there is a small and smooth decrease (total ca. 40%) in rate as the chain length is reduced from 15 to 5 carbons; as the alkyl chain length further decreases there is a much sharper decrease, which is most pronounced in the series R = 3, 2, 1 (k_{obsd} = 0.68, 0.33, and 0.11 M^{-1} s^{-1}, respectively). In contrast, reactivity of trans[2,2] and cis[2,2] atropisomers increases sharply with decrease in chain length while reactivity of the [3,1] atropisomers remains nearly constant. Thus, overall reactivity of a series follows the "normal" solution order for H_2THA and H_2THex atropisomers but the reactivity sequence is exactly reversed for H_2TAc in reversed micelles. A limited study of metalation of H_2TAc atropisomers in SDS micelles shows trends similar to those for reversed micelles;[28] rates slightly slower than those in the reversed micelle are measured and the order is cis[2,2] ~ trans[2,2] > [3,1] > [4,0].[29] Thus, overall reactivity of all atropisomers is enhanced (Table I) relative to homogeneous solution, even after correcting for the concentrating effect of the microheterogeneous medium.

The striking changes in reactivity for metalation of different porphyrins in anionic surfactant media must be associated with the presence and reactivity of the reagents at an anionic interface. Enhanced reactivity of the porphyrin in general can be attributed to an effective augmentation of its basicity; similar increases have been observed for neutral bases in other studies.[31,32] Preliminary studies using the H_2TAc isomers in SDS indicate good correlation of porphyrin basicity with reactivity toward Cu^{2+}. To explain the striking differences between reactivity of atropisomers as the length of the alkyl chain is varied, we propose that a major factor for [4,0] atropisomers can be attributed to a change in preferred orientation. For these isomers two limiting orientations with respect to the aqueous phase at the interface, "face-in" and "face-out", may be defined as shown in Scheme I. When the "pickets" are long alkyl chains we expect the more hindered face to be strongly hydrophobic such that a "face-in" orientation should be favored; here it is reasonable that metalation should be quite rapid. When the pickets are shorter chain carboxamide groups, their hydrophilicity should increase, favoring the "face-out" orientation. This should lead not only to a decrease in reactivity as the chain length is decreased for the [4,0] isomers but to a reversal in the normal order among atropisomers. For trans[2,2] and cis[2,2] atropisomers the above-described orientations are degenerate and other configurations may be of lower energy; increases in reactivity as the chain length decreases could be most simply ascribed to an internal reduction in steric hindrance. For the [3,1] atropisomers it is reasonable that changes in "face-in"-"face-out" equilibria similar to that proposed for the [4,0] and a variation in the steric effect play nearly offsetting roles in maintaining an overall constant reactivity through the series.

In summary, the present results demonstrate striking net effects which can be obtained by the interplay of hydrophobic and steric interactions for reactions at interfaces in microheterogeneous media. The control of reactivity by a charged interface observed in these studies shows a clear relationship to the topological control of thermal and photochemical reactivity observed for quite different processes.[33,34] Further studies of other metalation reactions are under way.

Acknowledgment. We are grateful to the U.S. Army Research Office (Grant DAAG29-84-K-0011) and the National Science Foundation (Grant CHE-8616361) for support of this research.

(28) For cis[2,2] and trans[2,2] H_2TAc in SDS, addition of Cu^{2+} produces an intermediate species, whose spectrum resembles the porphyrin diacid,[8] which converts to metalloporphyrin.

(29) Interestingly, Hambright et al.[30] have found a parallel order for a water-soluble porphyrin with isonicotinamide "pickets" for Zn^{2+} incorporation but the "normal" order for Cd^{2+}.

