Preassociation, Free-Ion, and Ion-Pair Pathways in the Electrophilic Bromination of Substituted *cis*- and *trans*-Stilbenes in Protic Solvents

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Abstract: Rates and products of electrophilic bromination of ring-substituted *cis*- and *trans*-stilbenes have been investigated in acetic acid, trifluoroethanol, ethanol, methanol, and water−methanol mixtures. The mY_{Br} relationships (linear for nucleophilic solvents only, with $m = 0.8$), the deviations of the two nonnucleophilic solvents from the mY_{Br} plots (Δ_{AcOH} and Δ_{TFE} positive, negative, or negligible), the kinetic solvent isotope effects ($k_{MeOH}/k_{MeOD} = 1.1-1.6$), the chemoselectivity (predominant dibromide, DB, or solvent-incorporated adducts, MA), and the high dependence of the stereochemistry on the solvent and the substituents (from stereoconvergency to stereospecificity) are discussed and interpreted in terms of a mechanistic scheme, analogous to the Jencks scheme for aliphatic nucleophilic substitutions, in which preassociation, free-ion, and ion-pair pathways compete. In particular, the stereochemical outcome of these reactions is consistent with a marked change in the nucleophilic partners of the product-forming ionic intermediate arising from different ionization routes. Return, i.e. change in the rate-limiting step from ionization to product formation, is shown to be related to substituent-dependent, but not solvent-dependent, bromine bridging.

Introduction

The multistep mechanism of electrophilic bromination of ethylenic compounds of Scheme 1 is well documented by a large variety of kinetic and product investigations.[1] Recent work on this basic reaction of organic chemistry is mainly focused on its early steps[2] and, in particular, on the formation[3] of bromine−olefin charge-transfer complexes, CTC, and on the structure of the bromonium ion intermediates.[4] Many current studies deal with the reactivity of crowded double bonds,[5] which involves return enforced by a slow product-forming step because of steric retardation of the nucleophilic trapping of congested bromonium ions. In this context, much attention has been paid to the reversibility of the CTC ionization leading to the ionic intermediate.[5−7] The occurrence of this reversibility emphasizes the similarity between the bromination mechanism and that of S_N1-like solvolysis and nucleophilic substitutions previously revealed by kinetic solvent and substituent effects.[8] Both reactions involve the formation of an ion pair by ionization of a neutral substrate, CTC, or alkyl derivative. For both, the products are obtained by nucleophilic trapping of a cationic intermediate. Moreover, nucleophilic solvent assistance has been shown to occur in the ionization steps of the two reactions.[7,9,10] With regard the last steps and, in particular, the nature of the ionic species from which the products are formed, the corresponding data for bromination are almost inexistent, whereas in solvolysis or nucleophilic substitutions, it is widely

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In memoriam of Professor Giuseppe Bellucci, deceased March 3, 1996.

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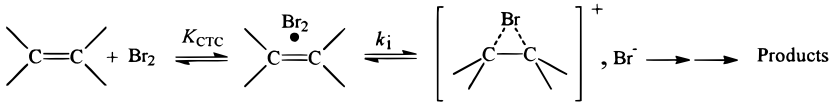
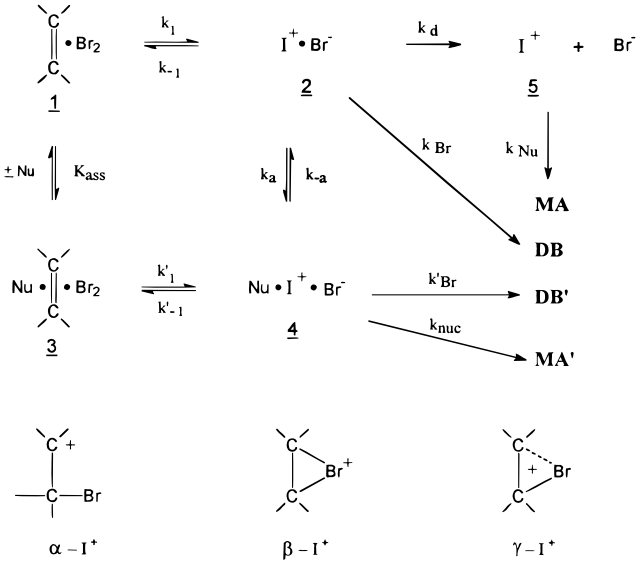
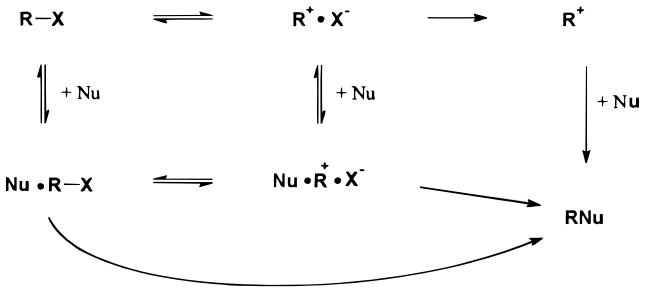
Scheme 1



Scheme 2



Scheme 3

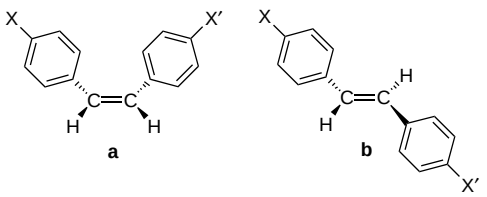


accepted that free ions, ion pairs, or triple ion complexes can be the precusors of the reaction products.[11]

In this paper, we report a kinetic and product investigation of the bromination of uncrowded ring-substituted stilbenes in protic solvents which sheds light not only on solvent assistance and bromine bridging in the ionization step but also on the role of counterion and solvent association with the ionic intermediate in the product-forming step. We show that the marked dependence of kinetics and stereochemistry on the solvent and the substituents is consistently interpreted in terms of Scheme 2, which is analogous to Scheme 3 well established for aliphatic nucleophilic substitutions.[11] In Scheme 2 for bromination, the substrate is the CTC, **1**; the nucleophile can be the solvent; I^+ is the bromocationic intermediate which, depending on the double-bond substituents, can be open, α-I^+, fully bridged, β-I^+, or weakly bridged, γ-I^+; the products are the solvent-incorporated, or mixed adducts, MA, and the dibromides DB. As in nucleophilic substitutions, the CTC ionization can be reversible or irreversible and assisted (preassociation route, **1** → **3** → **4**) or unassisted (**1** → **2**), and the products can be obtained from free ions, **5**, ion pairs, **2**, or ion−dipole sandwiches, **4**, formed via preassociation or ion-pair pathways. Species **4** in which bromocation I^+ is associated with its counter-bromide ion and, on its opposite side, with a molecule of a nucleophilic solvent, is called an ion−dipole sandwich by analogy with the nomenclature used in nucleophilic substitutions.[11] In Scheme 2, the concerted pathway which can occur in nucleophilic substitution (S_N2 route) is not considered since concerted bromination of carbon−carbon double bonds has never been observed.[1] The reported kinetic and product results exhibit subtle variations in rate- and product-determining ionic species which are rationalized in terms of Scheme 2.

Results and Discussion

1. Bromination Kinetics. Bromination rate constants of *cis*-stilbenes **6a**−**11a** and of their *trans* isomers **6b**, **7b**, **9b**, and **11b** were measured in a variety of solvents, acetic acid, ethanol,



6: X = CH_3O, X′ = H; **7**: X = X′ = CH_3; **8**: X = CH_3, X′ = H
9: X = X′ = H; **10**: X = H, X′ = CF_3; **11**: X = X′ = CF_3

trifluoroethanol, methanol, and the aqueous mixtures of the last: M10, M20, and M30 (10−90, 20−80, and 30−70 H_2O−MeOH, v/v, respectively). The results are shown in Table 1. The bromination kinetics followed by conventional spectrophotometry and/or by stop-flow technique[12] were rigorously second order, first order in olefin, and first order in bromine (eq 1), regardless of the stilbene or the solvent. In particular in acetic

$$v = k\,[Ol]\,[Br_2] \qquad (1)$$

acid, second-order bromine terms, which have previously been observed,[13] were not found with the small bromine concentrations used. In methanol and its aqueous mixtures, although, the tribromide ion concentration[14] was not controlled by the addition of external bromide ions (eq 2), eq 1 was always

$$Br_2 + Br^- \rightleftharpoons Br_3^- \qquad (2)$$

rigorously followed, showing that the kinetic term related to bromide concentration[15] (eq 3) was not significant under these experimental conditions.

