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Solvent effects on the transition states for nucleophilic additions to substituted acetaldehydes

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bonds between helices. The crystal structure has alternating sheets of aromatic residues (Phe, Δ Phe) and aliphatic residues (Val, Ala) parallel to the *ab* plane and separated by half translation along the *c* direction. Hydrophobic sheets have been observed in other peptide crystal structures also.¹⁴ Adjacent helices are parallel to each other. Head to tail hydrogen bonding is commonly observed in short helical structures containing Aib or Δ Phe residues, packed in either parallel to antiparallel fashion.^{3a,4a,b,15}

The high propensity of Δ Phe residues for helix formation is clearly demonstrated as the three Δ Phe residues present in the sequence overcome the effect of the remaining five residues, most of which are known to be poor α -helix formers.¹⁶ The nonapeptide sequence containing three Δ Phe residues shows seven consecutive overlapped type III β -turns. Hence, there is no one to one correspondence between the number of β -bonds and the number of Δ Phe residues.^{4a} It is worth noting that even though Δ Phe² and Δ Phe⁶ are contiguously separated by three saturated residues, viz. Phe³-Ala⁴-Phe⁵, the 3_{10} -helical nature is retained. Thus, the utility of Δ Phe residues in designing polypeptide helices for the eventual design of protein mimics stands established.

Whether dehydro residues can also be used in designing α -helices and the role of the number and positioning of the dehydro residues in relation to the non-dehydro residues for defining the polypeptide conformation need to be further investigated by carrying out more peptide syntheses and structural studies.

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Supplementary Material Available: Synthesis and X-ray experimental details and tables of positional and thermal parameters, bond lengths, and bond angles for peptide I (27 pages); table of observed and calculated structure factors (24 pages). Ordering information is given on any current masthead page.

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Solvent Effects on the Transition States for Nucleophilic Additions to Substituted Acetaldehydes

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The origin of the π -facial selectivity in nucleophilic additions to carbonyl groups has been of considerable recent interest both experimentally¹ and theoretically,²⁻⁴ and several models have been

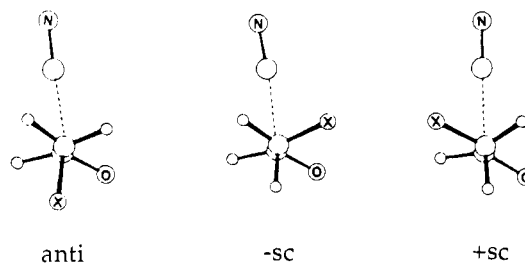
Table I. Effect of Solvents on the Relative Energies (kcal/mol) of Transition States

X	ϵ	anti	-sc	+sc
CH ₃	1	0.62	0.00	1.42
	7.2	0.00	0.82	1.20
	78.5	0.00	1.09	1.19
F	1	0.00	3.67	0.49
	7.2	0.80	2.99	0.00
	78.5	1.06	2.91	0.00
SiH ₃	1	0.85	0.00	3.26
	7.2	0.00	1.19	3.57
	78.5	0.00	1.64	3.61
CN	1.0	0.00	2.53	1.41
	7.2	0.03	0.22	0.00
	78.5	0.30	0.00	0.03

proposed to explain the experimental observations.⁵ A series of careful theoretical studies of the addition to substituted acetaldehydes in the gas phase has recently been reported using both cyanide ion^{2,4} and lithium hydride as nucleophiles.^{3,4} However, in practice, all nucleophilic additions to carbonyl groups are carried out in solution. The addition of a molecule of lithium hydride across a C=O group in the gas phase would appear to have little to do with nucleophilic additions of hydride ions in solution. Here, the reaction need not proceed via a concerted addition, and it is likely to involve ion pairs or free ions. The addition of cyanide ion is a fundamentally simpler process, and the gas-phase calculations may well have a bearing on the process in solution.

Wong and Paddon-Row² have noted that there are important electrostatic effects in the addition of cyanide ion to substituted acetaldehydes. The electrostatic interactions will be mediated by solvents, and the relative energies of the several conformationally different transition states may vary significantly on going from the gas phase to solution. The Onsager reaction field model⁶ as incorporated into ab initio MO theory using a spherical cavity for the solute has been found to be remarkably successful in reproducing the effects of solvents on the relative energies of conformers.⁷ Therefore, we have applied it to the study of cyanide ion additions using the RHF/6-31G* level of theory.⁸

The anti, +sc, and -sc transition-state conformers were examined by geometry optimization at the RHF/6-31G* level for $\epsilon = 1$ (gas phase), $\epsilon = 7.2$ (a weakly polar solvent such as dimethoxyethane or tetrahydrofuran ($\epsilon = 7.6$)), and $\epsilon = 78.5$ (a highly polar solvent; any value over ~ 50 would give the same result) where X = CH₃, F, CN, and SiH₃. The relative energies



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- (8) The reaction field model used herein, i.e., a spherical cavity and considering just the dipole, is the simplest implementation. It, however, remains the only model for which analytical gradients (ref 7a) and second derivatives (Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Chem. Phys.* 1991, 95, 8991) are available. In view of the success of this model in other cases (ref 7), the present calculations would be expected to correctly reproduce the trends of relative energies with changing the dielectric constant.

χ	conf	ϵ	$r(\text{C}=\text{O})$	$\text{NC}\cdots\text{C}$	$\angle\text{NC}\cdots\text{C}=\text{O}$	μ
CH_3	anti	1.0	1.2386	1.9364	113.39	6.91
	anti	78.5	1.2532	1.8411	111.12	7.75
	+sc	1.0	1.2402	1.9188	112.44	6.47
	+sc	78.5	1.2512	1.8691	110.16	7.65
	-sc	1.0	1.2415	1.9142	113.00	5.72
	-sc	78.5	1.2515	1.8531	111.28	6.62
F	anti	1.0	1.2362	1.9055	113.94	5.00
	anti	78.5	1.2457	1.8575	111.80	5.83
	+sc	1.0	1.2302	2.0095	113.06	6.09
	+sc	78.5	1.2433	1.9091	111.16	6.70
	-sc	1.0	1.2276	1.9837	113.98	6.17
	-sc	78.5	1.2406	1.8959	111.34	6.94
SiH_3	anti	1.0	1.2358	1.9824	113.37	7.84
	anti	78.5	1.2526	1.8572	110.88	9.07
	+sc	1.0	1.2394	1.8933	112.61	6.79
	+sc	78.5	1.2494	1.8616	110.05	8.67
	-sc	1.0	1.2391	1.9640	113.25	7.42
	-sc	78.5	1.2491	1.8847	111.60	7.84
CN	anti	1.0	1.2255	1.9673	114.07	4.39
	anti	78.5	1.2325	1.9271	112.21	5.31
	+sc	1.0	1.2230	2.0200	112.64	5.94
	+sc	78.5	1.2338	1.9206	111.21	6.49
	-sc	1.0	1.2225	1.9959	114.54	6.54
	-sc	78.5	1.2333	1.9191	112.00	7.42

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