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Double Diastereoselection in the Iodolactonization of 1,6-Heptadien-4-carboxylic Acids[1]

Mark J. Kurth* and Edward G. Brown

Department of Chemistry, University of California Davis, California 95616

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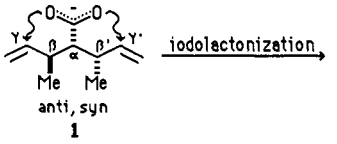
Synthetic strategies employing reactions which selectively engage one of two diastereotopic functional groups provide a unique exploitation of molecular symmetry. Notable examples of this concept include Hoye's kinetic hydroxyazelaic acid lactonization[2] and Schreiber's thermodynamic trihydroxynonanone spiroketalization.[3] We describe here the efficient stereoselective functionalization of heptadienoate **1** via its iodolactonization, *a transformation which proceeds with concomitant group and face selectivity*. Consider the four isomeric iodolactones possible from iodolactonization of **1**: **2** and **3** versus **4** and **5** reflects diastereotopic olefin selectivity (i.e., *group selectivity*) and **2** and **4** versus **3** and **5** reflects diastereotopic re versus si selectivity (i.e., *face selectivity*). A preponderance of one product would thus evidence concomitant group and face selectivity.



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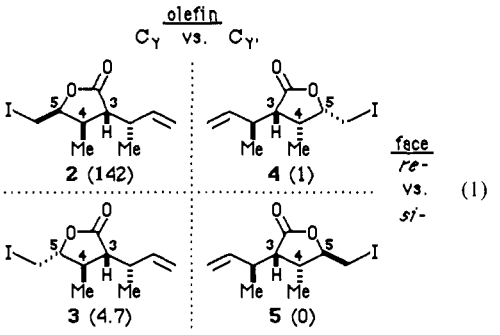

(1)

It is noteworthy that Barlett's pioneering iodolactonization studies[4] suggested significant potential for the thermodynamic cyclization of **1** (e.g., 10:1 thermodynamic selectivity with 3-methylpent-4-enoic acid)[4a] but offered little encouragement with regard to the kinetic cyclization of **1** (e.g, 3:1 kinetic selectivity with 3-methylpent-4-enoic acid).[4a] Moreover, at the outset the question of olefin selectivity was a matter of conjecture as there were no previous reports of diastereotopic olefin selectivity in this type of transformation.

Preliminary attempts to iodolactonize **1**[5] under thermodynamic

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(5) (a) The heptadienoic acids corresponding to carboxylates **1**, **6**, and **9** were prepared from (*E*)-crotyl 3-methylpent-4-enoate by an Ireland "kinetic enolate" Claisen rearrangement.[5c] As anticipated, this process delivered a 4:1:4.1 **1**:**6**:**9** mixture paralleling the well-precedented 7 to 11:1 (i.e., **1** + **9**:**6**, 8.1:1) erythro selectivity[5b] anticipated for this transformation. *meso*-**9** was easily differentiated from *dl*-**1**, thus corroborating these stereochemical assignments, by ^{13}C-NMR: *meso*-**9** [($CDCl_3$) δ 16.3, 37.6, 55.7, 114.6, 141.4, and 180.1] and *meso*-**6** [($CDCl_3$) δ 18.1, 37.7, 56.3, 115.0, 140.4, and 180.2] each give only six carbon resonances while *d,l*-**1** [($CDCl_3$) δ 17.8, 19.0, 37.7, 37.8, 56.0, 115.7, 115.23, 139.7, 141.3, and 180.1] gives 10 carbon resonances. (b) See: Table III, p 2871 in ref 5c. (c) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

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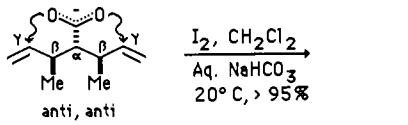
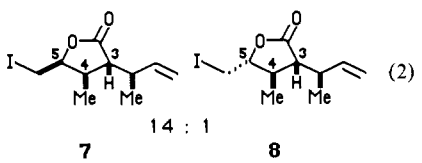
conditions,[6] however, proved unsatisfactory. In contrast and to our delight, *kinetic iodolactonization of* **1** *resulted in excellent olefin selectivity* (*147:1*) *as well as unprecedented face selectivity* (*30:1*), delivering iodolactones **2**, **3**, and **4**[7] in a 142:4.7:1 ratio, respecitvely, and in 79% combined yield.[8]