$$k_{exp}\,(1 + K[Br^-]) = k + Kk_{Br_3}[Br^-] \qquad (3)$$

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Table 1. Rate Constants,[a] k (M^{-1} s^{-1}), for Bromination of X,X′-*p*-Substituted *cis*- and *trans*-Stilbenes in Various Solvents at 25 °C

compd	X	X′		EtOH	AcOH	MeOH	M10[b]	M20[b]	M30[b]	TFE[c]	KSIE[d]
			Y_{Br}[e]	−2.4	−2.1	−1.1	−0.14	0.70	1.42	2.53	
			N[f]	0.09	−2.05	0.01	0.02	−0.02	−0.07	−3.93	
6a	*p*-OMe	H		1.9×10^3	4.2×10^3	3.3×10^4	1.0×10^6				
6b	*p*-OMe	H			2.0×10^3	2.9×10^4					
7a	*p*-Me	*p*-Me		3.16×10	16	3.0×10^2	2.2×10^3	1.0×10^4	9.2×10^4		1.33
7b	*p*-Me	*p*-Me			2.2	2.8×10^2					
8a	*p*-Me	H		5.01	3.98	1.4×10^2	1.0×10^3	3.9×10^3	1.8×10^4	8.6×10^5	1.42
9a	H	H		0.95	1.0×10^{-1}	12.5	80	4.0×10^2	1.8×10^3	1.2×10^4	1.10
9b	H	H			5.5×10^{-2}	13.4					
10a	*p*-CF_3	H		3.0×10^{-2}	7×10^{-2}	7.9×10^{-1}	7.3	4.3×10	2.0×10^2	3.7×10^2	1.52
11a	*p*-CF_3	*p*-CF_3		2.8×10^{-3}	7.8×10^{-4}	1.0×10^{-2}	6.0×10^{-2}	3.0×10^{-1}	1.1	2.1×10^{-1}	1.55
11b	*p*-CF_3	*p*-CF_3			7.0×10^{-5}	1.1×10^{-2}					

[a] Reproducibility better than ±5%. [b] M10, M20 and M30: 10−90, 20−80, and 30−70 H_2O−MeOH (v/v) mixtures. [c] 3% (w/w) aqueous trifluoroethanol. [d] Kinetic solvent isotope effects (k_{MeOH}/k_{MeOD}). [e] Reference 17. [f] Reference 18a.

Table 2. $m_{Br}Y_{Br}$ Relationships for *cis*-Stilbene Bromination

	p-OMe	*p*,*p*′-di-Me	*p*-Me	H	*p*-CF_3	*p*,*p*′-di-CF_3
m_{Br}[a]	≥1.4[b]	0.85[c]	0.83	0.85	0.92	0.81
log k_o		3.43	3.07	2.02	1.00	−1.10
Δ_{AcOH}[d]	0.0	−0.45	−0.73	−1.24	−0.20	−0.30
Δ_{TFE}[d]			0.76	−0.10	−0.75	−1.63
m^i_{Br} [e]		1.1	1.1	1.1		
log k^i_o		3.6	3.0	1.3		

[a] Calculated from k in M^{-1} s^{-1} at 25 °C, in EtOH, MeOH, and H_2O−MeOH mixtures only, using Y_{Br} as solvent parameters; standard errors ≤ 0.03; correlation coefficients ≥ 0.998. [b] Estimation from MeOH and M10 only (see text). [c] From MeOH, M10, and M20; M30 deviates markedly (see text). [d] log k_{exp} − log k_{calc} with log k_{calc} calculated from the corresponding $m_{Br}Y_{Br}$ relationships; Δ values smaller than 0.3 l.u. are negligible. [e] Coefficients of the $m_{Br}Y_{Br}$ relationships for the unassisted pathways estimated from k in AcOH and TFE only (see text).

Rate constants for free bromine addition to stilbenes **6a**−**11a** in methanol were also obtained by extrapolation to [Br^-] = 0 of kinetic measurements carried out in the presence of several concentrations of added bromide ions, using eq 3 (Table S1). The agreement between the two sets of results is within the experimental errors and confirms that bromide ions do not play a significant role when they are released by formation of solvent-incorporated products (vide supra).

2. Kinetic Solvent Effects and m_{Br} Values. The kinetic solvent effects for **7a**−**11a** are satisfactorily described by Winstein−Grunwald equations,[10a,16] log $k/k_o = m_{Br}Y_{Br}$, using Y_{Br} parameters,[17] when data in acetic acid and trifluoroethanol are omitted. The coefficients of these relationships are given in Table 2. An extended Winstein equation,[10a] log $k/k_o = mY + lN$, in which the effect of the solvent nucleophilicity is also taken into account, is not applied for statistical reasons. Ethanol, methanol, and its aqueous mixtures having very similar nucleophilicities,[18] the lN term is constant and l can, therefore, be evaluated from the deviations of two barely nucleophilic solvents only. Therefore, the positions of the rate data in acetic acid and trifluoroethanol, Δ_{AcOH} and Δ_{TFE}, with respect to the log $k - Y_{Br}$ plots, are also shown in Table 2.

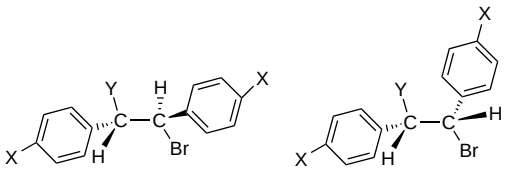
All the m values, close to 0.8, are consistent with nucleophilically assisted rate-limiting ionizations, as previously found in solvolysis[10] and in brominations of noncongested olefins.[7,9] Nevertheless, the values of Δ_{AcOH} and Δ_{TFE} do not support this interpretation for all the stilbenes investigated. If nucleophilic assistance occurs, deviations, increasingly negative with reactivity decrease, are expected, as the result of a demand on the nucleophilic solvent increasing with the decrease in the charge stabilization of the transition states by the substituents.[10] While the Δ_{AcOH} trend from **6a** to **9a** agrees with this requirement, the negligible values of this deviation for **10a** and **11a** suggest a change in the bromination mechanism. Analogously, the positive value of Δ_{TFE} for **8a** cannot be readily interpreted in terms of a variable assistance by the nucleophilic alcohols.

The kinetic solvent isotope effects (KSIE = k_{MeOH}/k_{MeOD}) for **7a**−**9a** reactions (Table 1) are usual as compared to those previously observed in bromination[7a,19] which are generally close to 1.35 or smaller when return occurs, i.e., when the product-forming step is rate limiting.[6e] However, the KSIEs found for **10a** and **11b** are markedly larger and point to a mechanism different from those involved in the bromination of the more reactive olefins.

Finally, for the most reactive stilbene **6a**, for which nucleophilic solvent assistance is not expected,[9] a markedly upward curvature of the mY plot is observed, which is also unusual in bromination.

Therefore, depending on the solvent and the substituents, other reaction pathways prevail or compete with the preassociation mechanism involving nucleophilically solvated transition states of the ionization step of stilbene bromination.

3. Product Analysis. Authentic samples of *erythro* (or *meso*) and *threo* (or *d*,*l*) dibromides (DB) were synthesized by reaction of *trans*- or *cis*-olefins **6**−**11** with $Bu_4N^+Br_3^-$ in 1,2-dichloroethane in the presence of an excess of $Bu_4N^+Br^-$.



Y = Br: *erythro*-**DB** *threo*-**DB**

Y = OMe, OCOMe or OCH_2CF_3: *erythro*-**MA** *threo*-**MA**

Because this reaction is known to give only the products from *anti* addition,[20] the stereochemistry of these dibromides was unequivocally established. The *erythro*- and *threo*-acetoxy bromides[21] were obtained by acetylation of the corresponding

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bromohydrins. These bromohydrins were prepared, with the exception of the *p,p′*-bis(trifluoromethyl) derivatives, by reacting the *trans*- and *cis*-olefins, respectively, with *N*-bromosuccinimide (NBS) in aqueous dimethyl sulfoxide, a reaction known to give products from *anti* addition stereospecifically.[22] The stereochemistry of these bromohydrins was further confirmed by submitting samples to dehydrobromination, which gave the corresponding epoxides with the same stereochemistry as the starting olefins. The regiochemistry of the reactions of **6a**, **6b**, **8a**, and **8b** was assumed on the basis of the obvious formation of an open bromocarbenium ion at the benzylic carbon bearing the *p*-substituted phenyl ring, while that of **10a** and **10b** was achieved by assuming water attack at the benzylic carbon farthest from the electron-withdrawing CF_3-substituted phenyl group of the intermediate bromonium ion. The latter assignment was also consistent with the course of HBr ring opening of the epoxides derived from **10a** and **10b**, giving the bromohydrins of opposite regiochemistry.

In the case of **11a** and **11b** the NBS reactions yielded essentially the *meso* and *d,l*-dibromo adducts, instead of the expected bromohydrins. It is likely that the strong electron-withdrawing effect of the two *para* substituents deactivates the olefins toward the NBS reagent so much as to make competitive its decomposition to Br_2, which adds to the double bond. The *threo*- and *erythro*-bromohydrins were, therefore, prepared by HBr ring opening of the corresponding epoxides, obtained by *m*-chloroperoxybenzoic acid oxidation of olefins **11a** and **11b**. The *anti* opening of the oxirane ring was proved by recyclization of the bromohydrins to the starting epoxides.

