 Ar H), 5.50 (m,  $w_{1/4}$  = 18 Hz,  $>\text{CHO}$ -, 1 H), 4.70–4.35 (2 overlapping m,  $>\text{CHBr}$ , 2 H), 2.60–0.90 (6 cyclohexane H); IR  $\nu$  1720, 1600, 1450, 1330, 1270, 1160, 1105, 1065, 1030, 930, 840, 800, 705, 680, 665, 650  $\text{cm}^{-1}$ .

Anal. Calcd for  $\text{C}_{13}\text{H}_{14}\text{Br}_2\text{O}_2$ : C, 43.12; H, 3.90; Br, 44.15. Found: C, 43.31; H, 4.02; Br, 44.19.

An authentic sample of **4a** was also prepared as follows. Acetyl hypobromite in carbon tetrachloride (0.08 M, 170 mL) was added to 3-bromocyclohexene (2 g, 12.4 mmol) in the same solvent (50 mL) at 0  $^\circ\text{C}$ ,<sup>4c</sup> and the products were transformed with 1.5% methanolic sulfuric acid into a mixture (1.9 g) of **6**, **7**, and **8** in a ratio of 3:80:17 (GC). This mixture was reacted with benzoyl chloride (2.5 g) in dry pyridine (25 mL) for 5 h at room temperature. The crude product (3.0 g), consisting of a mixture of benzoate esters, was subjected to separation by preparative TLC. The faster moving band consisted of pure **4a**, with IR and NMR spectra identical with the above-reported ones. The slower moving band consisted of the main product **3a**.<sup>5</sup>

**5a:** mp 114–116  $^\circ\text{C}$  (from methanol);  $^1\text{H}$  NMR  $\delta$  8.06, 7.50 (m, 2 and 3 Ar H), 5.45 (t,  $J$  = 10 Hz,  $>\text{CHO}$ -, 1 H), 4.00 (dt,  $w$  = 30 Hz,  $>\text{CHBr}$ , 2 equivalent H), 2.60–0.90 (6 cyclohexane H); IR  $\nu$  (Nujol) 1705, 1600, 1450, 1370, 1310, 1270, 1210, 1160, 1120, 1105, 1060, 1025, 945, 905, 830, 700, 685, 670  $\text{cm}^{-1}$ .

Anal. Found: C, 43.15; H, 3.98; Br, 44.32.

An authentic sample of **5a** was prepared as follows. 3-Bromocyclohexene (2 g, 12.4 mmol) in  $\text{CHCl}_3$  (50 mL) was reacted with 85% 3-chloroperbenzoic acid (3.15 g, 15.5 mmol) at 0  $^\circ\text{C}$  for 2 days. After cooling at  $-25$   $^\circ\text{C}$ , the precipitated *m*-chlorobenzoic acid was filtered off and the solution washed with saturated aqueous  $\text{Na}_2\text{CO}_3$ , water, and dried. The oily residue (2.1 g), consisting of a 93:7 mixture of *trans*- and *cis*-3-bromo-1,2-epoxycyclohexane (GC),<sup>4c</sup> was chromatographed on silica gel (70–230 mesh ASTM). A 98:2 mixture of petroleum ether–ethyl ester eluted pure (GC) *trans*-3-bromo-1,2-epoxycyclohexane (1.2 g). This product was dissolved in  $\text{CHCl}_3$  (15 mL) and dry HBr was bubbled into the solution for 10 min at room temperature. Evaporation of the solution with a nitrogen stream gave a solid residue (1.3 g) consisting of products **9** and **8** in a ratio of 97:3 (GC). Crystallization from petroleum ether gave pure **9** (1.1 g), mp 95–96  $^\circ\text{C}$  (lit.<sup>4c</sup> mp 95.5–96.5  $^\circ\text{C}$ ), which was reacted with benzoyl chloride (0.85 g) in pyridine (15 mL). Crystallization of the product from methanol gave pure **5a** (1.5 g), mp 114–115  $^\circ\text{C}$ , having IR and NMR spectra identical with the above-reported ones.

