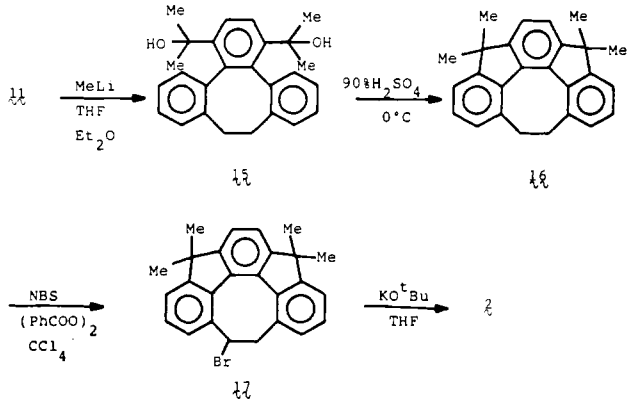
Scheme III



2 H), 7.05 (m, 8 H), 7.40 (s, 2 H). Conversion of **9** to **10** was accomplished by hydrogenation over 10% Pd–C using EtOAc as solvent. Compound **10** was not isolated and was oxidized directly with $RuO_2 \cdot H_2O$–$NaIO_4$[12] to ester **11** in 44% overall yield from **9**. Hydrogenation of **12**[8] over 10% Pd–C also yielded **11**, which formed colorless crystals[11] from cyclohexane: mp 155–156 °C; ^{1}H NMR ($CDCl_3$) δ 2.90 (s, 4 H), 3.50 (s, 6 H), 6.80–7.15 (m, 8 H), 7.90 (s, 2 H). In view that only intractable and polymeric products could be obtained through direct Friedel–Crafts cyclization of the diester **12** or its corresponding diacids, due perhaps to the reactivity of the olefinic bond toward acid conditions, the ester **11** was used instead as the pivotal intermediate in order to realize the synthesis of compound **1** (Scheme I). Thus, polyphosphoric acid smoothly converted **11** to the polycyclic ketone **13** in 58% yield. Ketone **13** formed light-yellowish needles[11] ($CHCl_3$–EtOH): mp 267–270 °C; ^{1}H NMR ($CDCl_3$) δ 2.58, 3.36 (dd, AB, J = 12 Hz, 4 H), 7.32–7.38 (dd, J = 7.14, 1.28 Hz, 2 H), 7.25–7.31 (t, J = 7.14, 7.14 Hz, 2 H), 7.68–7.72 (dd, J = 7.14, 1.28 Hz, 2 H), 7.75 (s, 2 H); UV (THF) λ_{max} 234 nm (ϵ 58 900), 290 (17 600), 318 (25 800). Introduction of a bromo group to **13** was effected by reaction with NBS and benzoyl peroxide in CCl_4 from which the monobromide **14** was isolated in 80% yield. The monobromide **14** was not purified further and was allowed to undergo dehydrobromination reaction with KO-*t*-Bu in THF to give the desired diketone **1** in 30% yield (Scheme II). Diketone **1** formed red needles[11] ($CHCl_3$): mp 305–310 °C (sealed capillary, rapid heating); ^{1}H NMR ($CDCl_3$) δ 5.83 (s, 2 H), 7.00–7.04 (dd, J = 7.48, 1.29 Hz, 2 H), 7.10–7.17 (t, J = 7.48, 7.48 Hz, 2 H), 7.44–7.48 (dd, J = 7.48, 1.29 Hz, 2 H), 7.49 (s, 2 H); UV (THF) λ_{max} 234 nm (ϵ 62 200), 299 (33 000), 313 (48 600); IR (KBr) 1700, 1595 cm^{-1}.

