

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

^aExperiments were performed by using poly(*p*-(acrylamido)phenylalanine) [$-\text{CH}_2-\text{CH}[\text{CO}-\text{NH}-\text{C}_6\text{H}_4-\text{CH}_2-\text{CH}(\text{COO}^-)\text{NH}_3^+-]_n$].

^bChemical yield for one enantiomer. ^cEnantiomeric excess measured by specific rotation, phases determined by X-ray powder diffraction.

^dResulting from a mixture of the α and β -(S) phases. ^ePoly(*N*⁴-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-H₂O 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*⁴-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. (\pm)-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?

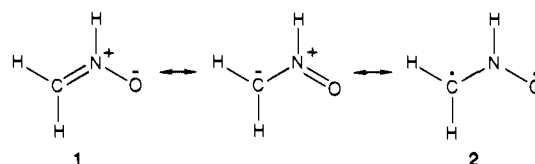
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The electronic structures of 1,3-dipoles are generally represented either as zwitterions, e.g., **1**, or alternatively as singlet diradicals, e.g., **2**. Their chemistry,¹ namely, 1,3-addition to double bonds,



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-workers³ 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 82⁶ and GAUSSIAN 85⁷ program systems have been employed.

(6) Binkley, J. S.; Frisch, M. J.; DeFrees, D. J.; Raghavachari, K.; Whiteside, R. A.; Schlegel, H. B.; Fluder, E. M.; Pople, J. A.; Department of Chemistry, Carnegie-Mellon University, Pittsburgh, PA.

(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.

Table I. UHF/6-31G* Geometries and RHF/UHF Energy Differences for Planar 4π Electron 1,3-Dipoles^a

1,3-dipole	equilibrium geometry			$E(\text{RHF}) - E(\text{UHF})$
	parameter	6-31G*	exptl	
22-Electron Systems				
	$r(\text{CN})$	1.157		0 ^b
	$r(\text{NC})$	1.291		
	$\angle(\text{CNC})$	180.0		
	$r(\text{CN})$	1.138		0 ^b
	$r(\text{NN})$	1.259		
	$\angle(\text{CNN})$	174.0		
	$r(\text{CN})$	1.130	1.168 ^c	0 ^b
	$r(\text{NO})$	1.201	1.199	
	$\angle(\text{CNO})$	180.0	180.0	
	$r(\text{NN})$	1.116	1.139 ^d	0 ^b
	$r(\text{NC})$	1.281	1.300	
	$\angle(\text{NNC})$	180.0	180.0	
	$r(\text{NN})$	1.099	1.133 ^e	0 ^b
	$r(\text{NN})$	1.239	1.237	
	$\angle(\text{NNN})$	173.8	180.0	
	$r(\text{NN})$	1.092	1.128 ^f	0 ^b
	$r(\text{NO})$	1.179	1.184	
	$\angle(\text{NNO})$	180.0	180.0	
24-Electron Systems				
	$r(\text{CN})$	1.360	1.343 ^g	14
	$\angle(\text{CNC})$	128.3	127.9	
	$r(\text{CN})$	1.351		11
	$r(\text{NN})$	1.310		
	$\angle(\text{CNN})$	130.2		
	$r(\text{CN})$	1.334	1.296-1.327 ^h	6
	$r(\text{NO})$	1.245	1.274-1.300	
	$\angle(\text{CNO})$	125.4	124.6-126.2	
	$r(\text{NN})$	1.300		12
	$r(\text{NN})$	1.303		
	$\angle(\text{NNN})$	125.0		
	$r(\text{NN})$	1.284		7
	$r(\text{NO})$	1.232		
	$\angle(\text{NNO})$	127.3		
	$r(\text{NO})$	1.219	1.224 ⁱ	5
	$\angle(\text{ONO})$	125.8	125.3	
	$r(\text{CO})^h$	1.340		34
	$\angle(\text{OCO})$	121.4		
	$r(\text{CO})$	1.350		29
	$r(\text{ON})$	1.332		
	$\angle(\text{CON})$	115.0		
	$r(\text{CO})$	1.354		9
	$r(\text{OO})$	1.286		
	$\angle(\text{COO})$	114.8		
	$r(\text{NO})$	1.334		43
	$r(\text{ON})$	1.335		
	$\angle(\text{NON})$	114.7		
	$r(\text{NO})$	1.343		38
	$r(\text{OO})$	1.290		
	$\angle(\text{NOO})$	111.4		
	$r(\text{OO})^h$	1.295	1.272 ^j	48
	$\angle(\text{OOO})$	111.6	116.8	

