bonds between helices. The crystal structure has alternating sheets of aromatic residues (Phe, ΔPhe) 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 ΔPhe residues, packed in either parallel to antiparallel fashion.[3a,4a,b,15]

The high propensity of ΔPhe residues for helix formation is clearly demonstrated as the three ΔPhe 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 ΔPhe residues shows seven consecutive overlapped type III β-turns. Hence, there is no one to one correspondence between the number of β-bends and the number of ΔPhe residues.[4a] It is worth noting that even though ΔPhe^2 and ΔPhe^6 are contiguously separated by three saturated residues, viz. Phe^3-Ala^4-Phe^5, the 3_{10}-helical nature is retained. Thus, the utility of ΔPhe 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.

Acknowledgment. The authors thank Prof. M. A. Viswamitra and Prof. K. K. Tewari for encouragement and the Department of Biotechnology, Government of India, for access to facilities. Dr. Rajashankar thanks CSIR, India, for a fellowship.

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.

---

(14) Gorbitz, C. H.; Etter, M. C. *Int. J. Pept. Protein Res.* **1992**, *39*, 93.
(15) Karle, I. L. *Biopolymers* **1989**, *28*, 1.
(16) Chou, P. Y.; Fasman, G. D. *Biochemistry* **1974**, *13*, 222.

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

Andrzej S. Cieplak* and Kenneth B. Wiberg*

Department of Chemistry, Yale University
New Haven, Connecticut 06517

Received August 17, 1992

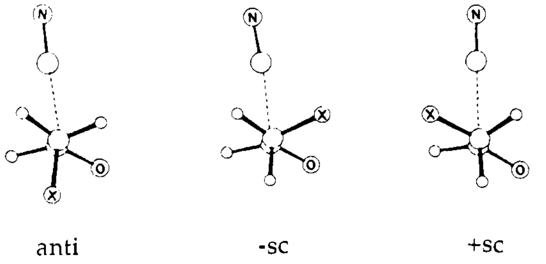
The origin of the π-facial selectivity in nucleophilic additions to carbonyl groups has been of considerable recent interest both experimentally[1] and theoretically,[2–4] and several models have been proposed to explain the experimental observations.[5] A series of careful theoretical studies of the 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.

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

Wong and Paddon-Row[2] 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 model[6] 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 = CH_3, F, CN, and SiH_3. The relative energies



---

(1) Danishefsky, S. J.; Langer, M. *J. Org. Chem.* **1985**, *50*, 3672. Cheung, C. K.; Tseng, L. T.; Lin, M. H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598. Fraser, R. R.; Stanciulescu, M. *J. Am. Chem. Soc.* **1987**, *109*, 1580. Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353. Mukherjee, D.; Wu, Y.-D.; Froczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328. Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447. Okada, K.; Tomita, S.; Oda, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 459. Mehta, G.; Kahn, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 6140. Halterman, R. L.; McElvoy, M. *J. Am. Chem. Soc.* **1990**, *112*, 6690. Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99. DiMaio, G.; Migneco, L. M.; Vecchi, E. *Tetrahedron* **1990**, *46*, 6053. Biesemans, M.; van de Woude, H.; van Hove, L. *Bull. Soc. Chim. Belg.* **1990**, *99*, 29. Nagao, Y.; Goto, M.; Ochiai, M. *Chem. Lett.* **1990**, 1507. Lange, J. H. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1991**, *47*, 1495. Li, H.; Mehta, G.; Padma, S.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2006. Hahn, J. M.; le Noble, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1916. Paquette, L. A.; Underiner, T. L.; Gallucci, J. C. *J. Org. Chem.* **1992**, *57*, 86. Mehta, G.; Praveen, M. *Tetrahedron Lett.* **1992**, *33*, 1759. Gmeiner, P.; Bollinger, B. *Ann. Chem.* **1992**, 273. Senda, Y.; Okamura, K.; Kuwahara, M.; Ide, M.; Itoh, H.; Ishiyama, J.-I. *J. Chem. Soc., Perkin. Trans. 2* **1992**, 799.

