Broad Spectrum Methods for the Resolution of Optical Isomers. A Discussion of the Reasons Underlying the Chromatographic Separability of Some Diastereomeric Carbamates

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Diastereomeric pairs of carbamates (**4a, b–26a, b**) were synthesized and separated chromatographically on a preparative scale. These carbamate diastereomers display a correlation between structure, stereochemistry, and elution order. In addition, consistent NMR spectral differences observed between pairs of diastereomers correlate with established stereochemistry. These spectral correlations, $Eu(fod)_3$ gradients, and "acylation shifts" indicate that the carbamate diastereomers uniformly show a preference for solution conformations **2a** and **2b**. The population of these conformations in solution appears related to the origin of the chromatographic separability of the diastereomers and a rationale for this relationship is presented. All of the diastereomeric carbamates so investigated show evidence of a dynamic equilibrium between the *E* and *Z* (*Z*:*E* ≃ 90:10) rotamers at 220 MHz and 27 °C in the presence of $Eu(fod)_3$. The possible effect of such an equilibrium on the chromatographic separability of these diastereomers is discussed.

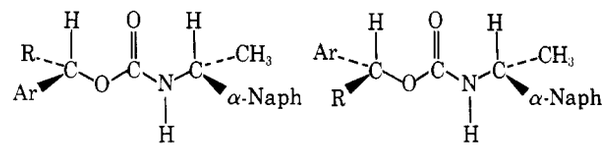
We recently reported[1] the resolution of 2,2,2-trifluoro-1-(1-naphthyl)ethanol, a useful chiral solvating agent, via the automated multigram chromatographic separation[2] of diastereomeric carbamate derivatives. In this paper, we address ourselves to the reasons underlying the chromatographic separability of this and other structurally similar carbamate diastereomers.

On the basis of our own work and the pioneering efforts of others, we feel that most "first time" resolutions of enantiomers will soon be effected almost solely by liquid chromatographic techniques. Historically, the usual approach to resolution has involved an empirical search for a chiral derivatizing agent (CDA) that will convert the racemate into a mixture of diastereomers separable by fractional crystallization.[3] This approach can be time consuming, inefficient in overall yield, and may provide but one enantiomer in appreciable (but possibly uncertain) optical purity. In contrast, the chromatographic behavior of many diastereomers will follow systematic rules that, once understood, will allow rational selection of CDA that afford predictable separations of the diastereomers. The widely held view that liquid chromatography is a cumbersome method for effecting preparative scale separations is obsolete; our recent reports[1,2] give a clear portent as to the future of large scale chromatographically effected resolutions. Apart from their potential predictability, chromatographic resolutions will generally afford both enantiomers in high yield and high optical purities. Finally, CDA of known absolute configuration potentially provide information concerning the absolute configurations of the derivatized solutes through differences in the spectral and chromatographic properties of the diastereomeric derivatives.

Results and Discussion

Chromatographic Behavior. The diastereomers derived from reaction of alkylarylcarbinols with chiral 1-(1-naphthyl)ethyl isocyanate[4] (1) are generally separable on a preparative scale by chromatography on alumina with benzene (Table I). In the present instances, we observe a correlation between structure, stereochemistry, and elution order of these diastereomers. The stereochemistry of the diastereomers entered in Table I has been determined by hydrolysis of the separated diastereomers and determination[5] of the absolute configuration of the liberated alcohols. We also note consistent NMR spectral differences between diastereomers that correlate with stereochemistry and thereby suggest uniform conformational behavior for these carbamates.

A recent NMR study[6] of esterlike derivatives of secondary alcohols similar to those presently employed discusses the use of "acylation shifts" and $Eu(fod)_3$ gradients to support carbinyl hydrogen bonding (CHB) as an effective agent for conformational control. As a consequence of CHB, the carbamate conformations (or their weighted time-averaged equivalents) depicted in **2a** and **2b** are thought to be substantially populated in nonpolar solvents. These conformations account for the consistent chemical shift differences observed (Table I) between the methyl doublets of diastereomeric pairs **4a,b–21a,b,** as well as the correlation of the sense of this chemical shift difference with known stereochemistry. Owing to the shielding effect of the cis aryl group, the methyl doublet resonance of **2b** occurs upfield to that of **2a.** To avoid continual recourse to stereochemical convention, these carbamate diastereomers are designated as "erythroid", **2a,** and "threoid", **2b.** These depicted conformations also represent a useful



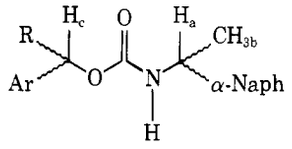
2a erythroid 2b threoid

initial vantage point for consideration of the observed correlations between structure, stereochemistry, and elution order as well as the NMR–stereochemical correlation. Although a more detailed conformational discussion is subsequently presented, we presently point out that the natures of the alkyl and aryl substituents appear to play but secondary roles in determining "backbone" conformational preferences for the diastereomers in Table I.