Treatment of **11** with excess methyllithium led to alcohol **15**. Compound **15** was not purified and was directly cyclized by treatment with concentrated H_2SO_4 to furnish **16** in 50% overall yield from **11**. Hydrocarbon **16** formed light-yellowish crystals[11] (EtOH): mp 187–189 °C; ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 6 H), 1.53 (s, 6 H), 2.85, 3.36 (dd, AB, J = 11.4 Hz, 4 H), 7.11–7.15 (dd, J = 7.24, 1.16 Hz, 2 H), 7.20–7.27 (t, J = 7.24, 7.24 Hz, 2 H), 7.32–7.36 (dd, J = 7.24, 1.16 Hz, 2 H), 7.44 (s, 2 H); UV (THF) λ_{max} 232 nm (ϵ 17 100), 259 (18 400), 268 (23 900), 306 (29 300), 319 (25 000). The introduction of a bromo group to **16** was not trivial. Indeed, due to the rigidity of the molecule, the ethano bridge could not acquire coplanarity with the benzene rings. Hence the ethano bridge is particularly difficult to functionalize.[13] Variable-temperature NMR studies show that the energy barrier for the free rotation of the ethano bridge is approximately 20 kcal/mol at 410 K, at which the two signals of the ethano bridge coalesce.[14] After some experimentation, it was finally found that reaction with 2.2 equiv of NBS and benzoyl peroxide in CCl_4 at reflux temperature converted **16** to the monobromide **17**, albeit in only very low yield. Monobromide **17** was subjected to dehydrobromination reaction with KO-*t*-Bu in THF to provide the desired compound **2** in merely 8% yield from **16** (Scheme III). Compound **2** formed light-yellowish needles[11] (EtOH): mp 215–217 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 12 H), 5.91 (s, 2 H), 6.80–6.86 (dd, J = 7.45, 1.46 Hz, 2 H), 7.00–7.10 (t, J = 7.45, 7.45 Hz, 2 H), 7.10–7.15 (dd, J = 7.45, 1.46 Hz, 2 H), 7.19 (s, 2 H); UV (THF) λ_{max} 242 nm (ϵ 15 600), 279 (61 700), 307 (7000), 351 (10 600), 370 (9600).

Compounds **1** and **2** are extremely stable both in crystalline and solution states. They presumably contain planar conjugated eight-membered rings. Thus, the electronic spectra of **1** and **2** indicate them to the highly conjugated systems by showing a bathochromic shift as well as a hyperchromic effect, which reflect a certain degree of π electron delocalization due to their coplanar geometry. The presence of a coplanar conjugated $4n$-membered ring in **1** and **2** should be reflected in a paratropic contribution to the ring currents. The high field positions of the olefinic proton resonances in the ^{1}H NMR spectra of **1** (δ 5.83) and **2** (δ 5.91) as compared to those of **12** (δ 6.90)[8] and **7** (δ 6.60)[8] convincingly support the presence of such a contribution. It is interesting to note that even the aromatic proton resonances of **1** and **2** experience high field shifts as compared to their nonplanar counterparts **13** and **16**. Furthermore, appearance of only one sharp singlet for the four methyl groups in the ^{1}H NMR spectrum of **2** also leads us to the conclusion that compound **2** should possess a coplanar structure so that all methyl groups are equivalent.

The X-ray diffraction study of **1** and **2** is in progress. The radical anion of **2** serves as a unique planar model for ESR study as compared to other presumably nonplanar radical anions of tribenzo[*a*,*c*,*e*]cyclooctene derivatives.[15] The possible conversion of the olefinic bonds of **1** and **2** to acetylenic bonds is also under investigation.

Acknowledgment. We thank Y. H. Law, K. W. Kwong, and C. W. Fung for measuring 250-MHz NMR spectra as well as accurate masses for some compounds.

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Design of Polymeric Inhibitors for the Control of Crystal Polymorphism. Induced Enantiomeric Resolution of Racemic Histidine by Crystallization at 25 °C

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Precipitation of metastable polymorphic crystalline phases is of topical importance in several fields of science. In previous studies we have described the design of low molecular[1] and polymeric additives[2] as enantioselective inhibitors of crystal nucleation and growth of conglomerates (i.e., racemic mixture of enantiomorphous crystals in monomorphic systems). The design took into account the packing arrangement in the crystal and the orientation and conformation of the molecules vis-à-vis the various

