

The Role of Primary–Secondary Orbital Interactions in Affecting Regioselectivities. Cycloaddition Reactions between 1,3-Dipoles and Electron-Deficient Alkynes

Michael D. Gordon,*^{1a} Peter V. Alston,^{1a} and Angelo R. Rossi^{1b}

Contribution from E. I. du Pont de Nemours and Company, Inc., Chemicals, Dyes and Pigments Department, Jackson Laboratory, Wilmington, Delaware 19898, and the Department of Chemistry,

The University of Connecticut, Storrs, Connecticut 06268. Received February 27, 1978

Abstract: The observed loss in regioselectivity displayed in a number of cycloaddition reactions between electron-deficient alkynes and some well-known hetero-1,3-dipoles is attributed to a unique long-range attraction between the primary carbon HOMO of the dipoles and the “secondary” adjacent atom LUMO of the electron-withdrawal group on the acetylenes. This primary–secondary interaction counterbalances the primary–primary preference which dominates for the olefinic cycloadditions. It is found to be of comparable magnitude to the primary interactions when the dipolarophile is a triple-bonded species as a result of its delocalized LUMO distribution and favorable overlap in the cycloaddition transition state. The highly delocalized nature of the LUMOs of electron-deficient alkynes was established with the aid of ab initio STO-3G and valence-electron CNDO/2 and MINDO/3 calculations performed on cyanoacetylene and acrylonitrile. Contrary to the semiempirical results, the ab initio calculations predict the proper ionization potential stabilization for each of the cyano-containing species compared to their parent hydrocarbons.

Introduction

Frontier molecular orbital theory has been used highly successfully to explain the relative rates and regioselectivity of 1,3-dipolar cycloaddition reactions.^{2–5} By a careful consideration of FMO characteristics in terms of energies and calculated orbital distributions it has been possible to account for a myriad of experimental findings. The elegant “generalized” frontier orbital approach of Houk represents a highly predictive application in this area.² A number of alternative methods^{6,7} have been formulated including the more quantitative procedure developed by Bastide et al.⁸ Encouragingly ab initio calculations on Diels–Alder and 1,3-dipolar reaction surfaces support the applicability of the frontier orbital concept.^{9,10}

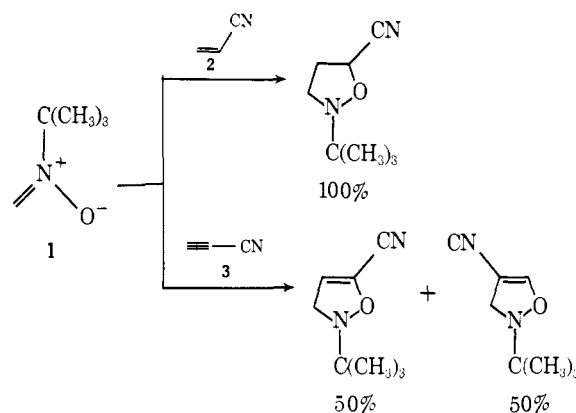
The vast majority of experimental observations on cycloaddition reactions can be understood by an assessment of the frontier orbital characteristics of the reacting atomic centers or primary orbitals. However, the importance of secondary orbital interactions is known and in some cases can alter the expected regioselectivity dramatically.¹¹ These nonbonding forces also allow a rationalization for the high degree of exo-endo stereoselectivity¹² which prevails in many cycloadditions. The significance of secondary orbital contributions is not surprising in light of the long-range bonding properties displayed by π orbitals¹³ which are manifested in charge-transfer complexes.¹⁴

In this paper, we propose an additional long-range attractive interaction between primary and secondary orbitals. By consideration of this stabilization force, it is possible to offer a consistent explanation for a number of experimental results in which well-known hetero-1,3-dipoles react with substituted alkynes and yield different regioisomeric distributions than are found for the corresponding alkenes. It will be shown that primary–secondary orbital attractions cannot be neglected when the dipolarophile is a triple-bonded compound as a result of its highly delocalized LUMO electronic distribution, and the opportunity for highly favorable overlap offered in the transition state.

Discussion

There are a number of examples^{8c,15–18} in the literature in which it has been observed that substituted alkynes display

different regiochemistry than the analogous substituted alkenes in 1,3-dipolar cycloadditions. Houk has offered theoretical interpretations for two cases involving nitrile oxides and nitrones.^{2b} For each dipole, reduced regioselectivity was observed when electron-deficient acetylenes were the dipolarophile. The latter system has been treated in some detail using *N*-*tert*-butylnitrone (**1**), acrylonitrile (**2**), and cyanoacetylene (**3**) as



models in conjunction with CNDO/2 calculations.^{2c} Experimentally a ~50:50 mixture is formed with the latter dipolarophile, while only the 5 isomer is observed with the double-bonded species. Similar trends are obtained with the methyl ester derivatives.¹⁷ In order to explain these findings it was assumed that normal dipole HO–dipolarophile LU control favored neither isomer and that an inverse dipole LU–dipolarophile HO interaction was significant for the olefins whose ionization potentials tend to be ~0.8 eV lower than the corresponding triple-bonded compounds.^{2c}