Mechanisms of Chromatographic Separation. There are two limiting general mechanisms for separation by adsorption chromatography. At one extreme, separability derives entirely from differential solvation of the solutes by the elution solvent. At the other,[7] separability stems solely from differential probabilities for or energies of adsorption for solutes and is independent of the solvent. A blend of both processes is operative in the separation of diastereomers.[8] Helmchen,[9] among others,[10] has used the concept of differential ease of approach to the adsorbent in rationalizing the separation of certain kinds of diastereomers by liquid chromatography. This rationale is closely related to that used earlier by Karger and co-workers[8,11a–c] to explain the gas chromatographic separability of diastereomeric esters and amides.

Helmchen's rationale, pertinent to our results, stems from

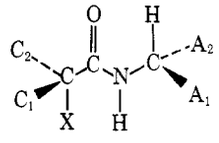
Table I. NMR and Chromatographic Properties of Some Carbamate Diastereomers



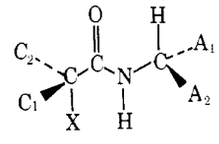
Compd	R	Ar	Chemical shift data[d] δ_a	δ_b	$\Delta\delta_a$[e]	$\Delta\delta_b$[e]	δ_c	$\Delta\delta_c$[e]	Chromatographic data K_1'	K_2'	α	Mp,[i] °C High R_f	Low R_f
4	CF_3	C_6H_5	5.54	1.48	0.01	0.05	6.04	0.00	3.3	5.2	1.58	130–131	120–121
5	CF_3	p-$CH_3C_6H_4$	5.62	1.54	0.02	0.04	6.06	0.00	2.9	4.4	1.52	137–139	133–133.5
6	CF_3	p-FC_6H_4	5.61	1.62	−0.03	0.04	6.18	0.02	2.4	4.9	2.04	131–133	130–131
7	CF_3	m-NO_2-C_6H_4	5.67	1.61	−0.05	0.07	6.26	0.00			1.58	137–139	
8	CF_3	α-Naph	5.58	1.46	0.02	0.08	7.02	0.01	3.0	4.7	1.56	139–140	123
9	CF_3	3-Pyrenyl	5.67	1.60	0.03	0.12	>7.00[g]		3.2	5.4	1.64	186–188	190
10	CF_3	9-Anthryl	5.50	1.56	−0.10	−0.36	>7.00[g]		3.8	5.3	1.40		
11	CF_3	10-CH_3-9-anthryl	5.42	1.55	0.03	−0.42	>7.00[g]		2.4	3.2	1.33	115–118	110
12	C_3F_7	C_6H_5	5.60	1.54	0.03	0.14	6.26	0.02	1.7	3.6	2.12	141–143	122–122.5
13	C_3F_7	α-Naph	5.57	1.44	0.04	0.14	>7.00[g]		1.7	3.6	2.12	j	j
14	C_3F_7	9-Anthryl	5.40	1.29	0.00	0.20	>7.00[g]				1.00	j	j
15	CBr_3	C_6H_5	5.62	1.62	0.00	0.07	6.27	0.01	6.0	9.3	1.55	j	j
16	CH_3	C_6H_5	5.55	1.44	−0.05	−0.08	5.71	0.00	15.0	19.5	1.30	j	j
17	CH_3	α-Naph[f]	5.67	1.62	0.01	−0.06	f	f			1.20	j	j
18	C_2H_5	α-Naph	5.64	1.58	0.00	0.08	6.44	0.00			1.25	j	j
19	C_2H_5	C_6H_5	5.37	1.50	0.02	0.08	5.57	0.02			1.22[h]	j	j
20	$C(CH_3)_3$	α-Naph	5.65	1.52	−0.11	0.08	6.45	−0.05	18.0	23.5	1.31	j	j
21	$C(CH_3)_3$	C_6H_5	5.48	1.46	−0.04	0.14	5.44	−0.08	25.2	33.7	1.30	j	j

[d] Chemical shifts (δ) are given for the *low* R_f diastereomer in parts per million, downfield of Me_4Si. [e] $\Delta\delta = \delta_{\text{high } R_f} - \delta_{\text{low } R_f}$. [f] Data for *l-d* substituted diastereomer. [g] Buried in the aromatic region. [h] This carbamate was chromatographed on silica gel with CH_2Cl_2–hexane (7:3). [i] All of the carbamates in this table gave satisfactory mass spectra or elemental analyses or both. [j] Not determined.

the observation that the diastereomers of certain amides appear to preferentially populate conformations **3a** and **3b** in



3a



3b

solution. The diastereomers having the smallest A and the smallest C substituents on the same conformational face are found to be chromatographically the least mobile, and Helmchen suggests that steric hindrance of approach to the adsorbent determines elution order. Feibush[12] has expressed this same concept in terms of "bulkiness chirality".