(2) Wong, S. S.; Paddon-Row, M. N. *Aust. J. Chem.* **1991**, *44*, 765. Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327; **1990**, 456.

(3) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5027. Wu, J.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908.

(4) (a) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1991**, *47*, 9005. (b) Frenking, G.; Köhler, K. F.; Reetz, M. *Angew. Chem.* **1991**, *103*, 1167. (c) Coxon, J. M.; McDonald, D. Q. *Tetrahedron* **1992**, *48*, 3353.

(5) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205. Ahn, N. T.; Eisenstein, O *Nouv. J. Chem.* **1977**, *1*, 61. Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 1. Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

(6) Onsager, L. *J. Am. Chem. Soc.* **1936**, *56*, 1486.

(7) (a) Wong, M. W.; Frisch, M.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776. (b) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 523, 1645.

(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.

0002-7863/92/1514-9226$03.00/0

Table II. Effect of Solvents on Transition-State Geometries and Dipole Moments

X	conf	ϵ	r(C=O)	NC···C	∠NC···C=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

are given in Table I. It can be seen that the preferred conformer is solvent dependent. When X = CH_3, the −sc conformer is predicted to be preferred in the gas phase, and it has the lowest dipole moment (5.72 D). If everything else were equal, one would expect the conformer with the lowest dipole moment to be favored in the gas phase. In solution, the anti conformer is predicted to be more stable. With X = SiH_3, the −sc form is favored in the gas phase, as was found with X = CH_3. Here, the +sc form has the lower dipole moment, but the −sc form would have a favorable attractive interaction between the positively charged silicon and the negatively charged oxygen. In solution, this would be less important, and now the anti form is favored. With X = F, the anti form with the lower dipole moment is favored in the gas phase, but the +sc form is favored in solution. Finally, with X = CN, the anti form with the lowest dipole moment is again favored in the gas phase, but now all conformers have comparable energies in solution. It appears that the conformational preferences for the gas phase are largely determined by electrostatic interactions which are minimized on going to a solvent.

It is, of course, possible that the change in conformer preference might reflect a change in the ground-state conformational energies of the reactant aldehydes on going from the gas phase to solution.[4a] This was examined in the case of fluoroacetaldehyde. The +sc transition state corresponds to the 180° (anti) ground-state conformer, whereas the anti and −sc transition states correspond to the 70° (gauche) rotational transition state for fluoroacetaldehyde. The anti → gauche energy difference for the aldehyde is calculated (RHF/6-31G*) to be 5.7 kcal/mol in the gas phase, and it decreases to 3.5 kcal/mol in solution. Thus, if the change in ground-state conformer energy difference applied to the cyanide addition transition states, the anti TS should drop in energy by 2.2 kcal/mol relative to +sc on going from the gas phase to solution. However, the contrary is true, with the anti TS going up in energy by 1.6 kcal/mol relative to +sc.

Some key structural parameters for the transition states are recorded in Table II. The effect of solvents is to increase the C=O bond length, decrease the NC···C distance, decrease the angle at which the CN^- attacks the carbonyl, and increase the dipole moment. Therefore, the reaction appears to have progressed further toward products in solution than in the gas phase.

These data indicate the importance of considering solvent effects in determining π-facial selectivity. The origin of the conformational preferences in solution will be considered in detail in a full paper describing this work.

Calculations. The calculations were carried out using GAUSSIAN-92.[9] The SCRF calculations need a cavity size. It was chosen in each case using a molecular volume derived from the 0.001 e/B^3 surface[10] plus an empirically derived value of 0.5 Å to account for the nearest approach of solvent molecules.[7a] The cavity radii used were the following: X = CH_3, 3.91 Å; X = F, 3.70 Å; X = SiH_3, 4.09 Å; X = CN, 3.93 Å.

Acknowledgment. This investigation was supported by a grant from the National Institutes of Health.