The *erythro*- and *threo*-methoxy bromides were isolated as the solvent-incorporated mixed products (MA) from the *anti* addition of bromine to the *trans*- and *cis*-olefins, respectively, performed at $[Br_2] \approx 10^{-3}$ M, under conditions in which the methoxy bromide yields were always >90%. Only in the case of **6a** and **6b** were the reactions stereoconvergent to the formation of the *erythro* adduct, whose regiochemistry was easily predicted from the carbocationic nature of the *p*-methoxy-substituted carbon of the intermediate. This structure was also consistent with the resistance of the product to solvolysis, which can take place easily when a bromine is bonded preliminary to a methoxyphenyl-substituted carbon, as in 1-bromo-2-methoxy-1,2-bis(*p*-methoxyphenyl)ethane.[23] The stereochemistry was attributed on the basis of an equilibration of the open bromocarbenium ion intermediate formed from both **6a** and **6b** to the more stable conformation with *anti* oriented phenyl rings, followed by backside attack by the solvent. The regiochemistry of the reactions of **8a**, **8b**, **10a**, and **10b** was assumed on the basis of the regiochemical behavior of the reactions with NBS−H_2O, discussed above.

The ^{1}H NMR spectra of all *threo*-bromohydrins, acetoxy bromides, and methoxy bromides so obtained showed ^3J values between the α protons slightly higher than those of their *erythro* isomers, opposite to the generally reported behavior of *erythro*−*threo* pairs.[24] The same trend was found also for the *erythro*- and *threo*-acetoxy bromides and chlorides derived from *β*-methylstyrenes[25] and lent support to the assigned configurations of all mixed adducts. In particular, for methoxy bromides further direct evidence came, in the case of unsubstituted stilbenes, from the preparation of both *erythro* and *threo* diastereoisomers by O-methylation of the corresponding bromohydrins of known configurations[22] with methyl triflate. The same method was used to identify the *threo*-*p*-methoxy-substituted adduct, which was formed in amounts too small to be isolated from the brominations of **6a** and **6b** in methanol.

The brominations of all olefins **6**−**11** were carried out in acetic acid, methanol, and trifluoroethanol at 10^{-2} M olefin and 5×10^{-3} M Br_2, at 25 °C. The olefin to Br_2 ratios were always kept at 2:1, so that during the reactions of olefins **6a**−**11a** the *cis* isomers were always in large excess over the eventually formed *trans*-olefins **6b**−**11b**, which could, therefore, accumulate in the reaction medium. The assumption of an isomerization of the *cis*-olefins to their *trans* forms, because of the presence of amounts of hydrogen bromide equivalent to those formed during the course of the reaction as a consequence of solvent incorporation, was preliminarily investigated. No *cis*−*trans* isomerization was ever observed by HPLC analysis. The stability of *erythro*- and *threo*-dibromides and mixed adducts toward solvolysis and Br_2- or HBr-promoted isomerization was checked by exposing the products to solutions of Br_2 at the concentration employed, and to HBr at the maximum concentrations released in the corresponding reactions. All products were quantitatively recovered after times comparable to those required for the olefin brominations. This assured that the product distributions were actually obtained under kinetic control. The products were stable to solvolysis, with the exception of the *p*-methoxy-substituted dibromo adducts, which were slowly transformed to the corresponding methoxy bromides on standing in the reaction medium. This problem was obviated by extracting the products from the mixtures immediately after the end of the brominations, which were much faster than solvolysis. This procedure was followed for all the olefins examined. Since significant amounts of *trans*-olefins **9b** (in trifluoroethanol), **10b** (in trifluoroethanol), and **11b** (in acetic acid, methanol, and trifluorethanol) were found in the reactions of the corresponding *cis* isomers, the brominations of the latter olefins were also carried out in the presence of *trans*-1,2-dichloroethylene. No isomerization to *cis*-1,2-dichloroethylene, which would have been produced in the presence of free radicals,[26] was ever observed. This excluded that the transformations **9a** → **9b**, **10a** → **10b**, and **11a** → **11b** were due to a competing free-radical bromination process,[41] and left the ionic process as the only one responsible for these isomerizations.

The product yields obtained from all the olefins in acetic acid and methanol were determined by HPLC after addition of an appropriate standard. For the least reactive olefins the product ratios were determined at several conversions and found to be independent of the progress of the bromination. This provided further evidence for the kinetic control of these reactions. The total yields of products and unreacted olefin (in the case of incomplete reactions) were always >95%, showing that no significant amounts of products other than those identified were formed. For the reactions in trifluoroethanol the *erythro*- and *threo*-trifluoroethoxy bromides were not isolated, but identified by the ^{1}H NMR spectra of the reaction mixtures, from which the distribution of all products was also obtained. These ^{1}H NMR spectra showed, besides the signals due to the *erythro*- and/or *threo*-dibromides, an AB quartet between 4.5−5.0 ppm, attributable to the benzylic protons of the trifluoroethoxy bromides, and a complex signal centered on *δ* 4.0 consisting of four quartets, interpretable as an AB quartet due to the

(22) Dalton, D. L.; Dutta, P.; Jones, D. C. *J. Am. Chem. Soc.* **1968**, *90*, 5498.

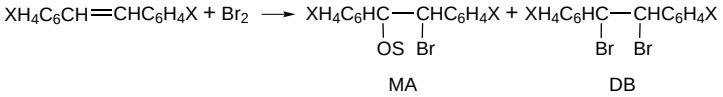
(23) (a) Attempts to brominate *p,p′*-dimethoxystilbenes in methanol yielded 1,2-dimethoxy-1,2-di(*p*-methoxyphenyl)ethane arising from the solvolysis of the first formed methoxybromo adduct. (b) Ruasse, M. F.; Argile, A. *J. Org. Chem.* **1983**, *48*, 202.

(24) Jackman, L. M.; Sternhell, S. *Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; p 291.

(25) Rolston, J. H.; Yates, K. *J. Am. Chem. Soc.* **1969**, *91*, 1469.

(26) Walling, C.; Rieger, A. L.; Tanner, D. D. *J. Am. Chem. Soc.* **1963**, *85*, 3129.

Table 3. Chemoselectivity (% MA)[a] and Stereoselectivity (% *anti* addition)[b] of the Reaction of *cis*- and *trans*-Stilbenes (10^{-2} M) with Bromine (5×10^{-3} M) at 25 °C



	MeOH			AcOH			TFE		
		stereo[b]			stereo[b]			stereo[b]	
X[c]	%MA[a]	MA	DB	%MA[a]	MA	DB	%MA[a]	MA	DB
p-OMe (**6**)									
a	97	5	-	1	-	22			
b	96	89	-	7	-	85			
		stereoconvergent[d]			stereoconvergent[d]				
p,*p*′-di-Me (**7**)									
a	90	85	-	17	55	35			
b	94	95	-	17	100	44			
		stereospecific[e]							
p-Me (**8**)									
a	98	85	-	7	70	30	50	18	20
b	98	95	-	12	85	60	50	82	80
		stereospecific[e]						stereoconvergent[d]	
H (**9**)									
a	97	97	-	25	85	45	55	25	54
b	100	100	-	28	100	60	65	99	80
		stereospecific[e]							
p-CF_3 (**10**)									
a	98	98	-	37	95	40	60	33	50
b	98	100	-	40	95	60	70	100	85
		stereospecific[e]							
p,*p*′-di-CF_3 (**11**)									
a	81	94	80	20	80	95	50	93	93
b	75	100	100	4	95	100	45	98	91
		stereospecific[e]			Stereospecific[e]			stereospecific[e]	

[a] %MA = [(MA)/(MA+DB)]% = chemoselectivity to ± 2%. [b] Stereochemistry of MA and DB = % *anti* addition to ± 2%; *anti* addition to *cis*- and *trans*-stilbenes gives *threo* and *erythro* adducts, respectively (see Table S2). [c] X: mono or disubstitution by X: **a** = *cis*-stilbene; **b** = *trans*-stilbene. [d] Stereoconvergent: the two stereoisomeric olefins give the same products. [e] Stereospecific: the two stereoisomers give different products.

Table 4. Isomerization[a] of *cis*-X-Substituted Stilbenes during Their Bromination[b]

	X	MeOH	AcOH	TFE
7a	*p*,*p*′-di-Me	0.00	0.03	(0.00)
8a	*p*-Me	0.00	0.05	0.01
9a	H	0.00	0.05	0.14
10a	*p*-CF_3	0.02	0.05	0.65
11a	*p*,*p*′-di-CF_3	0.41	0.51	0.45

[a] Isomerization of *cis*- to *trans*-olefin after bromination in the presence of bromine deficiency ([Ol] = 10^{-2} M and [Br_2] = 5×10^{-3} M). The reported figures are the ratios of the *trans*-olefin formed to the total adducts; reproducibility better than 1%. [b] Return is inferred from isomerization. When isomerization is 0.00, return is not significant.

diastereotopic methylene protons of the trifluoroethoxy bromides, each line of which was further split by three H−F couplings. The relative configurations of the two trifluoroethoxy bromides were attributed on the basis of the larger ^3J value always found for the *threo* diastereoisomers of the analogous methoxy bromides and acetoxy bromides.