Despite the success of the steric "ease of approach" type model, it is conceptually bothersome to suppose that the conformational behavior in solution of conformationally mobile molecules will exert control over chromatographic behavior. If two diastereomers are chromatographically separable, it is because their energies of adsorption are nonidentical. Conformation *while adsorbed* is surely relevant to adsorption energy. However, little is known about conformations of adsorbed molecules and they may be unlike those populated in solution. In general, the energy provided by adsorption of a moderately polar molecule upon silica gel or alumina should be great enough to disrupt most *solution* conformations should they be unfavorable *adsorption* conformations. If adsorption does cause conformational change, then the possibility arises that adsorption energies for separable diastereomers may differ, at least in part, because the energies required to disrupt the solution conformations of the diastereomers are different. Thus, diastereomers having stereochemically dependent intramolecular interactions should generally be separable by chromatography. For example, erythro and threo diol diastereomers differ in their degrees of intramolecular hydrogen bonding and hence also in their chromatographic behavior.[8] However, in Helmchen's amides,[15] in Karger's esters and amides, and in our carbamates, there is no reason to suspect the existence of significant differences in conformational "disruption energies" between diastereomers. Nevertheless, the diastereomers are chromatographically separable and the separations improve with a restriction of conformational mobility.[16] From the correlation noted between the solution conformations of a series of diastereomeric carbamates, structure, and stereochemistry, we infer that carbamate conformations *while adsorbed* are rather similar to those noted in solution. This surprising inference cannot be directly substantiated, yet it is consistent with a body of data.

In the case of the presently discussed carbamates, the principal adsorption site(s) presumably lies between the chiral centers. Hence, the most important aspects of conformational control are those that govern the spatial relationship of one chiral assembly with respect to the other. In carbamate conformations **2a** and **2b**, conformational control and rigidity is provided by carbinyl hydrogen bonding (CHB).[6] Superimposed upon this "backbone" effect will be conformational preferences of backbone substituents (i.e., the alkyl and aryl groups) and possible interactions between these substituents and the adsorbent.

Assuming the preferential population of conformations similar to **2a** and **2b**, it is clear from the elution orders in Table I that the Karger–Helmchen steric ease of approach model is only partially successful. For example, for methyl bearing carbamates **16** and **17**, the elution order is that expected on the basis of this model, in that the threoid isomers are the first to be eluted. For these diastereomers the erythroid isomer bears both "small" groups (i.e., the methyls) on the same face of the backbone and is expected to be most strongly adsorbed.

Unexpectedly, the elution order of the diastereomers *inverts* when R is *ethyl, propyl, trifluoromethyl,* etc. In terms of van der Waals radii, these groups are smaller than phenyl or other aryl substituents and no inversion of steric order has occurred.

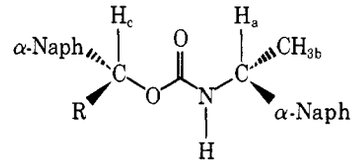
A serious omission of the steric model is that it neglects other possible modes of interaction between substituents and adsorbent. Even a partial understanding of the chromatographic behavior of diastereomers requires not only conformational knowledge but also an appreciation of the "effectiveness scale" for the ability of substituents to ward off (or bind to) the stationary phase. In the case of a homologous series of alkyl groups, "warding off" ability might well parallel size even though steric bulk alone may not be the *principal* source of this effect.

Insofar as silica gel or alumina presents a relatively polar surface to approaching molecules, the substituent "effectiveness scale" that seems to offer the best means for fitting the chromatographic behavior of carbamate diastereomers to an ease of approach type model is a "hydrophobic" scale. Bearing in mind that backbone rigidity has a marked chromatographic consequence, it appears that the "warding off" effect increases in the sequence methyl < phenyl ≈ ethyl < *n*-propyl < *tert*-butyl ≪ trifluoromethyl < heptafluoropropyl. The relative magnitudes of these "warding off" effects cannot be quantitatively ascertained for it must be borne in mind that the magnitude of such an effect is probably not independent of the other substituents present.

Introduction of trifluoromethyl groups onto the carbamate backbone has not seriously altered solution conformations judging by the consistent chemical shift differences observed between diastereomers. Trifluoromethyl groups are known to be quite hydrophobic[17] and appear to be extremely effective in "warding off" the polar adsorbent and reducing the probability that the carbamate will be adsorbed from the face presenting this group. This effect suffices to account for the "inverted" (from steric consideration only)[18] elution orders and for the hastened elution of both diastereomers relative to those of the nonfluorinated analogues. When the probability for adsorption from the trifluoromethyl bearing face is low, it makes little additional difference as to the identity (i.e., alkyl vs. aryl) of the second group of this face (provided that it is relatively nonpolar). The probability that adsorption will occur from the opposite face is somewhat greater and is significantly influenced by the identity of the second group. Thus, the overall adsorption probability for the trifluoromethyl carbamates is higher for the diastereomer having the aryl groups trans to one another. The improvements in chromatographic separability of the diastereomers that attend the trifluoromethyl substituents is presumed to stem largely from the increased degree of conformational control that this group confers through enhanced carbinyl hydrogen bonding.[6] The 9-anthryl substituted carbamates **10a,b** and **11a,b** are anomalous in that the usual elution order is inverted, presumably as a consequence of the greater "warding off" ability of 9-anthryl than trifluoromethyl. Elution order is normal for **14a,b** since the (now) greater hydrophobicity of heptafluoropropyl dominates the effect of the 9-anthryl substituent. These carbamate diastereomers show no anomalies in the chemical shift difference–stereochemical correlation, suggesting that no appreciable alteration of backbone conformation has occurred.