---

[9] Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzales, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, G. A. *GAUSSIAN-92*, Gaussian Inc.: Pittsburgh, PA, 1992.

[10] Wong, M. W.; Wiberg, K. B.; Frisch, M. J. Manuscript in preparation.

Bilayer-Bridging Bolaamphiphilic Lipids

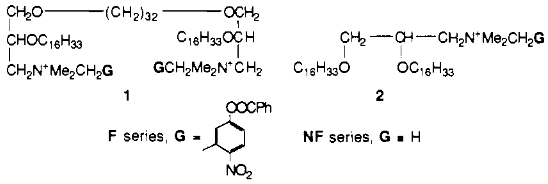
Robert A. Moss* and Jong-Ming Li

Department of Chemistry, Rutgers
The State University of New Jersey
New Brunswick, New Jersey 08903

Received July 23, 1992

The unusual bolaamphiphilic phytanyl lipids isolated from the thermophilic (50–80 °C) archaebacteria have been the subjects of structural, modeling, and synthetic studies.[1,2] Understanding the relation between their molecular structure and their function within the bacterial membranes could lead to "designer" lipids and liposomes of enhanced thermal stability. The 32-carbon main chain of such lipids permits them to bridge typical membranes, anchoring their head groups at both outer and inner aqueous/lipid interfaces.[1a] To explore whether this affords enhanced membrane stability, model lipids were synthesized.[1a,c,e,2b] Evidence from permeability[1c] and structural studies[1a,e] suggests greater robustness for liposomes bolstered by bridging bolaform lipids.

Our interest in lipid molecular structure and intraliposomal dynamics[2,3] led us to prepare the desmethylated, model functional bolaamphiphile ("bola") **1-F**.[2b] We dispersed **1-F** in conventional bilayer liposomes of the nonfunctional, monopolar host lipid **2-NF**,[2b] surface specifically cleaved[3c] the outer ester head groups of **1-F**, and followed the dynamics of **1-F** lipid reequilibration in the resultant "differentiated" coliposomes.[2b] At least 40% of the **1-F** molecules adopted nonbridging, U-plan arrangements in the outer leaflet of the **2-NF** bilayer (Figure 1, pattern x), and the observed inner → outer, transbilayer ("flip-flop") dynamics of the inner liposomal head groups of **1-F** were very similar to those of simple monopolar functional lipids in bilayers of **2-NF**.[2b] There was no evidence for extensive bridging by **1-F** or for enhanced thermal stability in these **1-F**/**2-NF** coliposomes.



---

[1] (a) Yamauchi, K.; Moriya, A.; Kinoshita, M. *Biochim. Biophys. Acta* **1989**, *1003*, 151. (b) Stewart, L. C.; Kates, M.; Ekiel, I. H.; Smith, I. C. P. *Chem. Phys. Lipids* **1990**, *54*, 115. (c) Yamauchi, K.; Sakamoto, Y.; Moriya, A.; Yamada, K.; Hosokawa, T.; Higuchi, T.; Kinoshita, M. *J. Am. Chem. Soc.* **1990**, *112*, 3188. (d) Yamauchi, K.; Yamada, K.; Kinoshita, M.; Kamikawa, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2088. (e) Kim, J.-M.; Thompson, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 637.

[2] (a) Moss, R. A.; Fujita, T. *Tetrahedron Lett.* **1990**, *31*, 7559. (b) Moss, R. A.; Fujita, T.; Okumura, Y. *Langmuir* **1991**, *7*, 2415.

[3] (a) Moss, R. A.; Okumura, Y. *J. Am. Chem. Soc.* **1992**, *114*, 1750. (b) Moss, R. A.; Ganguli, S.; Okumura, Y.; Fujita, T. *J. Am. Chem. Soc.* **1990**, *112*, 6391. (c) Moss, R. A.; Bhattacharya, S.; Chatterjee, S. *J. Am. Chem. Soc.* **1989**, *111*, 3680.