Equilibration of Diastereomeric Two-Chain Surfactants. Hydrophobic Control of Organic Stereochemistry

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Abstract: Four two-chain dicarboxylic acid surfactants linked with a carbonyl group were synthesized and studied. The compounds exist as meso and (±) diastereomers, and they form aggregates, presumably micelles, at concentrations $>10^{-5}$ M. Equilibration of the diacids in benzene at 60 °C (*p*-toluenesulfonic acid catalyst) gives a 50/50 mixture of meso and (±) diastereomers. Equilibration of the diacids in aqueous base with or without added cosurfactants (CTAB, DDAB) gives mixtures favoring the meso diastereomer by as much as 90/10. This perturbation of diastereomeric equilibria is discussed in terms of hydrophobic enforcement of organic stereochemistry.

Control of molecular stereochemistry has been a primary concern of organic chemists.[1-3] Recent advances in the synthesis of asymmetric compounds by either substrate or reagent[4-6] control rely primarily on the expression of classical steric effects in diastereomeric transition states.[3] An understanding of the fundamental aspects of these steric effects (i.e., $CH_3 > H$) was developed in studies of the stability and reactivity of simple ring systems[3] (e.g., equilibration of substituted cyclohexanes or hydrolysis of fused-ring carbocyclic esters). Thus, the recent elegant examples of acyclic stereocontrol[4-6] rely primarily on the fundamental ideas of steric interactions in ring systems developed in the 1950s. While energies involved in these steric interactions may be only on the order of 1.5-2.0 kcal/mol, the resulting stereochemical bias has played a central role in organic chemistry over the past 30 years.

We have embarked on a study of the control of organic stereochemistry by the use of molecular aggregates and the hydrophobic effect. While aggregation phenomena have been the focus of many studies associated with chemoselectivity and regioselectivity, few examples of stereoselective transformations controlled by aggregates, such as micelles and lipid bilayers, have been published.[7-14] In order to provide a fundamental framework for understanding the interaction of two or more stereocenters in molecular aggregates, we have prepared and studied a series of diastereomeric two-chain surfactants in which diastereomers could be equilibrated by base-catalyzed epimerization. We report here the results of these studies. We conclude that the hydrophobic effect and molecular aggregates can be used to distinguish between methylene chains attached to the same stereocenter, if the chains are differentiated by remote hydrophilic and hydrophobic substituents. This allows for stereoselection based, not on classical steric size fundamentals, but rather on the hydrophilic-hydrophobic index of substituent groups.

Scheme I

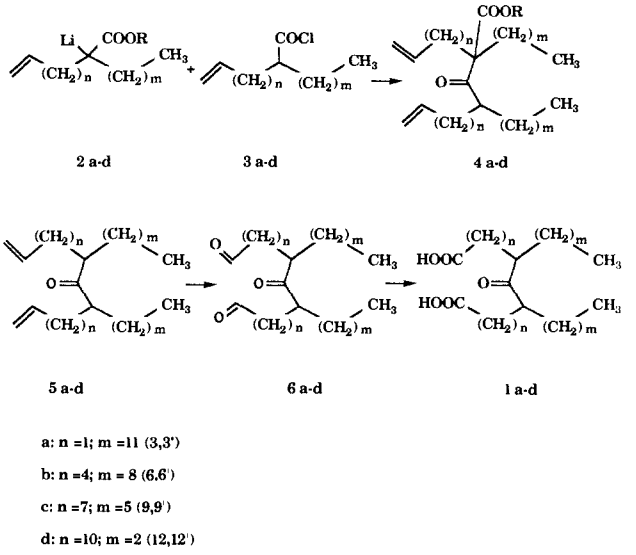

Table I. Chromatography Data for Separation of **1a-d**[a]

structure	k' values (±)	k' values meso	α
1a (3,3')[b]	11.0	15.6	1.4
1b (6,6')	4.2	6.9	1.6
1c (9,9')	3.6	4.6	1.3
1d (12,12')[b]	4.3	4.5	1.1

[a] Chromatography on two Ultrasphere-ODS 5-μm columns with solvent 95/45/0.1 CH_3OH/H_2O/AcOH, flow rate 0.7 mL/min, refractive index detection. [b] First eluting compound assumed to be (±) diastereomer.

Results

Synthesis. Four systems, **1a-d** were synthesized for study. Each had two 15-carbon carboxylic acids linked by a carbonyl group. The general synthetic approach is outlined in Scheme I. Coupling of **2** with the acid chloride **3** provided the β-keto carboxylate **4**. The coupling reaction was carried out on either the **2** dianion (R = Li) or the ethyl ester ($R = C_2H_5$), and the dienone **5** was

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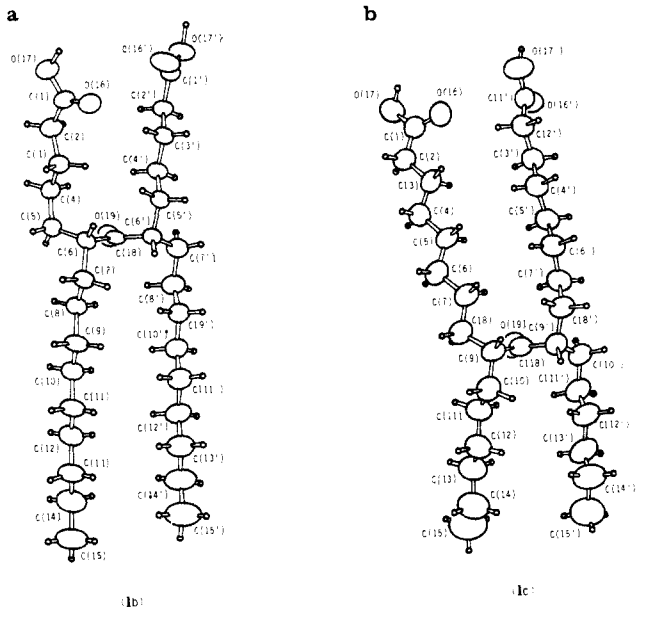