This 147:1 kinetic olefin selectivity can be rationalized on the basis of acyclic conformational control as illustrated in Scheme I. Minimizing gauche interactions,[9] the lowest energy {$C_\beta \rightarrow C_\alpha$}-Newman projection of **1** places the carboxylate and C_γ-olefin in close proximity, whereas the lowest energy {$C_{\beta'} \rightarrow C_\alpha$}-Newman projection places the carboxylate and C_γ-olefin antiperiplanar. To the extent that a similar bias is experienced in the two transition states (C_γ- versus C_γ-cyclization), the carboxylate of **1** would be predisposed toward C_γ-cyclization. In any case, $G^\ddagger$ for C_γ-cyclization (**1** → **2** + **3**) is ≈3 kcal/mol lower in energy than $G^\ddagger$ for C_γ-cyclization (**1** → **4** + **5**).

The 30:1 kinetic face selectivity obtained with **1** is also quite impressive, particularly in comparison with the relatively poor selectivity obtained with 3-monosubstituted pent-4-enoic acids. To understand the face selectivity control elements operative in the iodolactonization of **1**, *meso*-**6**[5] was studied next. In contrast

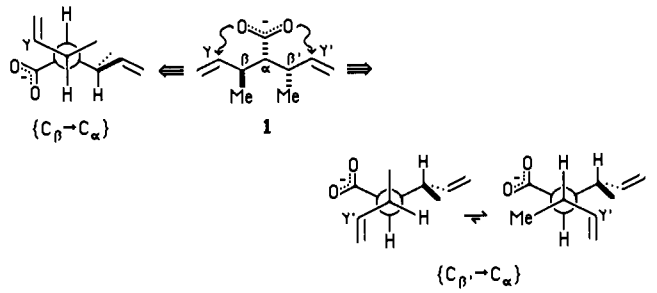




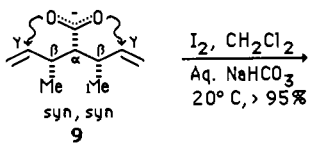
(2)

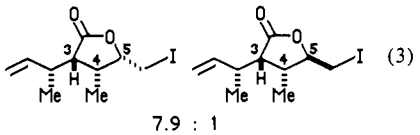
to the anti,syn-C_β,C_α,$C_{\beta'}$ stereochemistry of **1**, *meso*-**6** is anti,anti making the two olefins enantiotopic rather than diastereotopic. Thus, the iodolactonization of **6** represents an ideal substrate to further probe the generality of face selectivity for 2,3-disubstituted pent-4-enoic acids since it confronts only those issues which govern face selectivity. Indeed, subjecting this acid to kinetic iodolactonization resulted in the formation of iodolactones **7** and **8**[7] in a 14:1 ratio, respectively. Moreover, iodolactones **2** and **7** differ only in that they are epimeric at their acyclic stereocenter and yet **1** → **2** (versus **3**) is >2 times more selective than **6** → **7** (versus **8**) indicating that subtle nonbonding interactions can significantly influence the observed internal asymmetric induction.

Scheme I



Meso acid **9**[5] offered an additional interesting probe of internal asymmetric induction in kinetic iodolactonization since, in contrast to **6**, it contains syn,syn stereochemistry. Indeed, kinetic cyclization of **9** resulted in the formation of two iodolactones, **10** and **11**,[7] in a 7.9:1 ratio, respectively. While internal asymmetric induction with **9** is lower than with either **1** or **6**, one important trend emerges: *all three heptadienoiates deliver the major iodolactone product* (***2***, ***7***, and ***10***) *with cis* C_4*-methyl and* C_5*-iodomethyl groups*. C_4,C_5-Cis selectivity is also observed for C_β-monosubstituted pent-4-enoic acids[4] indicating that C_α,C_β-disubstitution enhances, but does not alter, the intrinsic kinetic face selectivity.