The present model says nothing about the site(s) of interaction of the adsorbent with the carbamate diastereomers. Although one might intuitively expect the carbonyl oxygen to be the major site for interaction with the adsorbent, the observation (subsequently to be discussed) that the αs and K's increase in the order acidic < neutral < basic alumina and the much reduced K' (and α) values for analogous N-methylated carbamate diastereomers leads to speculation that perhaps the hydrogen on nitrogen plays some role in the adsorption process. Identification of the site(s) at which adsorption occurs is of interest and importance even though the present model does *not* hinge upon explicit identification of this site. However, the model does imply that adsorption occurs principally in the central polar region of the carbamate between the chiral carbons.

Table II. $Eu(fod)_3$ Induced Chemical Shift Gradients for Aryl Alkyl Carbamates



	Gradient,[a] ppm/mol $Eu(fod)_3$ in CCl_4		
R	H_a	H_b	H_c
CF_3	4.3	2.6	8.7
CH_3	5.7	3.7	7.4

[a] Gradients are presented as least-squares slopes of the essentially linear portion of the curves noted for $Eu(fod)_3$: substrate ratios of less than 0.2. The correlation coefficients of the least-squares slopes range from 0.999 to 0.988.

The chromatographic data in Table I were obtained using a 1 × 26 cm column packed with Woelm 18–32 μ neutral alumina and benzene eluent. The activity and increased surface area of this adsorbent cause the K' values reported to be somewhat larger than those observed on the adsorbent (Brinkmann 63–200 μ neutral alumina) used in the large (5 × 120 cm) multigram columns. However, α values are relatively unchanged. Acidic alumina affords smaller αs and K's than does neutral alumina of the same brand and particle size whereas basic alumina affords increased α and K' values. Silica gel is usually less effective than alumina for separating these diastereomers, although there are exceptions to this generalization. Variation of adsorbent or solvent has thus far produced no change in elution order. Increases in the polarity of the eluting solvent hastens elution and lessens α. Presumably, this latter diminution stems from less effective conformational control (by intramolecular carbinyl hydrogen bonding).

Solution Conformations. From magnitudes of the $Eu(fod)_3$ induced chemical shift gradients [ppm/mol $Eu(fod)_3$] shown in Table II, it is evident that both the carbinyl and methine hydrogens are near the site of $Eu(fod)_3$ coordination, the carbonyl oxygen.[19-21] The effect of the electronegative trifluoromethyl is to enhance the degree of CHB and to decrease the extent of coordination by $Eu(fod)_3$ to carbonyl oxygen. Enhanced CHB is noted in Table II by the relatively larger gradients for the carbinyl than for the methine proton when R is trifluoromethyl rather than methyl. Similarly, a reduced coordination level is indicated by the lesser methine and methyl (i.e., H_b) gradients for the fluorinated carbamates relative to the nonfluorinated analogues. This inference is strengthened by the results of competition experiments on structurally similar carbamates.[6] Significantly, the erythroid and threoid diastereomers do not preceptably differ in their $Eu(fod)_3$ gradients as evidenced by representative data in Table III. This suggests that $Eu(fod)_3$ does not discern appreciably between diastereomers and is consistent with the two diastereomers having solution conformations similar to **2a,b** (or the weighted, time-averaged equivalent) and the $Eu(fod)_3$–oxygen bond lying essentially along the carbon–oxygen axis of the carbonyl group. It cannot be rigorously inferred that $Eu(fod)_3$ binds differently to the carbamates

Table III. Eu(fod)$_3$ Induced Chemical Shift Gradients and Chemical Shift Data for Diastereomeric Pairs of Carbamates

			Gradient,[d] ppm/mol Eu(fod)$_3$ in CCl_4					Chemical shift data[f]								
Compd	R	R$_1$	H$_a$	H$_b$	H$_c$	Elution order	α[e]	δ_a	δ_b	δ_c	$\Delta\delta_a$[g]	$\Delta\delta_b$[g]	$\Delta\delta_c$[g]	δR^h	δR$_1$[h]	$\Delta\delta$RR$_1$[i]	$\Delta\delta$R$_1$R$'$[j]	Mp,[k] °C
22a	Methyl	Ethynyl	3.80	1.05	3.41	High R_f	1.13	5.66	1.65	5.45	−0.02	−0.01	0.01	1.49	2.49	−0.02	0.05	116
22b	Ethynyl	Methyl	3.69	1.09	3.26	Low R_f		5.68	1.66	5.44				2.44	1.51			116
23a	Ethyl	Ethynyl	4.90	1.85	4.55	High R_f	1.21	5.68	1.65	5.33	−0.02	−0.04	0.00	0.96	2.48	−0.10	0.02	91
23b	Ethynyl	Ethyl	4.78	1.88	4.29	Low R_f		5.70	1.69	5.33				2.46	1.06			119,
24a	n-Butyl	Ethynyl	2.44	0.89	2.44	High R_f	1.27	5.68	1.63	5.36	−0.02	−0.03	0.01	0.88	2.49	−0.06	0.04	110
24b	Ethynyl	n-Butyl	2.22	1.28	2.32	Low R_f		5.70	1.66	5.35				2.45	0.94			95
8a	α-Naph	CF_3	4.40	2.50	8.80	High R_f	1.56	5.54	1.54	7.03	−0.04	0.08	0.01					139–140
8b	CF_3	α-Naph	4.30	2.60	8.70	Low R_f		5.58	1.46	7.02								123