Figure 1. ORTEP plots of (a) **1b** and (b) **1c**. The small circles represent hydrogen atoms.

obtained by decarboxylation of **4** (R = H). Ozonolysis of **5** and Jones oxidation of **6** provided the dicarboxylic acids **1a–d**. Acceptable spectroscopic and analytical data were obtained for the carboxylic acid precursors to **2a–d**, **5a–d**, and **1a–d**. The acid chlorides **3a–d** and dialdehydes **6a–d** were not submitted for elemental analysis.

Diastereomer Separation. The compounds **5–6** and **1a–d** all exist as meso and (±) diastereomers, and the **1a–d** diastereomers could be separated chromatographically. Reversed-phase (C-18) chromatography was particularly useful for separation and analysis of the diacids **1a–d**, and several hundred milligrams of the separate diastereomers could be conveniently purified (Dynamax columns, Rainin Corp., CH_3CN/H_2O solvent). A structural dependence was observed for the separation of *meso*- and (±)-**1** diastereomers. Separation (maximum $\Delta k'$) occurred most readily for diacids linked close to the head group (**1a**, 3,3′-linkage) and was increasingly difficult as the ketone linkage was moved down the carboxylic acid chains (6,6′ → 9,9′ → 12,12′). Chromatographic data for the reversed-phase C-18 separations of **1a–d** are presented in Table I.

The dienes **5a–d** could not be separated by silica or reversed-phase chromatography, but conditions for analysis of **5c** were achieved on a 30-m capillary column [30 M Supelco SP-2330 fused silica, 185 °C (13 psi)]. Quantities of the separated dienones could be obtained by separation of the dialdehydes **6c** via flash chromatography and conversion of the separated dialdehydes to **5c** by Wittig coupling with methylenetriphenylphosphorane.

X-ray Crystal Structure Analyses. Diastereomers [meso or (±)] of **1a–d** could not be identified on the basis of spectroscopic data. Single-crystal x-ray analyses of the later-eluting diastereomers of **1b** and **1c**, however, established that both compounds were meso. The crystal structures were solved by direct methods.[15] Atomic positional and thermal parameters[16] were refined by full-matrix least-squares calculations to $R = 0.044$ ($R_w = 0.057$)[17] for **1b** and $R = 0.098$ ($R_w = 0.134$) for **1c**, over 2040 and 1980 reflections, respectively.

Crystals of **1b** and **1c** comprise molecules that have their CO-linked C_{15} carbon chains extended to the manner illustrated in Figure 1. The arrangement of molecules in the crystal is presented in Figure 2; **1c** molecules pack in a like manner. Thus, in crystals of both **1b** and **1c**, intermolecular O–H···O hydrogen bonding[18]

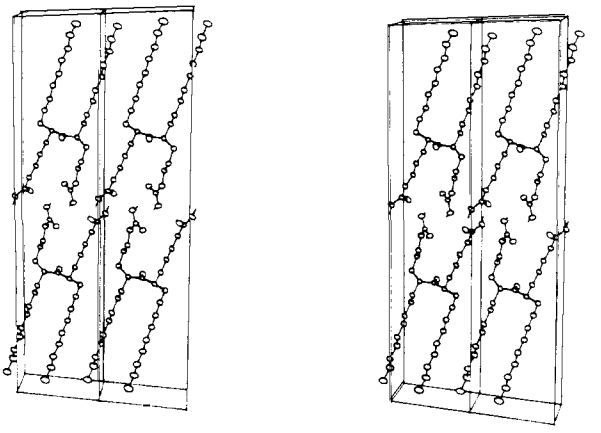

Figure 2. Stereoview of the arrangement of **1b** molecules in the crystal. The small circles represent carboxy hydrogen atoms.

associates carboxylic acid groups related by crystallographic centers of symmetry, while typical van der Waals distances separate the terminal methyl groups about other centers of symmetry, which are removed by $b/2$ from those involved in the hydrogen-bonded interactions, thereby yielding a bilayer-like arrangement. As is apparent from Figure 1, the $[CH_3(CH_2)_mCH]_2CO$ moieties in **1b** ($m = 8$) and **1c** ($m = 5$) have essentially identical conformations, whereas packing requirements associated with the geometric demands for formation of the intermolecular hydrogen bonds are presumably responsible for the adoption of a gauche conformation about the C_4–C_5 linkage in crystals of **1b**, in contrast to the trans dispositions found around the $C_{4'}C_{5'}$ bond, as well as about the C_7–C_8 and $C_{7'}$–$C_{8'}$ bonds in **1c**.