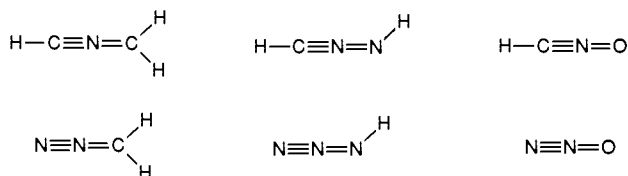
^a Bond lengths in angstroms, bond angles in degrees, and energies in kcal mol⁻¹. ^b Collapses to RHF solution. ^c Winnewisser, B. P.; Winnewisser, M.; Winther, F. *J. Mol. Spectrosc.* **1974**, *51*, 65. ^d Cox, A. P.; Thomas, L. F.; Sheridan, J. *Nature (London)* **1950**, *181*, 1000. Sheridan, J. *Adv. Mol. Spectrosc., Proc. Int. Meet., 4th 1962*, *1*, 139. ^e Winnewisser, M.; Cook, R. L.; *J. Chem. Phys.* **1964**, *41*, 999. Linear NNN arrangement assumed. ^f Townes, C. H.; Shawlow, A. L. *Microwave Spectroscopy*; McGraw Hill: New York, 1955. Burris, G. A., Jr.; Gordy, W. *Phys. Rev.* **1956**, *101*, 599. Rao, K. N.; *Ann. N. Y. Acad. Sci.* **1973**, *220*, 17. ^g Grigg, R.; Maloney, J. F.; Mongkolaussavaratana, T.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1986**, 421. ^h Range of values from X-ray crystal structures for substituted nitrones. Brown, J. N.; Trefonas, L. M. *Acta Crystallogr., Sect.*

Table I footnotes (Continued)

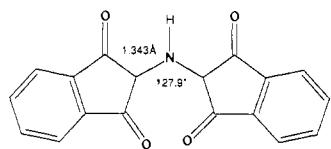
B: Struct. Crystallogr. Cryst. Chem. 1973, B29, 237 and references therein. Inouye, Y. *Ibid.* 1984, C40, 142. ⁴ Values for nitromethane from: Cox, A. P.; Waring, S. *Trans. Faraday Soc.* 1972, 68, 1060. NO bond length (1.202 Å) and ONO bond angle (130.6°) in ClNO₂ from: Miller, D. J.; Sinnott, K. M. *J. Chem. Soc.* 1958, 350. Clayton, L.; Williams, Q.; Weatherly, T. L. *J. Chem. Phys.* 1959, 30, 1328; 1959, 31, 554. Oka, T.; Morino, Y. *J. Mol. Spectrosc.* 1963, 11, 349. NO bond length (1.180 Å) and ONO bond angle (136°) in FNO₂ from: Legon, A. C.; Millen, D. J. *J. Chem. Soc. A* 1968, 1736. In HONO₂, 1.205 Å (average value) and 130.3°, from: Millen, D. J.; Morton, J. R. *J. Chem. Soc.* 1960, 1523. Cox, A. P.; Riveros, J. M. *J. Chem. Phys.* 1965, 42, 3106. ⁷ Tranbarulo, R.; Ghosh, S. N.; Burrus, C. A., Jr.; Gordy, W. D. *J. Chem. Phys.* 1953, 21, 851. Hughes, R. H.; *Ibid.* 1953, 21, 959. Tanaka, T.; Morino, Y. *J. Mol. Spectrosc.* 1970, 33, 539.

electron 1,3-dipoles investigated appear to be properly described in terms of closed-shell (RHF) wave functions (Table I). On the other hand, open-shell (UHF) solutions are preferred for all 24-electron (allyl type) 1,3-dipoles considered.⁹ Except for CH₂OO, energy differences for oxygen-centered dipoles are significantly larger than those for nitrogen-centered species, consistent with the notion that the more electronegative oxygen is less able than nitrogen to give up a π electron and bear positive charge, as demanded by closed-shell zwitterionic resonance structures.

Calculated heavy-atom bond lengths and skeletal bond angles for fulminic acid, diazomethane, hydrazoic acid, and nitrous acid (with 22 electrons) are in reasonable accord with their respective experimental structures. Comparison of calculated (and experimental) bond lengths for 1,3-dipoles with those found in two-heavy-atom hydrides¹⁰ suggests that each of these molecules incorporates essentially a fully formed double bond and a fully formed triple bond. These molecules appear to be most appropriately described in terms of *hypervalent structures* in which the central nitrogen is allocated more than its normal complement of valence electrons.