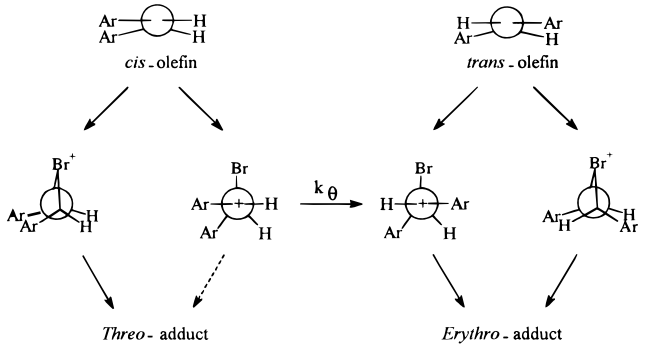
The distributions of dibromides (DB) and mixed adducts (MA) found for all *cis*- and *trans*-olefins **6**−**11** are reported in Tables 3 and S2, while the ratios of the *trans*-olefins formed during the bromination of the *cis* isomers to the total addition products are reported in Table 4. The physical constants and the ^{1}H NMR data of the olefins and of their bromination products are given in Tables S3−S7.

4. Stereochemistry and Chemoselectivity. In methanol, the main products are the solvent-incorporated adducts, MA, and in acetic acid, the dibromides, DB, in agreement with the relative nucleophilicities of the two solvents.[18] Nevertheless, the two adducts are obtained in similar yields in trifluoroethanol, although TFE is markedly less nucleophilic than AcOH.

The bromination of *trans*-stilbenes **6b**−**11b** leads almost exclusively to the *erythro* adducts (Table 3) via a 100% *anti* addition, regardless of the substituents and the solvent. In contrast, the stereochemistry of the reaction of the *cis*-stilbenes exhibits a considerable dependence on the substituents and on the solvent, the adducts, either *threo* or *erythro* resulting from *anti* or *syn* addition, respectively. Therefore the reaction of a couple of *cis*- and *trans*-stilbenes is either stereoconvergent (**6a**−**6b**) or stereospecific (**11a**−**11b**) or less than 100% stereoselective (**9a**−**9b**, for example, in AcOH or TFE).

A priori, these results could be rationalized within the usual framework of a spectrum of intermediates going from fully bridged bromonium ions, β-I^+, affording stereospecific and stereoselective product formation, to fully open carbocation, α-I^+, leading to stereoconvergency because of ready strain release by C^+−C bond rotation, in the conformation first obtained from the *cis*-olefin (Scheme 4). In agreement with this, the reaction of *p*-methoxy stilbenes **6a**−**6b**, necessarily[8b] via an open bromocarbocation, is stereoconvergent, whereas that of **11a**−**11b** via bromonium ions is stereospecific. In AcOH and TFE, there is a progressive change from stereoconvergency to stereospecificity for the reaction, implying an increase in bromine bridging when the substituents are more and more electron withdrawing. However, the role of the solvent is not readily understood in terms of variable bromine bridging. In MeOH, the bromination of **7**−**11** is stereospecific, regardless of the substituents. In contrast, in AcOH and TFE, the stereochemistry is solvent dependent but this dependence is not the same in the two solvents and, moreover, the two adducts

Scheme 4



are obtained with different stereoselectivities. There are several possible interpretations of these results: solvent-dependent bromine bridging, changes in the reaction pathways, in the nature of the product-forming intermediates and of their associated partners (**2**, **4**, or **5**), and in their lifetimes, depending on the solvent and the substituents. These suggestions are discussed now.

5. Kinetic Substituent Effects and Substituent- But Not Solvent-Dependent Bromine Bridging. The marked solvent dependence of the chemo- and stereoselectivities (Table 3) cannot be related to a change in the magnitude of bromine bridging with the solvent since this bridging is not solvent dependent.[8b] This is supported by the following kinetic and product data.

(i) If the magnitude of bridging of the bromination intermediates is the result of a competition among bromine, the substituents, and the solvent in the stabilization of the cationic charge, a stereoselectivity smaller in the nucleophilic methanol than in acetic acid or trifluoroethanol is expected. The greater the nucleophilicity of the solvent, the larger the stabilization of the carbocationic intermediates by solvation, the smaller the electronic demand on their bromine atoms and the smaller the bridging. In contrast, the reaction is fully stereoselective in methanol but not in the other two solvents.

(ii) Changes in bromine bridging with the substituents lead to markedly curved $\rho\sigma$ plots for arylolefin bromination[8b] and, in particular, for that of *trans*-stilbenes[27] in MeOH. The ρ^+ value decreases smoothly as the substituents are less and less electron donating, from -4.3 in the usual range for benzylic carbocations to about -1 when the intermediates are bridged, i.e. when their positive charge is on the bridging bromine. Similar curvatures are observed in the other solvents of Table 1 since there are rigorously linear log−log relationships (i) between the rate data of substituted *cis*- and *trans*-stilbenes in MeOH ($\log k_{trs} = 0.90 \log k_{cis} - 0.10$, correlation coefficient = 0.999) and (ii) between the data for *cis*-stilbenes in MeOH and in the other solvents (Figure 1). Therefore, the substituent dependence of the bridging is very similar in all these solvents.

These stereochemical and kinetic data are the first compelling evidence for a significant substituent dependence but insignificant solvent dependence of bromine bridging. This result has two kinds of consequences. First, if the intermediate is an open β-bromocarbocation, α-I$^+$, in a given solvent as shown by stereoconvergency, the intermediate is also α-I$^+$ in the other solvents. In particular, since the reactions of **6**−**8** are stereoconvergent in AcOH and/or TFE, their intermediates are necessarily the corresponding carbocations α-I$^+$ in these solvents

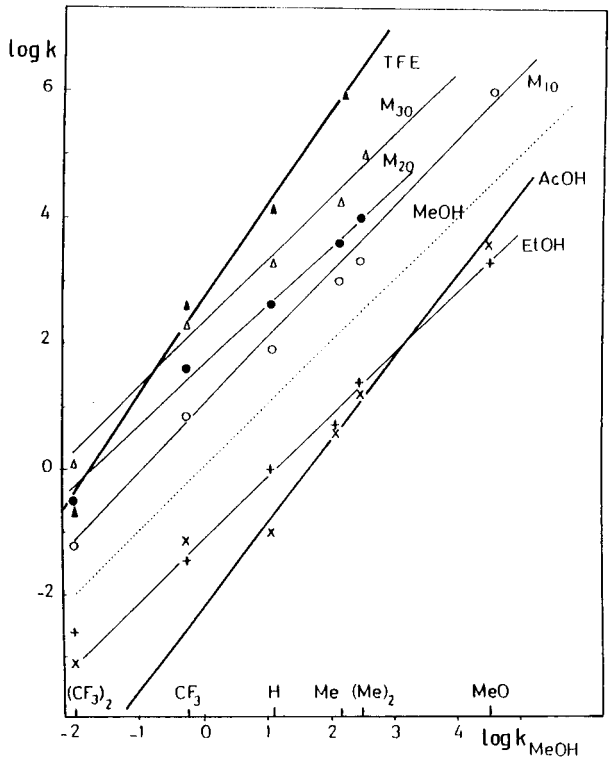


Figure 1. log−log relationships comparing substituent effects on *cis*-stilbene bromination in MeOH (*x* axis) and in other solvents (*y* axis). In nucleophilic solvents, the slopes, ρ^S/ρ^{MeOH}, are close to unity (0.92, 1.07, 0.98, and 1.03 in EtOH, M10, M20, and M30, respectively; standard errors ≤ 0.05; correlation coefficients ≥ 0.994). In TFE, ρ^S/ρ^{MeOH} is 1.56 ± 0.04 and in AcOH, 1.35 ± 0.03 excluding **10a** and **11a** for which there is a change in the rate-limiting step. The linearity of these relationships shows that bromine bridging is not solvent dependent (see text).

and also in MeOH. Therefore, the stereospecificity of **7** and **8** in MeOH cannot be attributed to bromine bridging. Secondly, since α-I$^+$ from **7** and **8** react stereospecifically with MeOH only, the usual conformer rotation (Scheme 4) does not occur **before** they react with MeOH. In other words, the lifetimes of these intermediates are very short in this nucleophilic solvent as compared to those in the other solvents. A reasonable interpretation, in agreement with the *m* values and the deviations of Δ_{AcOH} and Δ_{TFE}, is that in MeOH bromination is nucleophilically assisted, as expressed in a preassociation mechanism, whereas in AcOH and TFE other pathways are preferred.

6. Preassociation Pathways in Nucleophilic Alcohols. There are several pieces of kinetic evidence for nucleophilic assistance to the ionization step by nucleophilic solvents in the bromination of **7**−**11** (vide supra). Now the questions are (i) Is this assistance satisfactorily described by a preassociation mechanism (eq 4)? (ii) If yes, what are the rate-limiting steps?

$$\mathbf{1} \rightleftharpoons \mathbf{3} \rightleftharpoons \mathbf{4} \rightleftharpoons \text{products} \qquad (4)$$

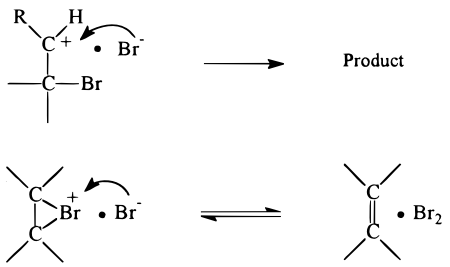
And (iii) are the products consistent with the collapse of complexes **4**?