[d] Gradients are presented as least-squares slopes of the essentially linear portion of the curves noted for Eu(fod)$_3$:substrate ratios of less than 0.2. The correlation coefficients of the least-squares slopes range from 0.998 to 0.989. [e] These carbamates were chromatographed on silica gel with CH_2Cl_2–hexane (7:3). [f] Chemical shifts (δ) are in parts per million downfield of Me_4Si. [g] $\Delta\delta = \delta_{high\ Rf} - \delta_{low\ Rf}$. [h] For ethyl and n-butyl substituents, δ refers to the chemical shift of the methyl protons distal to the carbinyl carbon. [i] $\Delta\delta RR_1$ refers to the chemical shift difference between the entry for R of diastereomer a and the entry for R$_1$ of diastereomer b, for a given pair of diastereomers. [j] $\Delta\delta R_1R$ refers to the chemical shift difference between the entry for R$_1$ of diastereomer a and the entry for R of diastereomer b, for a given pair of diastereomers. [k] All the carbamates in this table gave satisfactory elemental analyses and mass spectra.

than does alumina (or silica) simply because the shift reagent shows no marked preferential binding to one diastereomer whereas the adsorbents do. "Warding off" effects by substituents may be rather different toward Eu(fod)$_3$ than for an adsorbent.

Table III also contains chromatographic data for the diastereomeric carbamates derived from some acetylenic alcohols. The usual correlations between NMR spectral differences, elution order, and stereochemistry are observed for diastereomeric pairs **22a,b–24a,b.** One infers that ethynyl groups are more effective in warding off the adsorbent than methyl, ethyl, or n-butyl groups.

Shift reagent studies similar to those just described show that there is no notable alteration in backbone conformation between diastereomers **17a,b** and **18a,b,** even though an *inversion* in elution order of the diastereomers occurs. For these diastereomers, the Eu(fod)$_3$ gradients for each of the erythroid and threoid isomers indicate the carbinyl and methine protons to be in close proximity to the carbonyl oxygen, and the alkyl substituents to be equivalently disposed with respect to the backbone structure.

Conformational Equilibria. The Eu(fod)$_3$ experiments conducted on compounds appearing in Tables II and III were carried out at 220 MHz and at 27 °C. In the absence of shift reagent there were no spurious signals in the spectra of any of these diastereomers. However, upon incremental addition of Eu(fod)$_3$, all diastereomers so investigated gave rise to minor resonances, which were taken to indicate the "freezing out" of a dynamic equilibrium between the Z and E rotamers owing to hindered rotation about the carbonyl carbon–nitrogen bond.

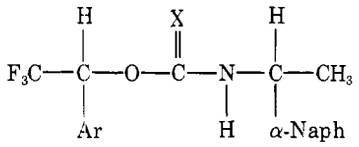
In the absence of shift reagent, the Z rotamer is more heavily populated than the E rotamer. However, the latter is

Z E

coordinated more strongly by Eu(fod)$_3$, and with increasing amounts of shift reagent, the observed time averaged ratio of Z:E rotamers progressively diminishes. Because of its greater binding toward Eu(fod)$_3$, the minor E rotamer shows larger gradients than the Z rotamer at the concentrations of shift reagent utilized. These data are readily rationalized on steric and electronic grounds. Coordination to Eu(fod)$_3$ occurs most readily when the larger group on nitrogen (the chiral assembly) is trans anti-periplanar to the carbonyl oxygen and no competing CHB from the methine hydrogen is possible. Extrapolation of the observed Z:E ratios to zero Eu(fod)$_3$ concentration indicates an initial ca. 90:10 rotamer mixture for all the carbamates so investigated. Apparently, the nature of the alkoxyl portion of the carbamate normally has little effect upon this ratio. Owing to the minor amount of the E rotamer originally present and its spectral similarity to the Z rotamer, the presence of the E rotamer can seldom be detected without the addition of shift reagent.

The population of the E rotamer has possible implications with regard to the chromatographic separability to the diastereomeric carbamates. To whatever extent coordination to Eu(fod)$_3$ resembles the adsorption process, one might expect the E rotamers to be more strongly adsorbed than the Z rotamers. Moreover, the E rotamer may have opposite relative placements of the backbone substituents and might consequentially tend to invert the elution orders of diastereomers relative to that which would be observed were only the Z rotamers populated. Data concerning E rotamer conformation

Table IV. Comparative NMR and Chromatographic Data (Carbamate vs. Thiocarbamate)



No.	X	Ar	$\Delta\delta^a$ (CH_3)/ field sense	High R_f	α
26	S	Phenyl	0.08 low	Erythroid	1.29
4	O	Phenyl	0.05 low	Erythroid	1.58

$^a \Delta\delta = \delta_{CH_3 \text{ high } R_f} - \delta_{CH_3 \text{ low } R_f}$.

are difficult to extract from shift reagent studies since most *E* resonances are buried beneath the major *Z* resonances.