**B. From 1b.** Four products were separated by preparative TLC using 70:30 hexane–ethyl ether (relative  $R_f$  on analytical plate: **2b**, 1.5; **4b**, 1.3; **3b**, 1.1; **5b**, 1).

**2b** and **3b** were identical with those prepared by bromination of **1b** with tetrabutylammonium tribromide.<sup>5</sup>

**4b:** oil;  $^1\text{H}$  NMR  $\delta$  8.0, 7.25 (AA'BB' system, 4 Ar H), 5.50 (m,  $w_{1/4}$  = 15 Hz,  $>\text{CHO}$ -, 1 H), 4.70–4.30 (2 overlapping m,  $>\text{CHBr}$ , 2 H), 2.40 (s,  $\text{CH}_3$ ), 2.35–0.80 (6 cyclohexane H); IR  $\nu$  1720, 1600, 1470, 1375, 1335, 1270, 1160, 1100, 1030, 940, 850, 760, 675  $\text{cm}^{-1}$ .

Anal. Calcd for  $\text{C}_{14}\text{H}_{16}\text{Br}_2\text{O}_2$ : C, 44.71; H, 4.29; Br, 42.49. Found: C, 44.88; H, 4.36; Br, 42.58.

**5b:** mp 143–145  $^\circ\text{C}$  (from methanol);  $^1\text{H}$  NMR  $\delta$  8.15, 7.35 (AA'BB' system, 4 aromatic H), 5.50 (t,  $J$  = 10 Hz,  $>\text{CHO}$ -, 1 H), 4.05 (dt,  $W$  = 30 Hz,  $>\text{CHBr}$ , 2 equivalent H), 2.40 (s,  $\text{CH}_3$ ), 2.50–0.90 (6 cyclohexane H); IR (Nujol)  $\nu$  1710, 1600, 1460, 1375, 1320, 1275, 1215, 1175, 1120, 1100, 1070, 835, 740, 700, 690  $\text{cm}^{-1}$ .

Anal. Found: C, 44.91; H, 4.39; Br, 42.61.

**C. From 1c.** Four products were separated by preparative TLC using 70:30 hexane–ethyl ether as the eluant (relative  $R_f$  on analytical plate: **2c**, 1.6; **4c**, 1.3; **3c**, 1.1; **5c**, 1).

**2c** and **3c** were identical with those prepared by bromination of **1c** with tetrabutylammonium tribromide.<sup>5</sup>

**4c:** oil;  $^1\text{H}$  NMR  $\delta$  7.90, 6.85 (AA'BB' system, 4 Ar H), 5.40 (m,  $w_{1/4}$  = 16 Hz,  $>\text{CHO}$ -, 1 H), 4.6–4.3 (2 overlapping m,  $>\text{CHBr}$ , 2 H), 3.80 (s,  $\text{OCH}_3$ ), 2.40–0.80 (6 cyclohexane H); IR  $\nu$  1715, 1600, 1500, 1470, 1375, 1320, 1275, 1250, 1170, 1100, 1020, 950, 840, 760, 700, 695  $\text{cm}^{-1}$ .

Anal. Calcd for  $\text{C}_{14}\text{H}_{16}\text{Br}_2\text{O}_3$ : C, 42.88; H, 4.11; Br, 40.76. Found: C, 43.00; H, 4.22; Br, 40.89.

**5c:** mp 88–90  $^\circ\text{C}$  (from methanol);  $^1\text{H}$  NMR  $\delta$  8.10, 6.95 (AA'BB' system, 4 Ar H), 5.50 (t,  $J$  = 10 Hz,  $>\text{CHO}$ -, 1 H), 4.00 (dt,  $w$  = 34 Hz, 2 equivalent H), 3.80 (s,  $\text{OCH}_3$ ), 2.65–0.90 (6 cyclohexane H); IR (Nujol)  $\nu$  1705, 1600, 1510, 1465, 1375, 1270, 1250, 1165, 1120, 1100, 1030, 845, 765, 720, 695  $\text{cm}^{-1}$ .

Anal. Found: C, 43.01; H, 4.27; Br, 40.91.