There are three main requirements for a preassociation pathway to occur.[11] The nucleophile, which in bromination is the solvent, must preassociate with the substrate. Methanol is not a strong nucleophile but bromine−olefin charge-transfer complexes **1** are highly polarizable, so the two species can interact strongly to form dipole−dipole complexes **3**. A second condition is that return from **4** to the preassociation complex is more rapid[11,29] than diffusion away of methanol leading to ion pair **2**, $k_{-a} < k'_{-1}$ (Scheme 2). In bromination, MeOH reacts

(27) (a) Ruasse, M. F.; Dubois, J. E. *J. Org. Chem.* **1972**, *37*, 1770. (b) Ruasse, M. F.; Dubois, J. E. *J. Org. Chem.* **1973**, *38*, 473; **1974**, *39*, 2441. (c) These curvatures cannot be interpreted in the usual terms of the Yukawa−Tsuno equation;[28] see footnote 14 in ref 27a.

(28) Tsuno, Y.; Fujio, H. *Chem. Soc. Rev.* **1996**, *25*, 129.

Scheme 5



rapidly with I^+ to give the mixed adduct (vide supra) and, therefore, does not diffuse rapidly from I^+, whereas the rate constant for return, the reaction of the counter-bromide ion with I^+, can be[5d] as large as 10^{11} s^{-1}. Finally, the collapse of I^+ to the products must have a significant barrier for **4** to exist as an intermediate. Preassociation mechanisms in some nucleophilic substitutions[11g,30] have been excluded because the lifetimes of complexes analogous to **4** are too short. In contrast, the lifetimes of ionic intermediates for alkene bromination in MeOH, which are also nucleophilically assisted,[7] are short but significant[31] ($k_{MeOH} = 10^9-10^{11}$ s^{-1}). Therefore, in nucleophilic solvents, assisted bromination can occur via a preassociation pathway.

When the intermediates are open carbocations (α-I^+) as those from **7** and **8**, return by reaction of the bromide ion with the bromine atom of I^+ is not likely[6c] because the carbon atom of I^+, and not the bromine, is charged. In contrast, bromonium ions from **10** and **11** can readily undergo return (Scheme 5). Evidence for this will be given (vide infra). Therefore, there is a change in the rate-limiting step from the **4**-forming step to the product-forming step when bromine bridging, i.e., the electron-withdrawing character of the substituents, increases.

The *anti* stereoselectivity of *cis*-stilbene bromination in MeOH and its independence of bromine bridging is consistent with product formation by collapse of complexes **4**, since methanol reacts necessarily with I^+ on the site opposite to the entering bromine. Therefore, bromine bridging is not the only prerequisite for stereospecific bromination; preassociation can be the source of stereospecificity also. Stereospecific brominations of *trans*-β-methylstyrenes via open β-bromocarbocations, in MeOH but not in halogenated solvents,[32] can also be attributed to preassociation.

Complex **4** collapses almost exclusively by reaction of I^+ with methanol and not with bromide, since dibromide is a very minor product regardless of the substituents. This is in agreement with usual findings that alkene bromination in methanol gives methoxybromo adducts but not dibromide, in the absence of added bromide ions.[31,33] Nevertheless, these results contradict solvolytic data which show that bromide and not methanol reacts at the diffusion-controlled rate with benzylic carbocations,[34] so collapse of **4** should afford mainly dibromide. In bromination intermediates, steric and electrostatic repulsions between the counter-bromide ion and the I^+-bromine atom disfavor capture of I^+ by Br^-, which should be *syn* since the usual *anti* addition would require methanol expulsion after Br^- rotation around I^+ (*trans* location). On the contrary, methanol can interact strongly with the empty orbital of the cationic centre, in particular when I^+ is a bromocarbenium ion. In agreement with this proposal, more dibromide (up to 25%) is obtained when I^+ is a bromonium ion (**11**) which interacts weakly with MeOH because of the negligible charge of its carbon atoms.

7. Free-Ion Pathway. In contrast with the other stilbenes, bromination of **6** is stereoconvergent in methanol and in acetic acid. This is readily interpreted in terms of the absence of any nucleophilic assistance and of fully open intermediates. In other terms, a free ion pathway (eq 5) in which the ionization is rate limiting (Scheme 2; $k_d > k_{-1}$, $k_{Br} > k_{-1}$) since I^+ is unbridged, is involved. In the moderately ionizing MeOH where MA is

$$\mathbf{1} \rightarrow \mathbf{2} \rightarrow \mathbf{5} \rightarrow \text{MA} \qquad \text{(5)}$$
$$\downarrow$$
$$\text{DB}$$

the only product, the dissociation of the ion pair, k_d, is faster than its collapse, k_{Br}, whereas it is the the reverse in AcOH in which DB is the main adduct. The upward curvature of the corresponding *mY* plot is, therefore, surprising and results probably from differences in the mechanisms of bromination and of the Y_{Br}-defining reaction.[17] As there is no return in the bromination of **6**, a number of results[29,35] suggests that 2-bromoadamantane solvolysis is reversible. Therefore, the kinetic data for the two reactions are not related to the same microscopic events.

Free-ion pathways are also involved in the nonnucleophilic and highly ionizing trifluoroethanol, regardless of the substituents. The trapping of free ions by TFE is not very fast[34] and, therefore, ion-pair collapse[36] competes extensively, as shown by the competitive formation of the two adducts (DB:MA = 1:1). This is consistent with the relative rates of carbocation trapping by MeOH and TFE[34d,e] ($k_{MeOH}/k_{TFE} = 10^6$), since in MeOH no dibromide is obtained ($k_{MeOH} \gg k_{Br}$, whereas $k_{TFE} \approx k_{Br}$). This result, in agreement with usual findings in bromination,[33] is in contrast with the diffusion-controlled rate of Br^- reaction with nonbrominated benzylic carbocations[34] and shows that the requirements for the collapse of ion pairs **2**, either *trans* (*trans* location of Br^-) or *syn* (bromine−bromine repulsions), are energetically expensive.[37]

Kinetic data in TFE and the corresponding Δ_{TFE}, i.e., the relative rates of the preassociation and free-ion pathways, suggest a possible competition between the two routes (eq 6).

$$\mathbf{4} \leftarrow\leftarrow \mathbf{1} \rightarrow \mathbf{2} \qquad \text{(6)}$$

In particular, for the irreversible bromination of **8a**, the unassisted route in TFE is favored over the assisted route in a nucleophilic solvent of similar ionizing power by about 1 kcal mol^{-1} ($\Delta_{TFE} = +0.76$), whereas for **9a** the two routes have similar barriers (Δ_{TFE}, negligible). The extent of the competition can be estimated by comparing the previously obtained *mY* relationships (Table 2) for the assisted process (**1** → **4**) to those for the unassisted pathway (**1** → **2**). The coefficients of the mY equations related to this latter path (m^i_{Br} and log k^i_o in

(29) Cox, B. G.; Maskill, H. *J. Chem. Soc., Trans. Perkin 2* **1983**, 1901.
(30) (a) Richard, J. P.; Amyes, T. L.; Vontor, T. *J. Am. Chem. Soc.* **1991**, *113*, 5871. (b) Toteva, M. H.; Richard, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 11434.
(31) Nagorski, R. W.; Brown, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 7773.
(32) Ruasse, M. F.; Argile, A.; Dubois, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 7645.
(33) (a) Dubois, J. E.; Chrétien, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 3506. (b) Ruasse, M. F.; Coudert, D.; Chrétien, J. R. *J. Org. Chem.* **1993**, *58*, 1917. (c) Ruasse, M. F.; Argile, A. *J. Org. Chem.* **1983**, *48*, 202.
(34) (a) Richard, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 1455. (b) McClelland, R. A.; Kanagasabapathy, V. M.; Steenken, S. *J. Am. Chem. Soc.* **1988**, *110*, 6913. (c) McClelland, R. A.; Chan, C.; Cozens, F.; Modro, A.; Steenken, S. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1337. (d) Das, P. K. *Chem. Rev.* **1993**, *93*, 119. (e) McClelland, R. A. In *Organic Reactivity: Physical and Biological Aspects*; Golding, B. T., Griffin, R. J., Maskill, H., Eds; The Royal Society of Chemistry: Cambridge, 1995; p 301.
(35) Paradisi, C.; Bunnett, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 8223.
(36) Dibromide formation by Br^- capture of free ions **5** is excluded because of the very low concentration of bromide ions resulting from the dissociation of the ion pair.
(37) It should be noted also that dibromide is obtained with a stereoselectivity better than that of MA, showing that the lifetime of the free ion is longer than that of the ion pair.