Aggregates of 1a–d. The dicarboxylic acids **1b–1d** (1 mM) form clear, soapy solutions in 1 M KOH. The 3,3′-diacid **1a** does not form a clear solution in KOH but rather gives a translucent solution, which sometimes deposits a fluffy solid. Solutions of **1a** or **1c** with CsOH (1 M) form soapy, clear solutions, and **1c** also gives soapy solutions with RbOH and NaOH. Precipitates form with the diacids and LiOH.

Surface tension experiments were carried out with the diacid **1c** in 1 M KOH at 30 °C. Both meso and (±) diastereomers of **1c** had CMC's less than 10^{-4} M: *meso*-**1c**, CMC = 9.7×10^{-5} M; (±)-**1c**, CMC = 1.6×10^{-5} M.

Further attempts to characterize aggregates of **1c** utilized differential scanning calorimetry (DSC) and low-angle X-ray analysis of emulsions of **1c** with up to 70% 1 M KOH added. DSC experiments with *meso*- and (±)-**1c** were carried out on emulsions consisting of 1/1 (w/w) diacid/1 M KOH. The first heating and cooling cycles for *meso*-**1c** resulted in broad transitions between 41 and 45 °C. Continued cycles led to a sharpened reversible transition ($T_c = 41.4 \pm 0.3$ °C; $\Delta H = 11.6 \pm 0.3$ kcal/mol). On the other hand, (±)-**1c** showed a transition at 41 °C on the first cycle. This transition disappeared gradually as the sample was repeatedly heated and cooled through the 40 °C temperature range.

Low-angle X-ray diffraction[19] showed that, upon the addition of 70% by weight aqueous 1 M KOH to *meso*-**1c**, the headgroup to headgroup distance (indicated by the lamellar repeat period) increased from 36 Å (nonhydrated) to 40 Å (hydrated) at 20 °C. Wide-angle reflections corresponding to chain to chain distances of 4.75, 4.14, and 3.82 Å were observed. At 42 °C (above T_c of *meso*-**1c**), however, no birefringence was observed in the sample of hydrated **1c** *meso*-diacid. The (±)-**1c** diacid hydrated at 70% by weight aqueous 1 M KOH showed a headgroup to headgroup distance of 42 Å from low-angle reflection data, with a chain to chain distance of 4.41 Å at 20 °C. At 42 °C, the (±)-**1c** diacid

(15) Crystallographic calculations were performed on a PDP11/44 computer by use of the Enraf-Nonius Structure Determination Package (SDP) incorporating the direct methods program MULTAN11/82.

(16) Supplementary material; see the paragraph at the end of the paper.

(17) $R = \sum||F_o| - |F_c||/\sum|F_o|$; $R_w = \sum w[(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$.

(18) Hydrogen-bonded distances (Å) follow: $O_{16}\cdots O_{17}$ (at $1-x, 1-y-z$) = 2.662 (4), $O_{16'}\cdots O_{17'}$ (at $2-x, 1-y, 1-z$) = 2.654 (4) for **1b**; $O_{16}\cdots O_{17}$ (at $1-x, 1-y, 1-z$) = 2.642 (8), $O_{16'}\cdots O_{17'}$ (at $2-x, 1-y-z$) = 2.658 (7) for **1c**.

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Table II. Equilibrations of **1b**, **1c**, and **5c** in Isotropic Solutions at 60 °C

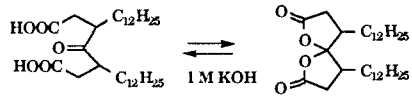
starting diastereomer	posn of ketone link in substr	equilibrium [meso/(±)] ratio[a]	conditions
meso-**5c**	10	50/50	benzene/DBU
(±)-**5c**	10	48/52	benzene/DBU
meso-**5c**	10	47/53	*t*-BuOH/*t*-BuO$^-$
(±)-**5c**	10	49/51	*t*-BuOH/*t*-BuO$^-$
meso-**1b**	6	48/52	benzene/toluenesulfonic acid
(±)-**1b**	6	48/52	benzene/toluenesulfonic acid
meso-**1c**	9	50/50	benzene/toluenesulfonic acid
(±)-**1c**	9	52/48	benzene/toluenesulfonic acid

[a] Triplicate analysis of duplicate experiments, standard error <±2%.

showed a very weak reflection corresponding to a headgroup to headgroup distance of 3.9 Å.

Several low-angle X-ray analyses of *meso*- and (±)-**1c** and dicetyldimethylammonium bromide (DDAB) were conducted. A headgroup to headgroup distance of 33 Å was indicated for DDAB, either dry or in 70% by weight aqueous 1 M KOH with chain to chain spacings of 4.71, 4.28, and 3.93 Å. After DDAB and *meso*-**1c** were mixed in $CHCl_3$ in a ratio of 4/1 DDAB/*meso*-**1c**, the solvent was evaporated and the residue hydrated by adding 70% by weight aqueous 1 M KOH. Headgroup to headgroup spacings of 33 and about 50 Å were observed in this experiment. A similar experiment with DDAB and (±)-**1c** gave a spacing of 33 and about 60 Å. These experiments were run at 20 °C [below T_c for *meso*-**1c**]. The intensity of the 33-Å repeat period dominates the 50-Å (±) or 60-Å (meso) reflection pattern. This indicates that a considerable amount of DDAB that has not incorporated (±)- or *meso*-**1c** is present. However, the 50- and 60-Å distances do not correspond to those of hydrated (±)-**1c** (42 Å) or *meso*-**1c** (40 Å).