**D. From 1d.** Three products were separated by preparative TLC using 70:30 hexane–ethyl ether (relative  $R_f$  on an analytical plate: **2d**, 1.9; **3d**, 1.5; **5d**, 1.0).

**2d** and **3d** were identical with those prepared by bromination of **1d** with tetrabutylammonium tribromide.<sup>5</sup>

**5d:** mp 201–203  $^\circ\text{C}$  (from methanol, lit.<sup>4c</sup> mp 202–204  $^\circ\text{C}$ );  $^1\text{H}$  NMR  $\delta$  8.35 (s, 4 Ar H), 5.55 (t,  $J$  = 10 Hz,  $>\text{CHO}$ -, 1 H), 4.05 (dt,  $w$  = 33 Hz,  $>\text{CHBr}$ , 2 equivalent H), 2.70–0.90 (6 cyclohexane H); IR (Nujol)  $\nu$  1720, 1600, 1510, 1460, 1375, 1350, 1310, 1270, 1110, 1100, 850, 705, 685  $\text{cm}^{-1}$ .

**trans-3-Bromocyclohexano-*cis*-1,2-(2'-anisyl-1',3'-dioxolan-2'-ylidene) Salts.** A 6 M solution of  $\text{Br}_2$  in  $\text{CCl}_4$  (1 mL) was added dropwise under vigorous stirring to a solution of 1.0 g (4.3 mmol) of 2-cyclohexen-1-ol *p*-methoxybenzoate (**1c**) in 3 mL of the same solvent at  $-30$   $^\circ\text{C}$ . A heavy orange-red oil, consisting of *trans*-3-bromocyclohexano-*cis*-1,2-(2'-anisyl-1',3'-dioxolan-2'-ylidene) tribromide (**10c**), separated immediately: IR  $\nu$  1600, 1540, 1505, 1455, 1425, 1280, 1255, 1165, 1105, 1010, 890, 840, 780, 760, 690  $\text{cm}^{-1}$ . The solvent was removed by decantation and the orange-red oil was repeatedly washed with dry *n*-hexane at  $-30$   $^\circ\text{C}$ . An excess of cyclohexene in *n*-hexane was finally added and the mixture was stirred at  $-30$   $^\circ\text{C}$ , while a colorless solid (**7c**) started forming. After several hours the colorless solid, consisting of *trans*-3-bromocyclohexano-*cis*-1,2-(2'-anisyl-1',3'-dioxolan-2'-ylidene) bromide, was collected (1.1 g, 65% yield) and stored at  $-30$   $^\circ\text{C}$ : IR (Nujol)  $\nu$  1600, 1510, 1455, 1445, 1425, 1415, 1325, 1310, 1250, 1160, 1100, 1025, 840, 760, 690, 660  $\text{cm}^{-1}$ .

Silver tetrafluoroborate (0.8 g, 4.1 mmol) in anhydrous ethyl ether (5 mL) was added to 1.0 g (2.5 mmol) of *trans*-3-bromocyclohexano-*cis*-1,2-(2'-anisyl-1',3'-dioxolan-2'-ylidene) bromide at  $-25$   $^\circ\text{C}$ . The mixture was stirred for 10 min and the formed yellow solid was rapidly collected, washed with ethyl ether, suspended in anhydrous acetonitrile (5 mL), and stirred for 10 min. The insoluble silver bromide was filtered off and the acetonitrile solution was diluted with 150 mL of ethyl ether. A white solid (**8c**), consisting of *trans*-3-bromocyclohexano-*cis*-1,2-(2'-anisyl-1',3'-dioxolan-2'-ylidene) tetrafluoroborate (**11c**), precipitated (0.6 g, 54% yield): mp 252–254  $^\circ\text{C}$  dec;  $^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ )  $\delta$  8.35, 7.20 (AA'BB' system, 4 Ar H), 5.80 (m,  $w_{1/2}$  = 9 Hz,  $>\text{CHO}$ -, 2 H), 5.0 (m,  $w_{1/2}$  = 5 Hz,  $>\text{CHBr}$ , 1 H), 4.10 (s,  $\text{OCH}_3$ ), 3.00–1.50 (6 cyclohexane H); IR (Nujol)  $\nu$  1600, 1505, 1455, 1425, 1270, 1250, 1165, 1100, 1010, 840, 760, 690  $\text{cm}^{-1}$ ; UV (dichloromethane)  $\lambda_{\text{max}}$  217 nm,  $\epsilon$  9500  $\text{M}^{-1} \text{cm}^{-1}$ .