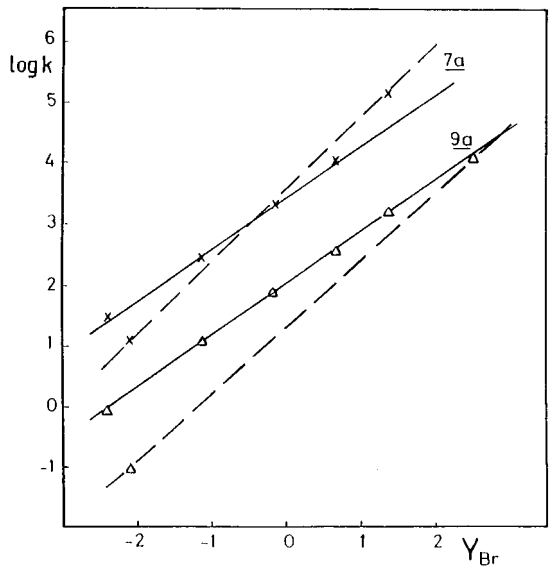


Figure 2. $m_{Br}Y_{Br}$ relationships for the bromination of **7a** and **9a** via assisted (full line from EtOH, MeOH, and H_2O−MeOH mixtures; m_{Br} and log k_o in Table 2) and unassisted (dotted line from AcOH, TFE or M30; m^i_{Br} and log k^i_o) rate-limiting ionizations.

Table 2) are evaluated from the rate data in the two nonnucleophilic solvents. The m^i_{Br} values, 1.1, agree with those previously found for unassisted brominations.[7] The comparison of the two series of *mY* plots (Figure 2) shows that the rate differences between the two types of ionization are not large in the solvents investigated. Nevertheless, it is observed that, for stilbene **8a** for example, the unassisted pathway would be the only one in nucleophilic solvents more ionizing than TFE. This result explains fairly well why, in highly aqueous trifluoroethanol ($Y_{Br} > 3$), no evidence was found for a preassociation pathway in the solvolysis of *tert*-cumyl derivatives.[30]

8. Ion-Pair Pathways in Acetic Acid. In AcOH, a Sneen mechanism[38] (eq 7) involving nucleophilic collapse of an ion pair is the most likely. In stilbene bromination, this pathway

$$\mathbf{1} \rightleftharpoons \mathbf{2} \rightleftharpoons \mathbf{4} \rightleftharpoons \text{products} \qquad (7)$$

is supported by kinetics and product data. The ρ value in AcOH, which is larger than that in MeOH and in the same range as that in TFE ($\rho^{AcOH} = 0.9\rho^{TFE} = 1.35\rho^{MeOH}$), is further evidence for the absence of nucleophilic assistance in the two barely nucleophilic solvents, as compared to what occurs in the other solvents[39] (Figure 1). In terms of Scheme 2, the first ionization steps are similarly unassisted in AcOH and TFE. However, the deviations of **10a** and **11a** from the log−log relationship (AcOH−MeOH in Figure 1) and their almost zero values for Δ_{AcOH} (Table 2) are unexpected. Since these two least reactive stilbenes fit the *mY* plots for the nucleophilic alcohols, the rate-limiting steps are the same in the two kinds of solvent. The only step common to the preassociation (eq 4) and ion-pair (eq 7) pathways is the product formation from complexes **4**. In other words, the mechanism in AcOH is necessarily that described by eq 7 involving solvent association with the ion pair (**2** → **4**) before product formation. Moreover, this product-forming step is rate-limiting in the two kinds of solvent for the reactions of **10a** and **11a** but not for the other stilbenes. Finally, the bromination intermediates of **11a** and also of **10a** are bridged, β-I^+, but not that of **9a** which must closely resemble α-I^+, since return and bridging are related.

Product data, and in particular the stereochemistry of DB formation as compared to that of MA from the open intermediates, are consistent with product formation from complexes **4**. Whereas MA results mainly from an *anti* addition, DB is obtained via a process close to *syn*. For example, in the reaction of **10a**, MA results from a 95% *anti* addition, whereas the formation of DB is 60% *syn*. It is not expected that complexes **4** live long enough for complete conformer rotation to occur. Therefore, Br^--*syn* addition cannot arise only from strain release in the initially formed α-I^+ conformation. The most reasonable interpretation is that products are obtained by collapse of **4** in which Br^--*anti* addition is hindered by the presence of AcOH. Br^--*syn* addition is, therefore, favored despite its drastic requirements.

9. Isomerization, KSIEs, and Return. Reversibility of the ionization steps of the bromination of **10a** and **11a** is evidenced by the zero values of their Δ_{AcOH} discussed above. Return is also supported by a series of experiments (Table 4) carried out with a bromine deficiency in which *cis*−*trans* isomerization of the starting *cis*-olefin can be observed. As previously discussed,[6c] large isomerization ratios are indicative of significant return. According to these results, return is important for **11a** in every solvent and for **10a** in TFE but not for the other stilbenes, in agreement with the already mentioned relationship between bridging and return. The isomerization involved in the bromination of the two poorly reactive stilbenes can be interpreted qualitatively in terms of competition between nucleophilic trapping of the bromonium ions and their *cis*−*trans* equilibration, as shown in Scheme 6. The trapping of bridged ions is extremely slow because of the absence of charge on their carbon atoms and, therefore, the barrier for their isomerization is probably in the same range as that for their reaction with nucleophiles. The fact that this phenomenon is observed for **10a** in the nonnucleophilic TFE but not in the other solvents suggests similar heights for the two barriers, while for **11a**, isomerization would be uniformly faster than nucleophilic trapping, even by methanol. It is reasonable to assume that the isomerization of the bromonium ions goes through open transition states or intermediates (Scheme 6), the strain of which is readily released by fast C^+−C bond rotation.[40] This is supported by the incomplete stereoselectivity of **11a** and **10a** (Table 3), which is unexpected from full bridging. Nucleophilic trapping of the highly unstable open ions probably occurs. Alternatively, the isomerization of the two poorly reactive stilbenes could suggest a change from an ionic to radical mechanism. Nevertheless, this interpretation is not plausible because the particular kinetic and stereochemical behavior[41] of radical bromination of stilbenes (zeroth order in stilbene, stereoconvergency) is not observed under the presently used reaction conditions, even for **10a** and **11a**.

KSIEs in methanol (Table 1) for the reversible bromination of **10a** and **11a** are unexpectedly large as compared to those usually found in this addition[7,19] (1.1−1.3). Moreover, small KSIEs have been taken previously as evidence for return in the reaction of highly congested alkenes.[7] Insofar as KSIEs are related to the extent of the solvation of the leaving bromide ion in the rate-limiting step,[7] these results imply highly solvated Br^- in the product-forming step of the bromination of **10a** and **11a**, but highly desolvated Br^- in that of the reaction of congested alkenes.[42] Inspection of the transition states of these

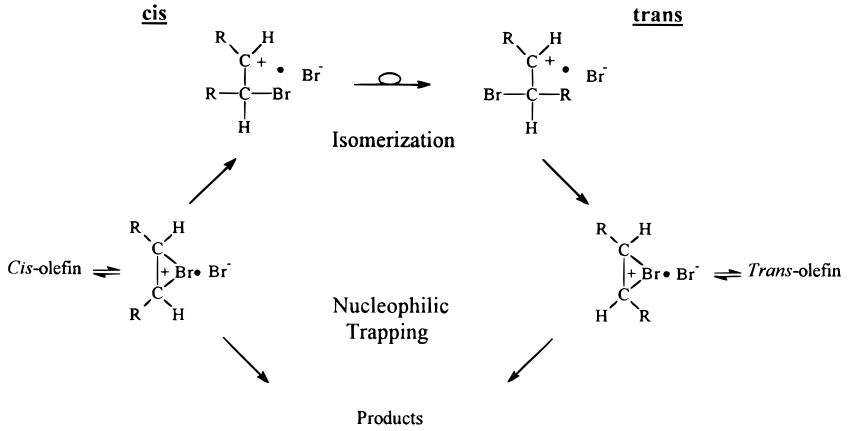
(38) (a) Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46. (b) Raber, D. J.; Harris, J. M.; Schleyer, P. v. R. In *Ions and Ion-Pairs in Organic Reactions*; Szwarc M., Ed.; Wiley: New York, 1974; Vol. 2, p 247.

(39) The same ρ ratio, $\rho^{AcOH}/\rho^{MeOH} = 1.35$, was previously observed for styrene bromination.[32]

(40) The rate of the conformer equilibration can be in the 10^9 s^{-1} range, according to preliminary measurements of lifetimes of stilbene bromination intermediates (Chiappe, C.; Lo Moro, G.; Ruasse, M. F, unpublished results).

(41) Bellucci, G.; Chiappe, C. *J. Phys. Org. Chem.*, in press.

Scheme 6



two reactions shows that this suggestion is reasonable. On the one hand, the rate-limiting step for the poorly reactive stilbenes involves Br^- diffusion from complexes **4** and, therefore, an increase in Br^- solvation. On the other hand, for crowded alkenes giving vinylic products,[5] the counterion which acts as a base in the proton elimination is transformed into hydrobromic acid.