The diacid **1a** is occasionally isolated as the spiro ketal **7**. While methods favoring formation of **7** from **1a** have not been thoroughly explored, base catalyzes the conversion of **7** to the potassium salt of **1a**. Thus, the conditions of base-catalyzed epimerization of **1a** (vide infra) do not lead to formation of **7**.



1a **7**

Epimerization of Ketone Diastereomers. The substrates **1a–c** were designed with the idea that diastereomers could be equilibrated by acid or base, since the stereocenters are enolizable carbons. Before studying equilibria in molecular aggregates, we sought to provide an isotropic base line for comparison of results in aggregates. We thus carried out equilibration studies on the dienones **5c** in organic solvents and on the diacids **1b** and **1c** in benzene solution. The dienone equilibration was base catalyzed (DBU, *tert*-butoxide), while the acid equilibrations in benzene were catalyzed by toluenesulfonic acid. The results of these isotropic equilibrations are presented in Table II. The equilibrium ratio was within experimental error of 50/50 in every experiment. It should also be noted that some diacid aggregates may be present in these experiments, but the nature of these aggregates is decidedly different than the micellar structures formed in aqueous base, at least in regard to their effect on stereochemistry.

Equilibration of the diacids **1a–c** was achieved by 1 mM substrate in strongly basic water. Equilibrations were generally run for 12–14 days. The kinetics of equilibration of the diacids in water and in ammonium surfactant hosts will be reported in a subsequent publication, but we note here that equilibrium is reached within 12–14 days for all systems reported. Table III presents data for equilibration of the diacid **1c** with several alkali metal hydroxides. In 1 M LiOH or $Ba(OH)_2$, precipitates of **1a–d** lithium or barium salts form and equilibrium values are not reproducible. In Table IV, equilibrium values for equilibration of all the diacids **1a–d** are presented. Reproducible equilibrium values could be obtained from **1a** only by the use of CsOH base. The

Table III. Equilibrium Values of 1 mM Diacid **1c** in 1 M Aqueous Base at 60 °C

starting **1c** diastereomer	posn of ketone link in substr	base (1 M)	meso/(±)[a]
(±)	9	KOH	72/28
meso	9	KOH	72/28
(±)	9	NaOH	74/26
meso	9	NaOH	76/24
(±)	9	RbOH	72/28
meso	9	RbOH	75/25
(±)	9	CsOH	72/28
meso	9	CsOH	72/28

[a] Triplicate analysis of duplicate experiments, standard error <±2%.

Table IV. Equilibrium Values of 1 mM Diacids **1a–d** in 1 M Aqueous Base at 60 °C

starting diacid	posn of ketone link in substr	base (1 M)	meso/(±)
(±)-**1a**	3	CsOH	86/14
meso-**1a**	3	CsOH	87/13
(±)-**1b**	6	KOH	82/18
meso-**1b**	6	KOH	82/18
(±)-**1c**	9	KOH	72/28
meso-**1c**	9	KOH	72/28
(±)-**1d**	12	KOH	64/36
meso-**1d**	12	KOH	64/36

[a] Triplicate analysis of duplicate experiments, standard error <±2%. [b] The meso and (±) diastereomers have been rigorously assigned for only **1b** and **1c** (X-ray analysis). The diastereomer assignments for **1a** and **1d** are tentative and are based on the HPLC retention trends in the series (Table I).

Table V. Equilibrium Values of 1 mM Diacids in 1 M KOH with Added Ammonium Surfactants

starting diacid diastereomer	posn of ketone link in substr	ammonium[a] salt	temp, °C	meso/(±)[b]
(±)-**1b**	6	CTAB[c]	60	84/16
meso-**1b**	6	CTAB	60	84/16
(±)-**1b**	6	DDAB[d]	60	89/11
meso-**1b**	6	DDAB	60	89/11
(±)-**1b**	6	CTAB	37	88/12
meso-**1b**	6	CTAB	37	87/13
(±)-**1b**	6	DDAB	37	90/10
meso-**1b**	6	DDAB	37	90/10
(±)-**1c**	9	CTAB	60	65/35
meso-**1c**	9	CTAB	60	65/35
(±)-**1c**	9	DDAB	60	82/18
meso-**1c**	9	DDAB	60	82/18
(±)-**1c**	9	CTAB	37	71/29
meso-**1c**	9	CTAB	37	70/13
(±)-**1c**	9	DDAB	37	87/13
meso-**1c**	9	DDAB	37	88/12
(±)-**1c**	9	TMAB[e]	60	72/28
meso-**1c**	9	TMAB	60	72/28

[a] 100 mM ammonium salt. [b] Triplicate analysis of duplicate experiments, standard error <±2%. [c] Cetyltrimethylammonium bromide. [d] Dicetyldimethylammonium bromide. [e] Tetramethylammonium bromide.

solutions of diacid **1a**/1 M KOH precipitated salts of the diacid.