(3)

In conclusion we note that Chamberlin[10] has reported a stereoelectronic allylic hydroxyl directed kinetic iodolactonization which, like the present examples, is C_4,C_5-cis-selective (3-hydroxypent-4-enoic acid giving 13:1 cis:trans selectivity), and Yoshida[11] has reported an *N*,*N*-dimethylamide A(1,3) strain directed kinetic iodolactonization which is C_3,C_5-trans-selective (both syn and anti isomers of *N*,*N*-dimethyl 2,3-dimethylpent-4-enamide giving 32:1 trans:cis selectivity). Thus, our results establish that a C_3,C_4-dialkyl substitution pattern functions as a third type of diastereoface control element in kinetic iodolactonizations. Furthermore, we have shown that conformational bias provides a powerful control element in the stereoselective reaction of diastereotopic olefins in the iodolactonization process.

Acknowledgment. These investigations were supported by the NSF (CHE-8405527) to whom we are grateful. M.J.K. is a 1987–1989 Alfred P. Sloan Research Fellow.

Supplementary Material Available: Tabular NMR data relevant to structure assignments for iodolactones **2**, **3**, **4**, **7**, **8**, **10**, and **11** (3 pages). Ordering information is given on any current masthead page.

(6) The acidic conditions (protonated iodolactone) required for equilibration[4] leads to extensive decomposition of **1** within 1 h at ambient temperature.

(7) (a) Structure assignments for **2**, **3**, **4**, **7**, **8**, **10**, and **11** were made on the basis of ^{1}H NMR, ^{13}C NMR, and NOESY spectral data (Supplementary Material). (b) We have found that chemical shift differences for C_5-H in C_4,C_5-cis versus C_4,C_5-trans disubstituted iodolactones are substantial and constitute a reliable means of stereochemical assignment (e.g., when the C_5-CH_2I group is cis to a C_4-methyl, C_5-H resonates 0.18–0.91 ppm downfield relative to C_5-H in its trans partner). A C_4-hydroxyl substituent in place of the C_4-alkyl substituent also deshields the cis relative to trans isomer.[10] Only one exception to this trend could be found: a C_4-acetoxy substituted iodolactone.[11] A similar chemical shift effect has been noted for tetrahydrofurans and furanoses;[7c] the chemical shift differences between cis/trans isomers in these cases (0.18–0.77 ppm) are surprisingly close to those found for iodolactones (0.18–0.91 ppm).[4,10,11] (c) Gaudemer, A. In *Stereochemistry*; Kagan, H. B., Ed.; Georg Thieme Verlag: Stuttgart, 1977, Vol. 1, p 90.

(8) Representative iodolactonization: Saturated aqueous $NaHCO_3$ (2.0 mL) was admixed with an equal volume of a CH_2Cl_2 solution of **1** (70 mg, 0.41 mmol), and the mixture was rapidly stirred at room temperature as solid iodine (111 mg, 0.44 mmol) was added in 1 portion. After stirring 20 min, excess iodine was quenched with aqueous $Na_2S_2O_3$/$NaHCO_3$ solution, the layers were separated, and the aqueous portion was extracted with CH_2Cl_2. The combined organics were washed with water and brine, dried (K_2CO_3), filtered, and concentrated to yield iodolactones **2**–**4** (96 mg, 79% crude) as a pale yellow oil. Capillary GC analysis [flame-ionization detection using a 30 m × 0.25 mm DB1701 capillary column, helium as the carrier gas (29.7 cm/s), 250 °C detector temperature, 200 °C injector temperature, and oven temperature programmed at 120 °$C_{initial}$ for 2.0 min then +2.0°/min; **2** at 22.76 min, **3** at 22.80 min, and **4** at 25.58 min] of this crude mixture established the product ratio which was further corroborated by 300 MHz ^{1}H NMR. Pure iodolactones **2**–**4** were obtained by medium-pressure liquid chromatography (silica gel 60 EM Reagents Lobar column, 16:1 cyclohexane/ethyl acetate, 2 mL/min).

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