Anal. Calcd for  $\text{C}_{14}\text{H}_{16}\text{BrF}_4\text{O}_3$ : C, 42.14; H, 4.04; Br, 20.03; F, 19.05. Found: C, 42.37; H, 4.09; Br, 20.23; F, 19.18.

**Transformation of trans-3-Bromocyclohexano-*cis*-1,2-(2'-anisyl-1',3'-dioxolan-2'-ylidene) Tribromide (10c) into Dibromides 4c and 5c.** Small samples (ca. 0.5 g) of the oily *trans*-3-bromocyclohexano-*cis*-1,2-(2'-anisyl-1',3'-dioxolan-2'-ylidene) tribromide (**10c**) were suspended or dissolved in 20 mL of each solvent reported in Table II and allowed to react for 24 h at room temperature. The solutions were then washed with saturated aqueous  $\text{NaHSO}_3$ , dried, and evaporated under reduced pressure. The residues were analyzed by HPLC under the conditions described below. The results are reported in Table II.

**Product Analyses.** The mixtures of **2a**–**5a**, **2b**–**5b**, **2c**–**5c**, and **2d**–**5d** were analyzed by HPLC using respectively 99:1, 96:4, 96:4, and 98:2 hexane–ethyl acetate as the eluants. The relative retention times were **2a**, 1; **4a**, 1.1; **3a**, 1.35; **5a**, 1.5; **2b**, 1; **4b**, 1.3; **3b**, 1.9; **5b**, 2.3; **2c**, 1; **4c**, 1.3; **3c**, 1.6; **5c**, 1.85; **2d**, 1; **4d**, 1.2; **3d**, 1.45; **5d**, 1.7.

**Kinetic Measurements.** The reactions of  $\text{Br}_2$  ( $10^{-3}$  M) with olefins **1a**–**c** ( $10^{-1}$  M) in 1,2-dichloroethane at 25  $^\circ\text{C}$  were followed with the stopped-flow technique,<sup>5</sup> monitoring at 380 nm ( $\text{Br}_2$ ,  $\epsilon$  145  $\text{M}^{-1} \text{cm}^{-1}$ ).

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**Registry No.** 1a, 3352-93-0; 1b, 103437-97-4; 1c, 103437-98-5; 1d, 38313-01-8; 2a, 103438-00-2; 2b, 103438-01-3; 2c, 103438-02-4; 2d, 103530-08-1; 3a, 103530-05-8; 3b, 103530-06-9; 3c, 103530-07-0; 3d, 53119-31-6; 4a, 108393-08-4; 4b, 108393-09-5; 4c, 108393-10-8; 4d, 53119-31-6; 5a, 108345-18-2; 5b, 108345-19-3; 5c, 108345-20-6;

5d, 56391-38-9; 6, 56391-35-6; 7, 56421-03-5; 8, 56421-04-6; 9, 56391-36-7; 10c, 108345-22-8; 10c (X<sup>-</sup>=Br<sup>-</sup>), 108345-23-9; 11c, 108345-24-0; 3-bromocyclohexene, 1521-51-3; *trans*-3-bromo-7,2-epoxycyclohexane, 56421-06-8; *cis*-3-bromo-7,2-epoxycyclohexane, 56421-05-7.