The equilibrium product ratios can be perturbed in some cases by ammonium surfactants and added salts. Data for equilibrations with added ammonium salts are presented in Table V. The diacid concentration is 5 mM, and the ammonium salt concentration is 100 mM in every case. Tetramethylammonium bromide was used as a control to determine whether the ammonium cation gave the same equilibrium as the potassium cation. Cetyltrimethylammonium bromide (CTAB) is known to form micellar aggregates, while dicetyldimethylammonium bromide (DDAB) forms lipid bilayer structures.[20-24]

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Discussion

The control of organic stereochemistry has received considerable research attention in the past two decades. Methods utilizing substrate or reagent control to express classical group size discrimination in diastereomeric transition states have been remarkably successful.[4-6] All of these approaches rely on group size differentiation to define stereochemistry (i.e., $CH_3 > H$), and these approaches do not distinguish between two methylene chains differing at positions remote from a stereocenter (e.g., $-(CH_2)_nCH_3$ vs $-(CH_2)_mX$). The role of molecular aggregation in stereoselection has only recently emphasized (e.g., in the context of alkylmetal reagent aggregation).[25-29]

Hydrophobic molecular aggregates offer another possible means for control of organic stereochemistry. Micelles and lipid bilayer aggregates are known to influence chemical reactivity, and micellar catalysis, for example, is a well-established and extensively studied phenomenon.[24] Micelles and lipid bilayers have also been used to promote enantioselective hydrolysis of chiral esters.[10] Furthermore, regiochemical and diastereochemical discrimination has been reported for reactions carried out in micelles.[14]

We have recently reported that the stereochemistry of radical-pair collapse is influenced by the state of aggregation of the pair.[29-31] Thus, radical pairs generated from two-chain surfactant diazenes couple with significant retention of configuration (80% diastereoselectivity), if the diazene precursor is photolyzed in micelles or lipid bilayers. The same chiral diazenes were photodecomposed in isotropic solutions, and no diastereoselectivity was observed in the conversion. This indicates that radical-pair coupling, a very fast kinetically controlled process, can be influenced by hydrophobic aggregates. The rule that radical pairs couple with random stereochemical configuration thus does not apply to reactions carried out in micelles and bilayers.

Since we know that very rapid, kinetically controlled processes are subject to hydrophobic stereoenforcement, we have now chosen to explore the other end of the reactivity scale, reactions under thermodynamic control. The two-chain surfactants, **1a–d**, were thus attractive candidates for study since (1) they are structurally analogous to the diazenes previously examined, (2) they exist in diastereomeric forms, (3) they are available by a reasonably concise synthesis, and (4) the diastereomers can be equilibrated by acid or base.

The results of the epimerization studies show clearly that hydrophobic stereoenforcement is possible with the two-chain surfactants **1a–d**. Compare, for example, epimerizations carried out in isotropic media, such as benzene or *tert*-butyl alcohol, with the experiments utilizing water as solvent. In isotropic media, the equilibria determined were within experimental error of a 50/50 meso/(±) product mixture for experiments carried out with dienone **5c** or the diacids **1b** and **1c** (Table III). In contrast to this behavior in isotropic media, equilibrations of diacids **1a–d** in aqueous base give product distributions significantly distorted from 50/50. Thus, meso/(±) product ratios as high as 87/13 can be obtained for the diacids in aqueous base (Table V). This equilibrium ratio is apparently independent of the carboxylate counterion, as illustrated in Table IV, where equilibria for the diacid **1c** are reported with sodium, potassium, rubidium, and cesium hydroxide base. Tetramethylammonium counterion also gives the same product ratio of ~72/28 as that reported for sodium → cesium. If precipitates are observed in the solutions prepared, reproducible equilibrium constants are not found. Lithium and barium salts of **1a–d**, for example, precipitate from aqueous solution, and equilibrium studies are thus not appropriate with these counterions.

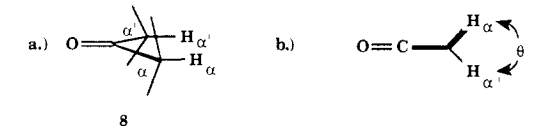

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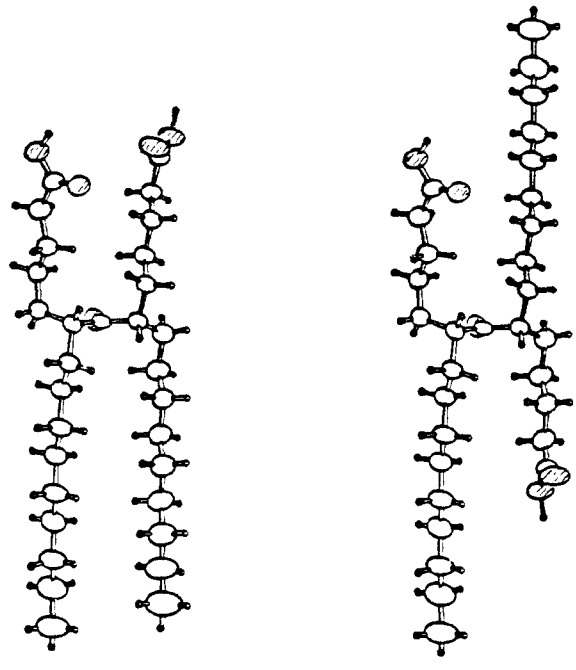
Figure 3. Conformations of substituted ketones.



Meso **1b** ± **1b**

Figure 4. Conformations of *meso*- and (±)-**1b** with minimum energy arrangement near carbonyl. *meso*-**1b** is from X-ray analysis; (±)-**1b** structure is constructed from *meso*-**1b** X-ray. Shaded atoms are oxygen.