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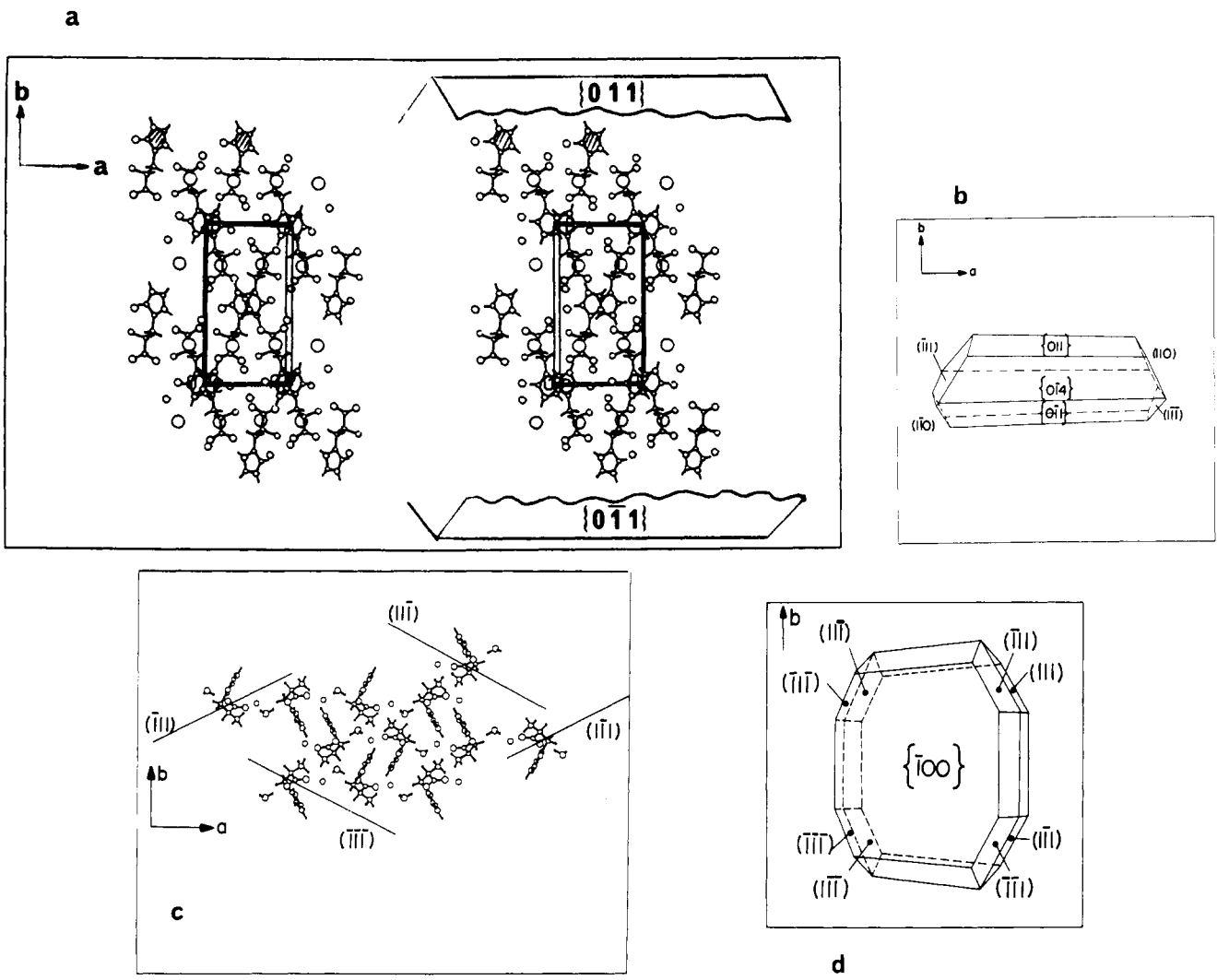

Figure 1. (a) Stereoscopic view of the packing arrangement of (*R,S*)-His·HCl·2H_2O viewed along the *c* axis; the shaded molecules of (*S*) configuration may be replaced by the (*S*)-amino acid moiety grafted onto the polymer; the orientation of the four symmetry related {011} faces is depicted. (b) Crystal morphology of (R,S)-His·HCl·2H_2O. (c) Packing arrangement of (*S*)-His·HCl·H_2O viewed along the *c* axis; the orientation of the four {1̄1̄1̄} faces are depicted. (d) Crystal morphology of (*S*)-His·HCl·H_2O.

crystal faces. This approach is now being tested for use in the precipitation of metastable phases of polymorphic crystals by kinetic control, illustrated here with the design of polymeric inhibitors for the induced resolution of racemic histidine.

Racemic histidine monohydrochloride crystallizes below 45 °C from aqueous solution in the centrosymmetric His·HCl·2H_2O phase (designated here as α). Above 45 °C it precipitates as a racemic mixture of enantiomorphous crystals of His·HCl·H_2O designated as phases β-(*S*) and β-(*R*).[3] This implies that the two phases are relatively close energetically, so that we may expect that it is possible to achieve precipitation of the metastable chiral phase by kinetic control. Many attempts by us to induce crystallization of the β phase by seeding, in the range 20–30 °C and starting from a racemic composition at the degree of supersaturation used were unsuccessful.[4] This notwithstanding, we were able to induce crystallization of the say β-(*S*) phase in the same temperature range with the assistance of optically active polymeric inhibitors of both α and β-(*R*) phases. These inhibitors were designed by considering the packing arrangements of the two crystalline forms of histidine (Figure 1a,b). The α form[5] is monoclinic ($P2_1/a$, a = 8.87 Å, b = 15.3 Å, c = 8.48 Å, β = 114.5°, Z = 4) and is an *ac* layered structure. The adjacent homochiral *ac* layers are related by a center of inversion. All the imidazole rings of (*S*)-histidine molecules point toward the $+b$ whereas those of the *R* molecules toward the $-b$ direction.