The importance of the inverse orbital interaction in the above reactions can be questioned from both an experimental and theoretical viewpoint. It has been observed that the reaction rate of nitrone cycloadditions is strongly accelerated by electron-withdrawing groups on the dipolarophile, and nitroethylene, which is expected to have a higher ionization potential than methyl propiolate, reacts with *N*-*tert*-butylnitrone and produces solely the 5 isomer.¹⁷ Also the best assessments of the frontier orbital gaps for the reaction of *N*-*tert*-butylnitrone with acrylonitrile indicate that the dipole HO–dipolar-

Table I. Ionization Potentials (IP) and Electron Affinities (EA)

molecule	ϵ_{HOMO} , eV			ϵ_{LUMO} , eV			experimental ^a	
	ab initio	CNDO/2	MINDO/3	ab initio	CNDO/2	MINDO/3	IP	EA
ethylene	-8.78	-16.03	-10.10	8.63	5.34	2.09	10.52	-1.5
acrylonitrile	-9.10	-14.46	-9.84	6.11	3.43	1.24	10.92	~0
acetylene	-9.52	-17.54	-10.77	10.79	7.46	3.20	11.40	
cyanoacetylene	-9.82	-15.24	-10.18	6.52	4.21	1.72	11.6	~0
nitron	-5.66	-11.45	-9.33	6.86	3.26	1.00		
<i>N</i> -methylnitron	-5.47	-10.99	-9.13	7.13	3.14	1.07	8.64 ^b	-0.5 ^b

^a Reference 2a. ^b Results for *N*-*tert*-butylnitron (ref 2a).

Table II. Frontier Orbital Coefficients

1. Acrylonitrile							
atom ^b	C_{LUMO}			normalized (C^2_{LUMO}) ^a			
	ab initio	CNDO/2	MINDO/3	ab initio	CNDO/2	MINDO/3	
C_{α}	0.752	0.657	0.669	0.451	0.432	0.448	
C_{β}	-0.592	-0.540	-0.569	0.277	0.292	0.324	
C_{cyano}	-0.322	-0.298	-0.290	0.096	0.089	0.084	
N	0.471	0.434	0.380	0.176	0.188	0.144	
2. Cyanoacetylene							
atom ^b	C_{LUMO}			normalized (C^2_{LUMO}) ^a			
	ab initio	CNDO/2	MINDO/3	ab initio	CNDO/2	MINDO/3	
C_{α}	0.651	0.569	0.575	0.325	0.324	0.331	
C_{β}	-0.460	-0.412	-0.440	0.169	0.170	0.194	
C_{cyano}	-0.491	-0.451	-0.460	0.201	0.203	0.212	
N	0.630	0.550	0.513	0.305	0.303	0.263	
3. <i>N</i> -Methylnitron							
atom	C_{HOMO}			normalized (C^2_{HOMO}) ^a			
	ab initio	CNDO/2	MINDO/3	ab initio	CNDO/2	MINDO/3	
C	0.698	0.680	0.717	0.495	0.463	0.514	
N	0.115	0.150	0.308	0.014	0.023	0.095	
O	-0.718	-0.713	-0.612	0.490	0.514	0.375	

^a Mulliken analysis was performed on ab initio results to obtain "normalized" data. See ref 30. ^b The C_{α} is the unsubstituted primary carbon atom and the C_{β} is the substituted primary carbon atom.

ophile LU orbital difference is smaller by at least 2.5 eV. An energy gap difference of ~ 1 eV has been offered as a cutoff point for the neglect of the less important FMO interaction.^{2c} Furthermore, inspection of the calculated CNDO HO coefficients of *N*-*tert*-butylnitron which are given in ref 2c reveals identical values for carbon and oxygen. Because of the greater overlap generated by π orbitals of a carbon atom relative to oxygen, one could interpret the observed alkene results in terms of conventional dipole HO-dipolarophile LU control.

Also, application of the quantitative approach which has been formulated by Bastide et al.⁸ leads to a similar prediction in that the 5 isomer should dominate independent of the number of unsaturated bonds in the electron-poor dipolarophile. Therefore the observed behavior of the acetylenic species in yielding isomer mixtures when reacted with *N*-*tert*-butylnitron can be considered as being unexpected, and not readily explainable.