Concluding Remarks

From this kinetic and product study of stilbene bromination over an exceptionally large reactivity range (10 powers of 10), several original conclusions on the mechanism of this reaction emerge.

(i) In contrast with the widely accepted postulate, bromine bridging is not the only stereochemistry-determining factor. The large solvent dependence of the stereochemistry does not arise from bridging variations with solvent, since this latter is substituent- but not solvent-dependent, as shown by the comparison of kinetic substituent effects in the several solvents studied. The stereochemical outcome of bromination is controlled not only by the bridged or unbridged structure of the cationic intermediate but also by its association with its nucleophilic partners and its lifetime. In this context, an important result is the substituent-independent stereospecificity of the reaction of *cis*-stilbenes and of *trans*-β-methylstyrenes[32] in MeOH, but not in nonnucleophilic solvents, which is the consequence of their preassociation with the nucleophile, well before the product-forming step itself.

(ii) Return, which is significant in protic and halogenated solvents[6c] when the intermediates are bridged but not when they are open, is also a result of interest. Until now, much work has been devoted to return enforced by steric inhibition of the nucleophile approach to crowded bromination intermediates.[2,43] A second origin, namely the magnitude of the charge borne by the bromine atom of these intermediates, is well established by the present results. Negligible values of Δ_{AcOH}, large KSIEs, and large isomerization ratios are converging pieces of evidence for this return. These conclusions, related to the still-open question of the equilibrium between bridged and unbridged structures of the bromination intermediates,[44] support a barrier for this equilibrium markedly higher than that for their nucleophilic trapping, except when they are strongly destabilized bromonium ions. Moreover, the severe energetic requirements of *syn* vs *anti* addition, which involve strong bromine−bromine repulsions and Br^- *trans* location, respectively, are fairly well exhibited by the absence of Br^- collapse of the ion−dipole sandwiches **4**, in contrast with the diffusion-controlled Br^- reactions with analogous non-brominated carbocations.[34]

(iii) Neither the kinetic results (*m* values, Δ_{AcOH}, Δ_{TFE}, KSIEs) nor the chemoselectivity dependence on the solvent (major solvent-incorporated adducts in MeOH, major dibromide in AcOH but not in TFE), nor the large variety of stereochemical outcomes (stereoconvergency to stereospecificity) can be rationalized without taking into account all the pathways of Scheme 2. Alternatively, changes in bromine bridging with the solvent and the substituents which were assumed previously from more limited data sets,[45] do not provide a satisfactory interpretation. Our results point to the need for extensive data on a very wide range of solvents and substituents in order to show the consistency of Scheme 2. The same comment probably applies in aliphatic nucleophilic substitutions for which Scheme 3 is not necessarily required in every investigation. Scheme 2 is not only a useful working assumption but also necessary since pathway crossings are observed. For instance, it is obvious a priori that preassociation and ion-pair paths are preferred in MeOH and AcOH, respectively, but the kinetic data for the two least reactive stilbenes can be interpreted only by a crossing between these two paths. Furthermore, the fact that the free ion route is sometimes energetically favored in nucleophilic solvents is compelling evidence for a competition between preassociation and free ion paths, which is readily understood within Scheme 2. Finally, a route corresponding to a concerted bromination, which has never been supported by any data,[1d,45] can be suggested by analogy with the S_N2 pathway of nucleophilic substitution. The positive deviation from EtOH to the *mY* plot of the least reactive stilbene could be attributed to a fully concerted bromine addition, although there is no direct evidence for it.

(iv) Lifetimes of the ionic intermediates of nucleophilic substitutions determine the pathway followed under given reaction conditions.[11] The longer these lifetimes, the more favored the pathways of the top of Scheme 3. Although the lifetimes of the bromination intermediates[31] are not measured

(42) A reviewer suggested an alternative interpretation which assumes reasonably the occurrence of a primary isotope effect on the rate-determing, product-forming step involving hydron departure in the I^+−MeOH reaction. This primary effect would superimpose to the KSIE on the ionization step resulting in the observed increase in the experimental value.

(43) Return in the absence of crowding was also supported by results on solvolysis of β-bromotriflates in the presence of bromide ions. Zheng, C. Y.; Slebocka-Tilk, H.; Nagorski, R. W.; Alvarado, L.; Brown, R. S. *J. Org. Chem.* **1993**, *58*, 2122.

(44) (a) Poirier, R. A.; Mezey, P. G.; Yates, K.; Cszimadia, I. G. *J. Mol. Struct.* **1983**, *94*, 137. (b) Galland, B.; Evleth, E.; Ruasse, M. F. *J. Chem. Soc., Chem. Commun.* **1990**, 898. (c) Hamilton, T. P.; Schaefer, H. F. *J. Am. Chem. Soc.* **1990**, *112*, 8260. (d) Klobukowski, M.; Brown, R. S. *J. Org. Chem.* **1994**, *59*, 7156. (e) Cossi, M.; Persico, M.; Tomasi, J. *J. Am. Chem. Soc.* **1994**, *116*, 5373.

(45) (a) Buckles, R. E.; Bader, J. N.; Thurmaier, R. J. *J. Org. Chem.* **1962**, *27*, 4523. (b) Heublein, G. *J. Prakt. Chem.* **1966**, *303*, 84.

in this work, the stereochemical results can be interpreted in these terms. In particular, the trapping rates of the open intermediates can be estimated by comparison with the rate of their conformational rotation[40] (Scheme 4). The intermediate from **6a** is long-lived in MeOH and also in AcOH since full rotation is achieved before its trapping by these solvents; accordingly, the enforced path is the free ion route. For **8a**, the lifetime of its intermediate is very short in MeOH (no rotation) but very long in TFE, in agreement with preassociation and free ion paths, respectively, and also in agreement with the relative rates of carbocation trapping by these solvents.[34] Our results suggest, therefore, that the conformational barriers can be used as clocks for measuring carbocation lifetimes, as an alternative to the more familiar azide clock.[11b−f,31,34a] More work is in progress to obtain data on the lifetimes of these bromination intermediates and on their conformational equilibria.

Experimental Section

Solvents (ethanol, methanol, acetic acid) were purified before use as previously described;[7] trifluoroethanol from Aldrich was used without further purification. Bromine (1 mL sealed ampules, Carlo Erba >99.5%) was used as supplied.

Melting points were determined on a Kofler apparatus and are uncorrected. ^{1}H NMR spectra were registered in $CDCl_3$ with a Bruker AC 200 instrument and TMS as the internal reference. HPLC analyses were carried out with a Waters 600E apparatus equipped with a diode array detector.

Olefins 6−11. Commercial *trans*-stilbene (**9b**) (Schuchard, >99%) was crystallized from ethanol, mp 124−125 °C. Commercial *cis*-stilbene (**9a**) (Aldrich, >97%) was fractionally distilled with a fraction with bp 93 °C (5 mmHg) collected resulting in >99% purity by HPLC. Olefins **6b**−**11b** were obtained in mixtures with the *cis* isomers **6a**−**11a** by Wittig reactions of the corresponding *para*-substituted benzaldehydes and *para*-substituted benzyltriphenylphosphonium chloride.[47] The separation of the resulting *cis*−*trans* mixtures was performed by column chromatography over alumina (aluminum oxide S, 100−290 mesh ASTM), with hexane as eluent. The *cis* isomers were always eluted first. All olefins were finally checked by HPLC and were found to be >99% pure.

Dibromides. All *cis*- or *trans*-stilbenes were brominated with $Bu_4N^+Br_3^-$ in 1,2-dichloroethane using the reported procedure.[6c] The crude products were crystallized from chloroform to give pure *erythro* (or *meso*) or *threo* (or *d*,*l*) dibromides.

Bromohydrins. *erythro*- and *threo*-bromohydrins were prepared from *trans*- and *cis*-olefins, respectively, with *N*-bromosuccinimide in DMSO, using the procedure reported by Dalton.[22] The crude products were purified by TLC (PSC Fertigplatten Kiesel-gel 60 F254, Merck, 9:1 hexane−ethyl acetate), followed by crystallization from hexane.

erythro- and *threo*-1,2-bis-[*p*-(trifluoromethyl)phenyl]-2-bromoethanol were prepared by HBr ring opening of *trans*- and *cis*-*p*-*bis*(trifluoromethyl)stilbene oxides respectively, obtained by treatment of the corresponding olefins with *m*-chloroperoxybenzoic acid in dichloromethane for 24 h. The opening reactions were carried out in HBr-saturated chloroform solution. After 4 h at room temperature the solutions were washed with water, dried ($MgSO_4$), and evaporated. The crude products were purified by TLC, as described above.

Acetoxy Bromides. *erythro*- and *threo*-acetoxy bromides were obtained by treating the corresponding bromohydrins with a 10-fold excess of acetic anhydride in pyridine. After 10 h at room temperature toluene was added and the mixtures were evaporated at reduced pressure. The crude residues were crystallized from hexane to give the pure products.