To determine the solution and chromatographic effects of less preferential population of *Z* rotamers **2a,b**, the diastereomeric carbamates **25a,b** derived from the chloroformate of (±)-1-(1-naphthyl)-2,2,2-trifluoroethanol and (*S*)-(−)-*N*-methyl-α-phenylethylamine were prepared and studied.

Both N-methylated diastereomers give NMR evidence of hindered rotation at 28 °C and 100 MHz in the *absence* of shift reagent and the relative ratio of the *E* and *Z* rotamers is nearly unity. Under chromatographic conditions that easily separate the diastereomers of the nonmethylated carbamates, the N-methylated diastereomers elute rather more rapidly and give little separation (compare, for example, the α value of carbamate **4** with that of the N-methylated analogue, 1.58 vs. 1.15). Use of less polar solvents increases the α value somewhat, but not to the magnitude of the nonmethylated analogues. The chromatographic behavior of the N-methylated carbamate diastereomers further supports the view that the chromatographic separability of these diastereomers is linked to the extensive population of one type of solution conformation. Finally, as an additional test of the observed chromatographic patterns, a pair of diastereomeric trifluoromethyl thiocarbamates **26a,b** were synthesized[23] and chromatographed. It may be seen (Table IV) that replacement of carbonyl oxygen with sulfur affects neither elution order (i.e., erythroid is first eluted) nor sense of NMR spectral differences. However, the thiocarbamates do not separate as well as their carbamate analogues.

In summary, we note that the preceding chromatographic rationale offers a foundation upon which the rational design of improved chromatographic resolving agents may be based. Clearly, the use of CDA which afford conformationally restricted diastereomeric derivatives will facilitate the chromatographic separation of these derivatives as will incorporation of substituents such as perfluoroalkyls that are capable of translating their necessarily different stereochemical arrangement into differential probabilities of adsorption for the diastereomers.

Experimental Section

^1H NMR spectra were obtained with Varian Associates A-60A, A56-60, HA-100, or HR-220 instruments. Chromatographic data in Table I were obtained upon Woelm 18–32 μ neutral alumina using benzene eluent. In many cases crude reaction mixtures were preparatively separated as described on 5 × 120 cm columns of Brinkmann 63–200 μ neutral alumina, again using benzene eluent. In all cases the effluent was monitored at 280 nm.

Carbamates. All carbamates[25] used in this study were prepared via one of two procedures.

Procedure A. A mixture of racemic alcohol (ca. 4.5 mmol), (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (0.89 g, 4.5 mmol), and *N,N*-dimethylethanolamine (1 wt %) in benzene (50 mL) was heated to 80 °C for 24–36 h, at which time the isocyanate band at 2260 cm^{-1} had mostly disappeared. Longer reflux times did not substantially increase yields, but rather caused cracking of the product. The mixture was chromatographed directly upon a preparative HPLC system using benzene–alumina. The effluent was monitored at 280 nm.

Procedure B. To a solution of phosgene (1.47 g, 15 mmol) in 15 mL of dry toluene[24] cooled to −5 °C was added dropwise a solution of racemic carbinol (ca. 7.5 mmol) and triethylamine (0.76 g, 7.5 mmol) in 25 mL of dry toluene.[24] After addition was completed, stirring was continued for 30 min at 0 °C. The amine hydrochloride was then removed by filtration under nitrogen and the filtrate concentrated at reduced pressure (ca. 50 mmHg) with heating (40–50 °C).

The crude chloroformate and 25 mL of CH_2Cl_2 were then placed in a three-necked round-bottom flask equipped with overhead stirrer, nitrogen inlet, and vented dropping funnel. A solution of triethylamine (0.76 g, 7.5 mmol), (*R*)-(+)-1-(1-naphthyl)ethylamine (1.28 g, 7.5 mmol), and 25 mL of CH_2Cl_2 was then added dropwise and stirring was continued overnight at room temperature. The reaction mixture was washed with two 50-mL portions of 3 N HCl and the organic layer dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated (ca. 50 mmHg, 30 °C) and the mixed carbamates chromatographed as described.