The β form crystallizes in the enantiomorphous space group $P2_12_12_1$ (a = 15.30 Å, b = 8.92 Å, c = 6.46 Å, Z = 4), displaying a {100} platelike morphology (Figure 1d). The C*–CH_2 (imidazole) bonds emerge at the {111} diagonal faces.

Following the mechanism we have proposed for inhibition, we expect that a resolved α-amino acid bearing an aromatic side group such as histidine itself, tyrosine, *p*-aminophenylalanine, or tryptophane, grafted onto a polymeric backbone (to yield a water soluble polymer with free amino-acid head groups), should be enantiospecifically adsorbed at the {011} faces of the racemic α form (Figure 1c). Adsorption will be governed by the stereochemical similarity of the amino acid head groups of the host and adsorbed guest molecules and inhibition of growth will ensue along the *b* direction of the α form. Analogously, the same polymers of say R configuration should be nucleation and growth inhibitors of β-(R) form. Consequently, resolution of the racemate should be accomplished by the preferred crystallization of (*S*)-His·HCl·H_2O.

(3) For a solubility diagram, see: Jacques, J.; Gabard, J. *Bull. Soc. Chim. Fr.* **1972**, 343.

(4) The resolution of His·HCl by entrainment was reported by Dushinsky (Dushinsky, R. *Chem. Ind.* **1934** *53*, *10*) but starting from supersaturated solutions of the enantiomers at the ratio of 2:1 and seeding at a temperature above the transition. Collet, A.; Brienne, M. J.; Jacques, J. *Chem. Rev.* **1980**, *80*, 215. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Wiley: New York, 1981.

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Table I. Crystallization from Aqueous Solution of Racemic His·HCl (2 M) in the Presence of Polymeric Additives at 25 °C

polymer concn, % w/w of His	seed type	chemical yield, %	ee, % (config)	crystallization time
none	*S*	90	rac compd[c]	16 h
0.05–0.1 (*R*)[a]	*S*	90	rac compd	16 h
0.2–0.7 (*R*)[a]	*S*	90	20–30[d] (*S*)	24–30 h
1.0 (*S*)[a]	*R*	45[b]	100 (*R*)	8 days
1.0 (*S*)[a]		60	50 (*R*)	3 days
2.0 (*R*)[a]	*S*	30[b]	100 (*S*)	3 days
3.0 (*S*)[a]		20[b]	100 (*R*)	3 days
3.0 (*R*)[a]	sand	26[b]	100 (*S*)	7 days
5.0 (*R*)[a]		25[b]	100 (*S*)	4 days
1–10.0 (*S*)[e]	*R*	90	rac compd	16 h

[a] Experiments were performed by using poly(*p*-(acrylamido)phenylalanine) $[-CH_2-CH[CO-NH-C_6H_4-CH_2-CH(COO^-)NH_3^+-]_n]$. [b] Chemical yield for one enantiomer. [c] Enantiomeric excess measured by specific rotation, phases determined by X-ray powder diffraction. [d] Resulting from a mixture of the α and β-(*S*) phases. [e] Poly(N^ϵ-methacryloyllysine).