The characterization of the salt of **1a–d** in aqueous media indicates that rather large aggregates form at concentrations above ~10^{-5}–10^{-4} M. At very high concentrations of the potassium salt of **1c**, aggregates with bilayer structure exist, as determined by low-angle X-ray analysis. Equilibrations within these bilayer structures have not been systematically investigated. All epimerizations reported here were carried out at diacid concentrations considerably above the CMC, and the equilibria reported presumably reflect the energetic preferences of the meso and (±) diastereomers in the molecular aggregates. Studies of rate and equilibria below the CMC are in progress and will be reported later.

Our previous report of molecular aggregate influence on radical-pair coupling diastereoselectivity[26] offers a framework for discussion of the hydrophobic equilibria perturbations reported here. In the radical-pair studies, we suggested that an azo link between two surfactant chains had a preferred conformational arrangement and that this conformational preference was translated into dramatic differences in the surface and aggregate properties of diastereomeric azo radical-pair precursors. We make a similar suggestion for the ketone diacids **1a–d**. Extensive molecular mechanics calculations on 2,4-dimethyl-3-pentanone (**8**) (a model for the ketone portion of our diacids) indicate that the preferred conformation of this ketone is as shown in Figure 3.[28] In Figure 3b a side view of **8** is presented with the α-methyl substituents omitted and the α tertiary hydrogens (H_α and $H_{\alpha'}$) and the pseudotorsional angle between those hydrogens, θ, shown. The molecular mechanics calculations indicate that the energy

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surface of **8** has a broad energy minimum when θ lies between 30° and 80°. Although the energy minimum calculated has θ = 60 °C, conformations with θ between 30° and 80° are only <0.5 kcal/mol above the low-energy form. Conformations with $\theta >$ 80° are of higher energy (i.e., θ = 120° gives an energy nearly 2 kcal/mol above the minimum) due to steric interactions between the α,α'-dimethyl substituents.

Consider now the diastereomers of **1a–d**. Assuming a minimum energy conformation about the ketone linkage, the meso diastereomer exists in an arrangement where both hydrophilic carboxylates are on the same "end" of the molecule and the hydrophobic alkyl chains are at the opposite end. This is shown in Figure 4, where both *meso*- and (±)-**1b** are shown. The structure shown for *meso*-**1b** comes from the X-ray analysis, while that of (±)-**1b** is a construct from the meso X-ray structure with the $-C_6H_{13}$ and $-(CH_2)_4COOH$ groups interchanged on one stereocenter. The meso diastereomer forms a "good" amphiphile in this minimum energy conformation near the ketone, while the (±) stereoisomer does not form a good amphiphile in this conformation. We suggest that the preference for the meso diastereomer in hydrophobic molecular aggregates relates to the fact that it exists in a good amphiphilic conformation, while the (±) diastereomer is not a good amphiphile. The isotropic equilibrium of 1/1 may be tipped in favor of the good amphiphile to 9/1 by this hydrophobic effect.

It is noteworthy that single-crystal X-ray analysis of both *meso*-**1b** and -**1c** illustrate that the meso compound conforms to a "good" amphiphile in the crystal. In fact, both meso compounds crystallize in a bilayer form with regions of hydrogen-bonded hydrophilic carboxylates separated by bilayer structure. In the crystal, the θ angle is found to be 74° for **1b** and 66° for **1c** in accord with the results from molecular mechanics calculations (vide supra).

Epimerizations carried out in ammonium surfactant hosts suggest that the host surfactant can influence the diacid equilibrium values achieved. Thus, at 60 °C, CTAB does not change the K_{eq} value for **1b**, while this host reduces the ratio for **1c** from 72/28 (no CTAB) to 65/35 (20-fold excess CTAB). The bilayer surfactant dimethyldicetylammonium bromide (DDAB) raises the equilibrium ratio for **1c** at 60 °C to 82/18 and **1b** K_{eq} is increased from 82/18 (no DDAB) to 89/11 (20-fold excess DDAB). These hosts (CTAB and DDAB) have the additional advantage that the approach to equilibrium is catalyzed in these surfactants by micellar catalysis. Thus, equilibria can be established in CTAB and DDAB at 37 °C in less than 1 week, while without these ammonium surfactants, little epimerization is observed at these temperatures and concentrations. At 37 °C, the equilibrium of **1b** or **1c** in DDAB approaches 90/10.

Summary

The hydrophobic effect can be used to influence organic stereochemical equilibria. In the substrates **1a–d**, two stereocenters serve as link carbons between two surfactant chains and two of the substituent groups on the stereocenters, $-(CH_3)_nCH_3$ and $-(CH_2)_mCOOR$, are virtually equivalent in steric size. Equilibrium established in isotropic organic solvents gives 50/50 meso/(±) ratios because of the equivalency of groups on the stereocenters, while in aqueous micellar media the hydrophobic $-(CH_2)_nCH_3$ group is distinguished from the hydrophilic $-(CH_2)_nCOOR$ group. The remote hydrophilic –COOR substituent then can be used to distinguish groups that are otherwise equivalent in steric size. It would appear from this first-generation study that a moderately rigid conformational link and substantial hydrophobic character are required for differentiation of diastereomers. While the energies associated with this hydrophobic effect are small (1–2 kcal/mol), they are comparable to energy differences associated with axial/equatorial ΔG's of ring substituents in cyclohexanes. A further examination of this phenomenon thus seems warranted.