UHF/6-31G* geometries for 24-electron 1,3-dipoles are in reasonable accord with the limited experimental structural data. The calculated CN bond length (1.360 Å) and CNC bond angle (128.3°) for the parent azomethine ylide are quite close to those recently reported in the X-ray crystal structure of the substituted system.¹¹ While calculations for the parent nitrene yield CN and



NO bond lengths which fall slightly outside of the range of experimental distances for substituted systems, the UHF/6-31G* NO bond length and ONO bond angle in HNO₂ (1.219 Å and 125.8°, respectively) are in excellent agreement with values found in nitromethane (1.224 Å and 125.3°). The OO bond distance calculated for ozone at the UHF/6-31G* level (1.295 Å) is also in reasonable accord with the experimental value (1.272 Å),

(8) Two or more geometrical (cis-trans) isomers exist for some of the systems investigated. Only the lowest energy structure (at UHF/6-31G) has been considered and has been depicted in Table I. A detailed description of the energy surfaces for 1,3-dipolar species will appear in our upcoming full paper.

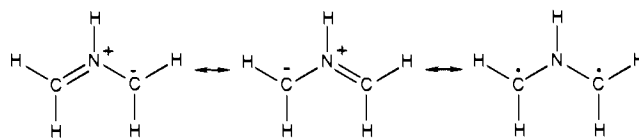
(9) These same trends have also been uncovered by Hiberty and Leforestier [Hiberty, P. C.; Leforestier, C. *J. Am. Chem. Soc.* 1978, 100, 2012] who performed RHF/STO-3G calculations followed by 6 × 6 CI on a selection of 1,3-dipolar intermediates. Specific diradical and zwitterionic contributions were assessed by expansion in terms of valence-bond wave functions. Hiberty and Leforestier noted that the diradical contributions to the 24-electron 1,3-dipoles ranged between 43% and 59% of the total (the largest contribution being found for ozone), while the corresponding contributions for 22-electron 1,3-dipoles ranged from 17% to 32%.

(10) For a summary, see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; p 146ff.

(11) Grigg, R.; Maloney, J. F.; Mongkolaussavaratana, T.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* 1986, 421.

although the calculated bond angle (111.6°) is significantly smaller than the experimental quantity (116.8°).

Aside from the nitro compound (the NO bond lengths of which are typical of normal double linkages), which appears to be most appropriately described as a hypervalent molecule, the calculated (and experimental) equilibrium structures for all of the 24-electron 1,3-dipoles incorporate two bonds which are midway between normal single and double linkages. This suggests description of this species, and of the other 22-electron 1,3dipoles, in terms of resonance structures in which the central atom is normal valent.



Structural differences between 22- and 24-electron dipoles may be rationalized in terms of differences in bond energies.¹² Hypervalent descriptions for 22-electron 1,3-dipoles each incorporate either a strong CN or a strong NN triple bond, whereas expansion of the valence octet about the central element in the 24-electron species results at best in the creation of two double bonds.

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(12) Dobbs, K. D.; Kahn, S. D.; Hehre W. J.; Pople, J. A., unpublished results.

Stereochemical Course of the Cryptic Elimination and Cyclization Steps in the Reaction Catalyzed by Dehydroquinase

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In a pivotal transformation in the shikimate pathway,¹ dehydroquinase catalyzes the conversion of the seven-carbon keto acid 3-deoxy-D-arabino-heptulosonic acid 7-phosphate (DAHP, **1**) to dehydroquinate (DHQ, **2**), the first carbocyclic metabolite in the biosynthesis of the three aromatic amino acids. Previous studies suggested that the enzymatic reaction may proceed in five steps. First, oxidation of the hydroxyl group at C-5 by a bound NAD⁺ would facilitate the β -elimination of phosphate; reduction at C-5, followed by ring opening, would then lead to an internal aldol reaction producing DHQ (Scheme I).² While this proposal accommodates the limited mechanistic information available,^{2,3} none of the postulated intermediates have

(1) (a) Haslam, E. *The Shikimate Pathway*; Wiley: New York, 1974. (b) Weiss, U.; Edwards, J. M. *The Biosynthesis of Aromatic Compounds*; Wiley: New York, 1980.

(2) (a) Srinivasan, P. R.; Rothschild, J.; Sprinson, D. B. *J. Biol. Chem.* 1963, 238, 3176. (b) Rotenberg, S. L.; Sprinson, D. B. *Proc. Natl. Acad. Sci. U. S. A.* 1970, 67, 1669.