Following our prediction, (*R*)- and (*S*)-*p*-acryloxytyrosine or *p*-methacryloxytyrosine and (*R*)- and (*S*)-(*p*-acrylamido)-phenylalanine or *p*-(methacrylamido)phenylalanine were prepared by coupling of acryloyl (or methacryloyl) chloride with tyrosine or *p*-aminophenylalanine, respectively, and were polymerized by radical catalysts.[2] Some typical results of the crystallization of racemic histidine at 25 °C in the absence and presence of various resolved monomeric or polymeric additives are given (Table I). Under the conditions of our experiments no crystallization occurred in the absence of seeds, without or in the presence of polymers. Upon addition of resolved polymers of say *R* configuration in an amount of 1–3% w/w, the enantiomorphous β-(*S*) form precipitated in the presence of seeds of the α, β-(*S*), or β-(*R*) forms or even of sand. No additional crystals of either the α or β-(*R*) forms could be detected after the crystallization, implying that under the conditions of experiment, the resolved polymers stereospecifically inhibited the heterogeneous or secondary nucleation of both these polymorphs, but much less, if at all, the nucleation and crystal growth of the β-(*S*) phase. When seeds of the α or β forms were added but only 0.1% of the polymer was used, the material precipitated in the form of racemic compound, α. With 0.2–0.7% w/w (of histidine) of the polymeric additives, a substantial inhibition of growth of the α phase was noticed, indicating that at these concentrations the polymer is interacting with the crystals (and presumably crystal nuclei) but not sufficiently to totally preclude their formation. The absence of crystals of the racemic compound, when 3% wt/wt or above of, say, (*S*) polymer is used, implies that the latter, adsorbed at the +*b* side of the nucleus, not only inhibits growth along the +*b* direction but completely smothers the growth of the nucleus. The situation is different for the orthorhombic (*S*) phase, where the same (*S*) polymer affects all four symmetry-related crystal {111} faces. Thus when resolved (*S*)-His·HCl·H_2O is grown in the presence of 0.01–0.1% w/w of the polymer, the material precipitates as a powder, whereas 1% w/w additive is sufficient to preclude its crystallization.

The need for a fine geometric match between the molecular structure of the amino acid groups grafted onto the polymer and that of the component of the crystal is further demonstrated by experiments performed with poly(N^ϵ-methacryloyllysine). This polymer was found not to prevent crystallization of the α form, even when present in concentrations as high as 10% w/w of the substrate.

The present approach has been extended to additional systems, the energetic difference between the stable and metastable phases so permitting. We expect that it will ultimately provide not only a general method for preferential crystallization of metastable polymorphs, but also a deeper understanding into the phenomenon of crystal nucleation and growth in general.

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Registry No. (±)-Histidine, 6459-59-2; (D)-poly(*p*-(acrylamido)-phenylalanine), 106520-74-5; (L)-poly[*p*-(arylamido)phenylalanine], 106520-76-7.

Hartree–Fock Descriptions of 1,3-Dipoles. Zwitterions, 1,3-Diradicals, or Hypervalent Species?

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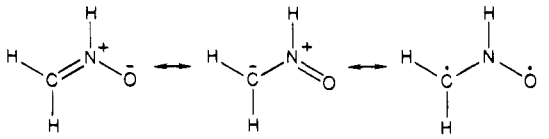
The electronic structures of 1,3-dipoles are generally represented either as zwitterions, e.g., **1**, or alternatively as singlet diradicals, e.g., **2**. Their chemistry,[1] namely, 1,3-addition to double bonds,



1 **2**

may be rationalized on either basis. Significant computational efforts have already been directed toward the characterization of 1,3-dipoles, and the literature in this area has recently been reviewed by Houk and Yamaguchi.[2] Here, we examine the utility of Hartree–Fock theory to account for the known geometries of 1,3-dipoles, restricting ourselves at present to unsubstituted 1,3-dipoles represented by planar structures and incorporating 4π electrons. A more comprehensive investigation is underway.

Yamaguchi and co-workers[3] have already noted that the best single determinant for 1,3-dipoles is not necessarily a spin-restricted Hartree–Fock (RHF) function and that a lower energy may result from the corresponding unrestricted Hartree–Fock (UHF) treatment, in which electrons of different spin are no longer constrained to occupy the same orbitals. These authors have proposed that the overlap between the two highest singly occupied molecular orbitals relates to the diradical character. Here, we suggest that the difference in energies between the closed-shell (RHF) and open-shell (UHF) singlet wave functions also provides indication of relative diradical character. The more the UHF singlet energy falls below that of the corresponding RHF quantity, the greater the diradical character of the intermediate.

At the 6-31G* level,[4,5,8] planar 4π electron forms for all 22-

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(1) For a comprehensive review, see: Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 1.
(2) Houk, K. N.; Yamaguchi, K. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1985; Vol. 2, p 407.
(3) See: Yamaguchi, K. *THEOCHEM* **1983**, *12*, 101 and references therein.
(4) (a) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta*, **1973**, *28*, 213. See also: (b) Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *66*, 217.
(5) All systems have been optimized at the UHF/6-31G* level subject to the constraint of planar structures. Where different single-bond conformers are possible all have been investigated; the data presented in Table I correspond to the lowest energy form. The GAUSSIAN 82[6] and GAUSSIAN 85[7] program systems have been employed.
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(7) Hout, R. F., Jr.; Francl, M. M.; Kahn, S. D.; Dobbs, K. D.; Blurock, E. S.; Pietro, W. J.; Steckler, R.; Hehre, W. J.; program to be submitted to Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN.

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