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Registry No.—**4a,** 61787-33-5; **4b,** 61787-34-6; **5a,** 61787-35-7; **5b,** 61787-36-8; **6a,** 61787-37-9; **6b,** 61787-38-0; **7a,** 61787-39-1; **7b,** 61787-40-4; **8a,** 61848-81-5; **8b,** 61848-82-6; **9a,** 61787-41-5; **9b,** 61787-42-6; **10a,** 61787-43-7; **10b,** 61787-44-8; **11a,** 61787-45-9; **11b,** 61787-46-0; **12a,** 61848-83-7; **12b,** 61848-84-8; **13a,** 61787-47-1; **13b,** 61787-48-2; **14a,** 61787-49-3; **14b,** 61787-50-6; **15a,** 61787-51-7; **15b,** 61787-52-8; **16a,** 61787-53-9; **16b,** 61787-53-9; **17a,** 61787-54-0; **17b,** 61787-55-1; **18a,** 61787-56-2; **18b,** 61787-57-3; **19a,** 61787-58-4; **19b,** 61787-59-5; **20a,** 61787-60-8; **20b,** 61787-61-9; **21a,** 61787-62-0; **21b,** 61787-63-1; **22a,** 61787-64-2; **22b,** 61787-65-3; **23a,** 61787-66-4; **23b,** 61787-67-5; **24a,** 61787-68-6; **24b,** 61787-69-7; **25a,** 61787-70-0; **25b,** 61787-71-1; **26a,** 61787-72-2; **26b,** 61787-73-3; (+)-1-(1-naphthyl)-2,2,2-trifluoroethanol, 17556-44-4; (*S*)-(−)-*N*-methyl-α-phenylethylamine, 19131-99-8.

Supplementary Material Available. Spectral data (NMR, IR, and mass spectra) as well as elemental analyses (15 pages). Ordering information is given on any current masthead page.

References and Notes

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(3) For example, of approximately 1200 "practical resolutions" listed in S. H. Wilen, "Table of Resolving Agents and Optical Resolutions", University of Notre Dame Press, Notre Dame, Ind., 1972, and occurring between 1950 and 1970, only 35 are indicated to involve chromatographic techniques. Not all of these involve the separation of diastereomers but include the use of chiral stationary phases such as quartz or cellulose acetate.
(4) Diastereomeric carbamates derived from 1-phenylethyl isocyanate have previously been separated on an analytical scale by thin layer and gas chromatography.[13,14] This reagent has been used to convert most of the carbinols appearing in Table I into diastereomeric carbamates. Without exception, these diastereomers do *not* separate as well as the 1-naphthylethyl analogues. However, elution orders and senses of NMR nonequivalence are the same for both series of diastereomers.
(5) Where absolute configurations had previously been assigned (see W. Klyne and J. Buckingham, "Atlas of Stereochemistry", Oxford University Press, New York, N.Y., 1974, for a useful compilation) polarimetry could be used. In most instances, however, configurations were determined by NMR (using chiral solvating agents of known configuration) and have not been reported previously. Although a more complete description of this method will appear elsewhere, our earlier report [W. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **89,** 4585 (1967)] is illustrative of the technique.
(6) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **41,** 801 (1976).
(7) These extremes can be realized during the separation of enantiomers upon either an achiral adsorbent using a chiral eluent or a chiral adsorbent using an achiral eluent. Both types of resolutions are known.
(8) For an excellent and extensive review of the separation of diastereomers by gas chromatography, see E. Gil-Av and D. Nurok, *Adv. Chromatogr.*, **10,** 99 (1975). Possible mechanisms of such separations are thoroughly discussed. We wish to emphasize that several of the separation mechanisms considered in this paper are antedated by the work of others even though such work is largely confined to gas chromatography.
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(12) B. Feibush, *Anal. Chem.*, **43,** 1098 (1971).

(13) W. Freytag and K. H. Ney, *J. Chromatogr.*, **41**, 473 (1969).
(14) M. Hamberg, *Chem. Phys. Lipids*, **6**, 152 (1971).
(15) Helmchen believes[9] that, in view of the distances involved, the C substituents do not interact with the A substituents.
(16) The consequences of conformational immobility have been recognized and demonstrated[11b,c] insofar as diastereomeric amides derived from some chiral cyclic acids and chiral cyclic amines separate better than those similarly derived from acyclic components.
(17) M. Hudlicky, "Chemistry of Organic Fluorine Compounds", Macmillan, New York, N.Y., 1961, p 304, and references cited therein.
(18) When the diastereomeric carbamates derived from (±)-1,1,1-trifluoro-3,3-dimethyl-2-butanol and (+)-1-(1-naphthyl)ethylamine are chromatographed, the diastereomer which has *tert*-butyl and α-naphthyl on the *same* face (erythroid) is *first* eluted. Since the van der Waals radius of *tert*-butyl is larger than trifluoromethyl (6.1 vs. 5.1 Å respectively), this elution order reflects that the greater "warding off" effect of the trifluoromethyl group is not simply steric in nature, but has other origins.
(19) C. S. Springer, Jr., S. R. Tahny, and M. Pickering, *J. Am. Chem. Soc.*, **95**, 6227 (1973).
(20) R. A. Bauman, *Tetrahedron Lett.*, 419 (1971).
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(22) H. Kessler and M. Molter, *J. Am. Chem. Soc.*, **98**, 5969 (1976).
(23) Thiocarbamates with Ar = α-naphthyl and Ar = 9-anthryl were also synthesized. Although NMR and chromatographic properties appear to be analogous to those of the corresponding carbamates, the instability of these thiocarbamates did not permit thorough characterization.
(24) Diethyl ether, tetrahydrofuran, and methylene chloride as well as toluene may be used as solvents with essentially *no* diminishment in overall yield.
(25) Ethynyl carbamates were prepared by C. Boeder.