Experimental Section

General Procedures. ^1H NMR spectra were obtained on a Varian XL-300 (300 MHz) with $CDCl_3$ as the solvent. ^{13}C NMR spectra were obtained on a Varian XL-300 (75.43 MHz) with $CDCl_3$ solvent as the reference. IR spectra were determined with a Perkin-Elmer 297 spectrometer. Melting points were measured on a Thomas-Hoover Unimelt apparatus. GC analyses were performed on a Supleco SP-2330 30-m highly polar fused silica capillary column with a Hewlett-Packard 5830A gas chromatograph equipped with a flame ionization detector and an HP 1850A GC terminal integrator. Elemental analyses were carried by Galbraith Laboratories, Inc., Knoxville, TN.

Preparative HPLC was performed on a Dynamax Macro HPLC C-18 column accompanied by Waters Associates M6000A solvent delivery system, R401 differential refractometer, and U6K injector. Analytical HPLC was performed on two Altex Ultrasphere ODS analytical HPLC columns (5 μm, 4.6 mm × 25 cm) obtained from Beckman, Inc. An LDC Refractomonitor III was used for peak detection.

THF was distilled from potassium and benzophenone prior to use. HMPA and diisopropylamine were distilled from CaH_2. Other solvents were used without further purification. All air-sensitive reactions were carried out under an Ar atmosphere. All starting materials and reagents were obtained from Aldrich, except for 11-bromoundecanol, which was obtained from Sigma Biochemicals. Solvents were obtained from Mallinckrodt, Inc.

Synthesis. The synthesis of diacids **1a–d** follows the route that is outlined in Scheme I. Details for the synthesis of **1d** are presented here, and methods for preparation of **1a–c** follow the same general format.

(±)- and *meso*-Dienones 5d. The acid **2d**(2.5 g, 9.33 mmol) was added to a 100-mL three-neck flask equipped with a reflux condensor. At room temperature, $SOCl_2$ (2.7 mL, 0.037 mol) was added via syringe, with vigorous stirring. The solution was heated at 50 °C for 0.5 h, and excess $SOCl_2$ was removed by azeotroping with dry benzene under reduced pressure, followed by high vacuum. Acid chloride **3d** was used without further purification.

The dilithium salt of acid **2d** was prepared as follows: To a 250-mL dry three-neck flask under argon, equipped with a reflux condensor and rubber septum, was added 100 mL of dry THF. To this was added 3.0 mL (0.0217 mol) of diisopropylamine via syringe. After cooling to –20 °C, 8.5 mL of *n*-BuLi (2.4 M in hexane, 0.0208 mol) was added over 10 min. After it was allowed to warm to 0 °C, the solution was cooled to –20 °C, and acid **2d** (2.5 g, 0.009 33 mol) was added over 5 min. The solution was allowed to warm to room temperature, followed by heating to 50 °C for 2 h.

The dilithium salt of acid **2d** was converted to the dienone **5d** as follows: The solution from above was cooled to 0 °C, and acid chloride **3d** (2.75 g, 0.009 33 mol) was added. This mixture was allowed to stir for 3 h at room temperature. Decarboxylation of the resulting β-keto acid **4d** was accomplished by refluxing the reaction mixture for 24 h in THF (either the free acid or lithium salt can be decarboxylated; this procedure describes the decarboxylation of the lithium salt). After the mixture was quenched with 10% HCl, the solvent was removed under reduced pressure and the residue was extracted with ether, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel in 95/5 hexane/ethyl acetate afforded 2.7 g (61%) of pure dienone **5d**. Compounds **5a–c** were prepared in a similar manner, except that the decarboxylation of **4c** was accomplished by heating the crude β-keto acid **4c** neat to 180 °C for 0.5 h. Characterization data for dienones **5a–d** can be found in the supplementary material.

(±)- and *meso*-Diacids 1d. A solution of dienone **5d** (2.5 g, 0.0053 mol) in CH_2Cl_2 (100 mL) was cooled to –78 °C. Ozone gas was bubbled into a flask until a blue color persisted. The resulting mixture was allowed to warm to room temperature until a colorless solution was obtained. After 1 mL of glacial acetic acid was added to this solution, 1 g of Zn metal was added slowly with a spatula with stirring. After 1 h, TLC showed complete quenching of ozonide. The reaction mixture was filtered, and the organic layer was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated to furnish dialdehyde **6d** (yield not determined). Jones oxidation of the dialdehyde gave crude diacid **1d** (2.1 g, 78%). Compounds **6a–c** and **1a–d** were prepared in a similar manner, except that in the preparation of **1a** and spiro lactone **7** was obtained and hydrolyzed to **1a** by stirring in aqueous KOH. Characterization data for dienones **5a–d**, diacids **1a–d** (±) and **1a–d** (meso), are shown in Tables 6 and 7 of the supplementary material.

Diacid Epimerization Studies. Equilibrations were run in either sealed tubes or a tightly capped round-bottom flask. The vessels were submerged in oil baths equipped with a thermistor and ultrasensitive relay (Princo T-688) connected to heating coils. The oil baths were stirred and maintained at either 60 (±0.1) or 37 (±0.1) °C for equilibrations.