Methoxy Bromides. *erythro*- and *threo*-methoxy bromides were obtained by addition of a methanolic solution of Br_2 (0.4 M, 5 mL) to 500 mL of a 3×10^{-3} M solution of the *trans*- or *cis*-olefin, respectively, in the same solvent. After 4 h at room temperature for **6**−**10**, or 24 h for **11**, a saturated solution of $NaHCO_3$ was added and the products were extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) extracts and crystallization of the crude solid residues from hexane, or Kugelrohr short-path distillation in the case of oils, gave pure methoxy bromides.

The *erythro*- *and threo*-1-bromo-2-methoxy-1,2-diphenylethanes were also obtained by methylation of *erythro*- and *threo*-1,2-diphenyl-2-bromoethanols, respectively, with methyl triflate as follows: The bromohydrin (1 mmol), methyl triflate (10 mmol), and 2,6-di-*tert*-butyl-4-methylpyridine (8 mmol) were added to anhydrous dichloromethane (10 mL) under argon, the mixture was refluxed for 48 h, and then filtered. The solution was washed with 5% HCl and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to give a solid residue from which the *erythro*- or *threo*-methoxy bromide was obtained pure by preparative TLC using 9:1 hexane−ethyl acetate as the eluent.

The same procedure was used with *threo*-1-(*p*-methoxyphenyl)-2-bromo-2-phenylethanol to obtain the corresponding *threo*-methoxy bromide.

Bromination Procedures and Product Analysis. Solutions (5.5×10^{-2} M) of bromine in acetic acid, methanol, or trifluoroethanol (0.5 mL) were rapidly mixed with 5 mL of 1.1×10^{-2} M solutions of *cis*- and *trans*-stilbenes in the same solvent, and the reaction mixtures were stored in the dark at 25 °C. At the end of the reactions, or after stopping the reactions by addition of cyclohexene which rapidly consumed all the unreacted Br_2, the mixtures were diluted with water, repeatedly extracted with dichloromethane and analyzed by ^{1}H NMR and HPLC under the following conditions: Spherisorb S5CN (ps phase Sep), 25 cm, with hexane−THF (95:5 v/v) as the eluent, at a flow rate of 1.5 mL/min, for the reactions of **6a** and **6b** in acetic acid; Spherisorb S5CN (ps phase Sep), 25 cm, with hexane−THF (99:1 v/v) as the eluent, at a flow rate of 1.5 mL/min, for the reactions of **7a**, **8a, 10a, 11a**, **7b**, **8b**, **10b**, and **11b** in acetic acid; Spherisorb ODS2 (ps phase Sep), 25 cm, with methanol−water (75:25 v/v) as the eluent, at a flow rate of 1.0 mL/min, for the reactions of **9a** and **9b** in acetic acid; Spherisorb S5CN (ps phase Sep), 25 cm, with hexane−THF (95:5 v/v) as the eluent, flow rate of 1.5 mL/min, for the reactions of **6a** and **6b** in methanol; Spherisorb S5CN (ps phase Sep), 25 cm, with hexane−acetonitrile (99:1 v/v) as the eluent, flow rate of 1.5 mL/min, for the reactions of **7a**, **8a, 10a, 11a**, **7b**, **8b**, **10b** and **11b** in methanol; and Spherisorb ODS2 (ps phase Sep), 25 cm, with methanol−water (75:25 v/v) as the eluent, flow rate of 1.0 mL/min, for the reactions of **9a** and **9b** in methanol.

For the HPLC quantification of the products and of the unreacted olefins, *erythro*-1,2-dibromo-1-phenylpropane was added as an internal standard.

The product mixtures obtained in trifluoroethanol were analyzed by ^{1}H NMR on the basis of the signals of the benzylic protons of the dibromides and trifluoroethoxy bromides.

erythro-1-Bromo-2-(*p*-methylphenyl)-1-phenyl-2-trifluoroethoxyethane: δ 3.62 (qq, 2H, CH_2CF_3), 4.90 (d, $J = 6.8$ Hz, 1H, CHBr or CHO), 5.02 (d, $J = 6.8$ Hz, 1H, CHO or CHBr).

erythro-1-Bromo-1,2-diphenyl-2-trifluoroethoxyethane: δ 4.00 (qq, 2H, CH_2CF_3), 4.95 (d, $J = 5.4$ Hz, 1H, CHBr or CHO), 5.04 (d, $J = 5.4$ Hz, 1H, CHO or CHBr).

erythro-1-Bromo-2-phenyl-2-(trifluoroethoxy)-2-*p*-(trifluoromethyl)-phenyl]ethane: δ 3.70 (qq, 2H, CH_2CF_3), 4.90 (d, $J = 6.5$ Hz, 1H, CHBr or CHO), 5.02 (d, $J = 6.5$ Hz, 1H, CHO or CHBr).

erythro-1-Bromo-1,2-di-[*p*-(trifluoromethyl)phenyl]-2-(trifluoroethoxy)-ethane: δ 3.65 (qq, 2H, CH_2CF_3), 5.00 (d, $J = 7.0$ Hz, 1H, CHBr or CHO), 5.03 (d, $J = 7.0$ Hz, 1H, CHO or CHBr).

threo-1-Bromo-1,2-diphenyl-2-(trifluoroethoxy)ethane: δ 4.13 (qq, 2H, CH_2CF_3), 4.80 (d, $J = 6.6$ Hz, 1H, CHBr or CHO), 5.05 (d, $J = 6.6$ Hz, 1H, CHO or CHBr).

threo-1-Bromo-2-phenyl-2-(trifluoroethoxy)-1-[*p*-(trifluoromethyl)-phenyl]ethane: δ 3.80 (qq, 2H, CH_2CF_3), 4.80 (d, $J = 7.8$ Hz, 1H, CHBr or CHO), 5.03 (d, $J = 7.8$ Hz, 1H, CHO or CHBr).

threo-1-Bromo-1,2-bis-[*p*-(trifluoromethyl)phenyl]-2-(trifluoroethoxy)-ethane: δ 3.80 (qq, 2H, CH_2CF_3), 4.85 (d, $J = 7.2$ Hz, 1H, CHBr or CHO), 5.06 (d, $J = 7.2$ Hz, 1H, CHO or CHBr).

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(47) Novotny, J.; Collins, C. H.; Starks, F. W. *J. Pharm. Sci.* **1973**, *62*, 610.

All reactions were carried out at least in quadruplicate. Reactions stopped at several different conversions gave similar product ratios. Table S2 reports the average product distributions of dibromides (DB) and mixed adducts (MA). They were reproducible to ±1% for values <10, and to ±2% for higher values.

For each *cis*-olefin, reactions were also carried out in the presence of an equimolar amount of *trans*-1,2-dichloroethylene. No isomerization to *cis*-1,2-dichloroethylene, which would have indicated the occurrence of free radical processes,[26] was ever observed. Furthermore, HPLC analysis showed that no change in products was produced in any case by prolonged contact with Br_2 or HBr.

Kinetic Measurements. Rate constants below 1 M^{-1} s^{-1} were obtained by monitoring bromine concentration by conventional spectrophotometry under second-order conditions, reagent concentrations being less than 5×10^{-4} M. For the more reactive stilbenes, a multichannel stopped-flow apparatus[12] was used under pseudo-first-order conditions with a large olefin excess compared to bromine, the concentration of which was about 5×10^{-4} M. Bromine solutions (5×10^{-4} to 5×10^{-3} M), prepared shortly before use, were protected from daylight and adjusted to twice the initial concentration desired in the kinetic runs. Aliquots of these solutions, thermostated at 25 ± 0.05 °C, were mixed with equal volumes of thermostated solutions of olefins of suitable concentrations. A Cary 2200 spectrophotometer (for $k < 1$ M^{-1} s^{-1}), equipped with a 1 cm cell, or the stopped-flow apparatus[12] (for $k > 10$ M^{-1} s^{-1}) was used to monitor the reactions. Second-order conditions (first-order in both reagents, $[Br_2] = [\text{olefin}] < 5 \times 10^{-4}$ M) or pseudo-first-order conditions ($[Br_2] \approx 5 \times 10^{-4}$ M and large olefin excess) were employed. The absorbance/time data obtained at several different wavelengths were fitted to the appropriate rate equations in order to obtain the pertinent second-order rate constants. All reactions were carried out at least in triplicate. The *k* values are reported in Table 1. The rate constants for the bromination in methanol were obtained both directly from measurements carried out in the absence of external Br^- and, in several cases, by plots[15] of eq 3 (Table S1). Very satisfactory overall second-order kinetics were always found and very similar or identical values of *k* were obtained by the two methods. The kinetic constants for bromination in all the other solvents were, therefore, measured in the absence of Br^-.

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Supporting Information Available: Kinetic bromide ion effects, product distributions, physical constants, and ^{1}H NMR data of olefins **6**−**11**, of the corresponding dibromides, bromohydrins, acetoxy bromides, and methoxy bromides (13 pages). See any current masthead page for ordering and Internet access instructions.

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