Solid Phase and Solution Photochemistry of Coumalate Esters

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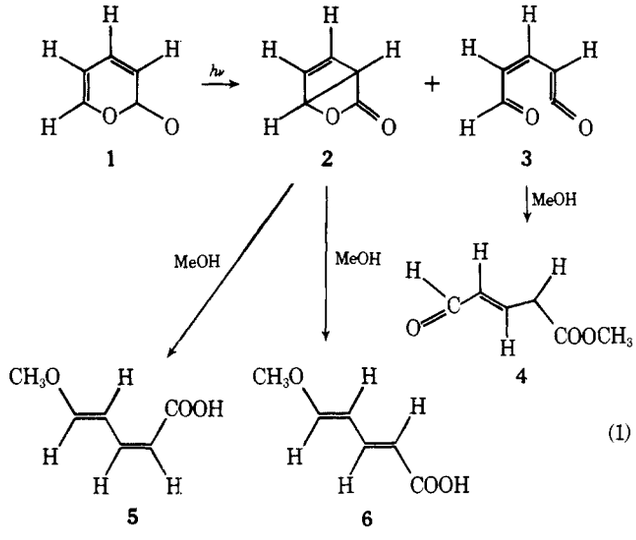
Photochemical reactions of coumalic acid (**12**) and its methyl, isopropyl, and benzyl esters have been investigated in solution and in the solid phase. In solution the photochemistry has been carried out in hydroxylic and nonhydroxylic solvents as well as in ethyl bromide. In the solid phase, the reaction has been studied in a potassium bromide matrix and as a sandwich between quartz plates. A particularly interesting effect of KBr, suggested to be a heavy atom effect of the matrix, has been observed in the photochemical reactions of coumalate esters.

The photochemistry of α-pyrone (**1**) and its derivatives has been the subject of several studies and the systems have proven to be rich in variation.[1-10] In spite of their apparent complexity, however, all the observed unimolecular primary photoproducts arise from the critical intermediates bicyclic lactone **2** and ketene **3** (eq 1). Thus, irradiation of α-pyrone

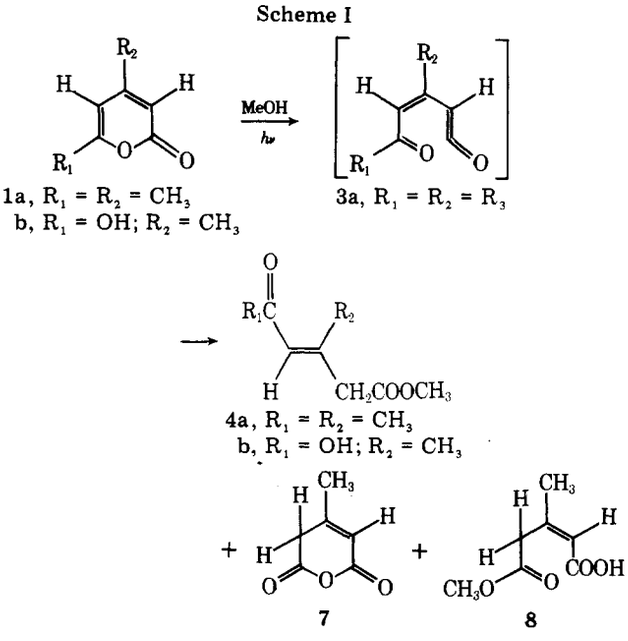


1 2 3 4 5 6 (1)

in ether at 300 nm produces only isolable **2** in quantitative yield[1-3] while in methanol under similar conditions, the three noncyclic products **4**, **5**, and **6** result. Compound **4** has been shown to derive from ketene **3**, whereas **5** and **6** are from the photolactone **2**.

Intermediate ketenes like **3** have been the subject of several studies. The current view is that, in the case of α-pyrone[2,3,9] and certain properly substituted ones,[5,6] such ketenes form, though in apparently analogous cases[8] ketenes seem not important. Thus irradiation of 4,6-dimethyl-2-pyrone (**1a**) in methanol produces **4a** through ketene **3a**[2], while 4-hydroxy-6-methyl-2-pyrone (**1b**), when irradiated in methanol, produces **4b** (in tautomeric form) in addition to anhydride **7**. The half-ester **8** which originates from lactone **2b**[6] is also formed, Scheme I. The analogous 4-methoxy-6-methyl-2-pyrone (**1c**),

Scheme I



1a, $R_1 = R_2 = CH_3$
b, $R_1 = OH$; $R_2 = CH_3$

3a, $R_1 = R_2 = R_3$

4a, $R_1 = R_2 = CH_3$
b, $R_1 = OH$; $R_2 = CH_3$

7 8

when irradiated in water at 300 nm, produces the half-esters **9a** and **10a** and the corresponding diacids **9b** and **10b**. Both these products are said to originate from lactone **2c**[5] (eq 2).

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