In a typical procedure, diacid and surfactant were placed in a flask (either directly or from stock solutions in $CHCl_3$). After any solvent present was removed by high vacuum, 1 M KOH [titrated (±0.01)] was added, and the resulting solution was vortexed (5–10 min) until all material was soluble. The soapy solution was then placed in a constant-temperature bath until equilibration had occurred (1–10 days). Epimerization was performed from both diastereomers in order to confirm that

equilibrium had been reached. Reactions were quenched (with 10% HCl, pH ~3-4) immediately after their removal from the constant-temperature bath. In cases where no CTAB or DDAB was present, a simple extraction by CH_2Cl_2 removed both diastereomers without affecting their ratio. However, in order to obtain acceptable analyses with CTAB or DDAB, the following workup procedure was used. After acidification with 10% HCl, the water was removed from the CTAB or DDAB solution by evaporation with benzene used to azeotrope the last traces of water. Diazomethane in ether was added to the residue and the resulting solution chromatographed on silica gel with EtOAc. Control experiments have verified that accurate analyses may be obtained with this procedure.

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Supplementary Material Available: Tables of spectroscopic data (^1H and ^{13}C NMR), mass spectral fragmentation data, and combustion analyses for dienones **5a-d** and diacids **1a-d**, atomic positional and thermal parameters, bond lengths and angles, and torsion angles for **1b** and **1c** (22 pages); calculated structure amplitudes (28 pages). Ordering information is given on any current masthead page.

A General Approach to the Stereoselective Synthesis of Spiroketals. A Total Synthesis of the Pheromones of the Olive Fruit Fly and Related Compounds†

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Abstract: A general, highly stereoselective approach to the synthesis of spiroketal systems of the 1,7-dioxaspiro[5.5]undecane and 1,6-dioxaspiro[4.5]decane families is discussed. The key reaction in the approach features oxidation of a suitably substituted furfurol derivative **1** to afford pyranone **2**, which subsequently undergoes stereoselective intramolecular ketalization under acidic conditions to furnish spiroketal **3**, carrying the 2,6-anti relationship. Analogous methodology is employed to synthesize in a stereoselective fashion model systems for the avermectin spiroketal moieties **9-11** and the pheromones of the olive fruit fly (**39** and **40**).

The spiroketal moiety is found in many natural products, ranging from insect pheromones[1] in which the spiroketal is devoid of substituents about the periphery to structurally and stereochemically complex systems found in monensin,[2] okadaic acid,[3] and the avermectin[4]/milbemycin[5] family of antibiotics. In addition to being a target for natural product synthesis, spiroketals are also excellent systems to study the role of the anomeric effect as a means of controlling the conformational mobility of heterocyclic systems.[6] Recently, several methods for the synthesis of spiroketal systems have been reported.[7] In the majority of these approaches, stereogenic centers on the heterocyclic framework were established prior to formation of the spiroketal center using established methods of acyclic stereocontrol.[8] A few strategies have addressed the problem of establishing the stereochemical relationships about the periphery once the heterocyclic framework has been constructed.[9] The synthetic strategy reported herein relies upon a short, efficient synthesis of highly functionalized spiroketals bearing a minimum of stereochemical information. Subsequent regio- and stereoselective transformations introduce the requisite functional groups. The concept is illustrated in Scheme I.

Previous studies had demonstrated that oxidation of furfurol derivatives such as **1** afforded pyranone **2**. It was anticipated that **2** would undergo highly stereoselective spiroketalization under equilibrating conditions to furnish spiroketals **3** and **4**. Spiroketal **3** should be the predominant product under equilibrating conditions and should exist exclusively as conformation **3A** (Chart I) in which it possesses two equatorial alkyl substituents at carbons 2 and 6 and dual anomeric stabilization at carbon 2.[10] That is, each of the oxygen atoms of the respective pyran systems occupies an axial orientation with respect to the other pyran ring. The alternative conformations of **3** (**3B-D**) are disfavored because they must either sacrifice one of the anomeric effects or the C-6 substituent must adopt an axial orientation (see Scheme I).

Scheme I

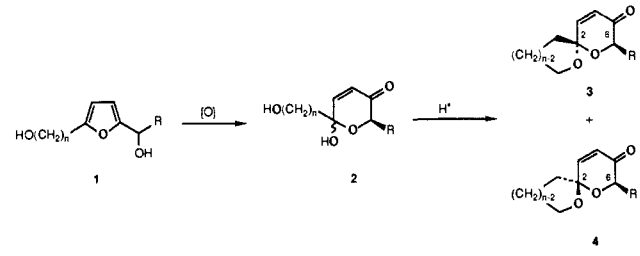
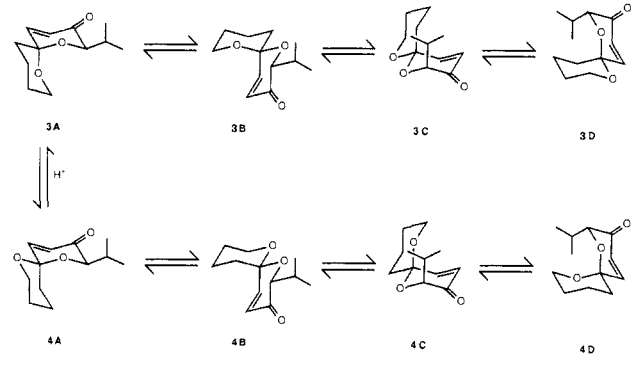


Chart I



† This paper is dedicated to Royston M. Roberts on the occasion of his 70th birthday.

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