## Transannular Interactions in Difunctional Medium Rings. 2.<sup>1</sup> Molecular Structure and Conformational Properties of 1-Alkylhexahydroazocin-5-ones

Gerhard Spanka,<sup>†</sup> Roland Boese,<sup>‡</sup> and Paul Rademacher<sup>\*†</sup>

*Institute of Organic Chemistry and Institute of Inorganic Chemistry, University of Essen, D-4300, Essen, West Germany*

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Conformational properties of 1-alkylhexahydroazocin-5-ones 1-4 with a methyl, ethyl, isopropyl, or *tert*-butyl group as a substituent have been studied by He I photoelectron, <sup>13</sup>C NMR, and IR spectroscopy as well as by MM2 and MNDO calculations. The molecular structure of the *tert*-butyl derivative 4 was determined by X-ray crystallography. Transannular interactions of the two functional groups in 1-4 have been determined from the first two ionization potentials with reference to the corresponding data of the respective monofunctional compounds. Since the  $\Delta IP(n_O)$  values of 1-4 are nearly identical, these molecules must have rather similar conformations.  $\delta_{13C}$  values of the carbonyl group in 1-4 show a systematic variation with substituent size, but this is probably caused by different solvation. From the IR spectra of 1 and 4 in the solid and liquid state and in solution it is concluded that phase transition is not accompanied by conformational changes. The eight-membered ring in 1-4 has a boat-chair conformation with the functional groups occupying positions with the shortest possible transannular distance (approximately 270 pm). It has been found difficult to determine the most stable conformation by theoretical methods, since transannular amide resonance is not treated correctly. For this interaction an energy of approximately 12 kJ/mol is estimated for 4 by comparison of experimental and calculated molecular structures.

### Introduction

Transannular interactions in difunctional medium-sized cyclic compounds can be studied by photoelectron spectroscopy.<sup>1,2</sup> As has been shown for cyclic amino ketones<sup>1</sup> and for aminoalkenes,<sup>1,3</sup> the interactions can be determined from the  $n$  and  $\pi$  ionization potentials by comparison with the respective data of the analogous monofunctional compounds. Since the size of transannular interaction (homoconjugation<sup>2</sup>) is determined by the intramolecular distance between the two functional groups, the PE data can be used for conformational analysis.

In order to achieve a quantitative basis for the relation between molecular structure and orbital interaction, we have investigated the hexahydroazocin-5-one system in detail by different methods. To establish that changes in spectroscopic findings caused by substituents are realized correctly, the N substituent was varied from methyl over ethyl and isopropyl to *tert*-butyl. The conformational properties have been studied by molecular mechanics (MM2)<sup>4</sup> and quantum theoretical (MNDO)<sup>5</sup> methods. In addition to PE spectroscopy, <sup>13</sup>C NMR and IR spectroscopic measurements were performed. The *tert*-butyl derivative, which is solid at ambient conditions, was analyzed by X-ray crystallography.

### Results and Discussion

**MM2 and MNDO Calculations.** Conformational properties of eight-membered rings like cyclooctane and its derivatives have been studied extensively by various experimental<sup>6</sup> and theoretical methods.<sup>7</sup> Several conformations have to be considered. Besides the most sym-

**Table I. Heats of Formation (kJ/mol) for Various Conformations of Cyclooctanone, 1-Methylhexahydroazocin-5-one (1), and 1-Methyloctahydroazocin-5-one (5) Calculated by the MM2 Method**

conformatn	ketone	5	1
crown	-239.9	-43.4	-155.9 (-169.4 <sup>a</sup> )
(+ +)BB	-236.6	-51.6	-172.8 (-154.4 <sup>a</sup> )
(00)BB	-225.7	-36.0	-151.2
(+ +)BC	-246.7	-51.2	-171.3 (-163.9 <sup>a</sup> )
(+ -)BC	-239.8	-46.7	-162.7
(- +)BC	-235.9	-56.2	-169.5
(00)BC	-241.2	-46.4	-162.3

<sup>a</sup> MNDO value.

metrical one, the crown, there are the boat-chair (BC), the chair-chair (CC), and the boat-boat (BB) forms and others. The most stable conformation of cyclooctane and simple derivatives is the BC form. In most cases the positions of the individual ring atoms are not equivalent.

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<sup>†</sup> Institute of Organic Chemistry.

<sup>‡</sup> Institute of Inorganic Chemistry.