Computational Results. In order to understand the above experimental findings from a theoretical viewpoint, we began by investigating in detail the orbital properties of select alkenes, alkynes, and nitrones. Acrylonitrile, cyanoacetylene, and the unsubstituted and *N*-methylnitron were employed as models. These molecules were characterized at the ab initio STO-3G¹⁹ and the valence-electron CNDO/2²⁰ and MINDO/3²¹ levels employing standardized geometries.²² Relevant theoretical data are presented in Tables I and II. For the dipolarophiles both semiempirical methods predict incorrectly that the addition of a cyano function to its parent hydrocarbon will decrease the ionization potential (i.e., less bonding). This shortcoming of the CNDO/2 parametrization has been noted

previously.^{23,24} Encouragingly not only do the ab initio calculations yield the proper qualitative trends but the predicted quantitative stabilization for each of the cyano-containing species is reproduced quite satisfactorily. Regarding electron affinities all of the methods predict a reduced EA for 3 compared to 2. We are not aware of any quantitative data in this area but available Diels-Alder kinetic results,²⁵ UV spectral data,²⁶ and reduction potentials²⁷ can be interpreted to mean that electron-deficient alkynes and alkenes have similar electron affinities. Ab initio calculations at the 4-31G basis level²⁸ support this contention.²⁹ Significant to this discussion, all three theoretical techniques predict that the LU levels of each cyano-containing compound are highly asymmetric with the unsubstituted carbon atom displaying a substantially greater coefficient. In fact, as shown in Table II, the normalized LUMO coefficients³⁰ generated by all the methods are remarkably similar.

For the parent nitron and its *N*-methyl derivative, each theoretical approach predicts that these compounds should display substantially lower ionization potentials and comparable EAs to the reported dipolarophiles, which is in good agreement with experimental data.^{2a} The ab initio and MINDO/3 results show that the HOMO-electron population on the carbon atom is equal to or greater than that on oxygen.

Thus, if one attempts to assess the preferred regioisomer from the primary orbital coefficients of the dominant dipole HO-dipolarophile LU interaction, the 5 isomer is favored for both the cyanoacetylene-nitron and acrylonitrile-nitron reactions. However, one significant calculational difference

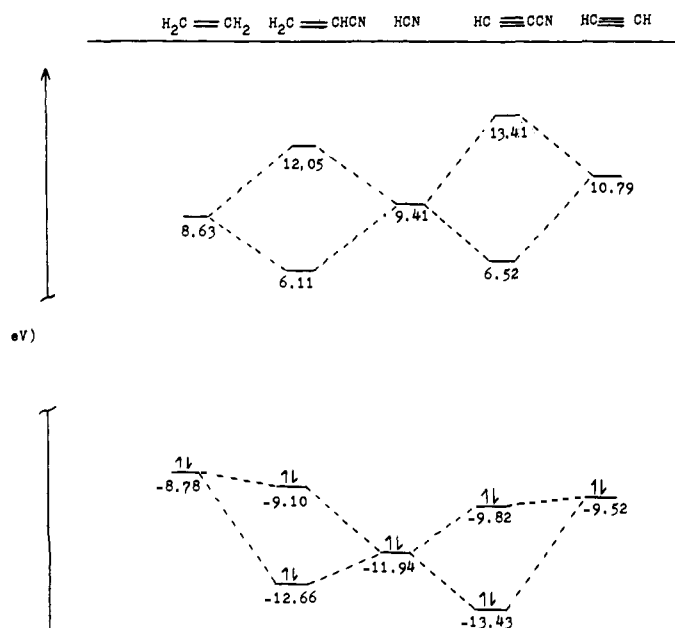


Figure 1. Orbital mixing diagrams for acrylonitrile and cyanoacetylene constructed from *ab initio* orbital energies.

between the LUMO characteristics of **2** and that of **3** is the degree of orbital delocalization displayed by the alkyne. Whereas all the MO approaches predict that ~25% of the electron density is on the cyano function of acrylonitrile in this key orbital, this number grows to ~50% for the triple-bonded compound (Table II). The enhanced LU orbital delocalization on cyanoacetylene can be understood by construction of an orbital mixing diagram employing ethylene, acetylene, and hydrogen cyanide as the components for the cyano-containing dipolarophiles. The results of such an operation using the STO-3G data are displayed in Figure 1. The LUMO of HCN is of lower energy than the LUMO of acetylene; consequently, the LUMO of cyanoacetylene will have more cyano character than acetylenic character. Conversely, the LUMO of HCN is of higher energy than the LUMO of ethylene; thus, the LUMO of acrylonitrile will have mainly ethylenic character.

Transition State Interactions. If these observations are incorporated into a molecular orbital model for the 1,3-dipolar cycloaddition transition state, the importance of a unique bonding interaction between the cyano carbon of cyanoacetylene and the primary orbital of the nearest approach atom of the nitron is revealed. The two possible concerted attacks of cyanoacetylene and acrylonitrile on *N*-methylnitron are schematically illustrated in Figures 2 and 3, respectively. The key dipole HO-dipolarophile LU orbitals are included. These transition states were derived by assuming that in order to maximize the primary $2p\sigma$ - $2p\sigma$ overlaps, the approach of the interacting species will be such that the unsaturated carbon atoms of the dipolarophiles will be nearly symmetrically situated above the dipole. Furthermore, geometrical changes in the molecular species will be small at the transition state which can be expected to occur at a molecular separation of 2-2.5 Å. These basic assumptions are consistent with *ab initio* potential energy calculations for diazomethane with ethylene and a number of other dipolarophiles including acrylonitrile¹⁰ as well as the Hammond postulate.³¹ As shown in Figure 2 a significant attractive interaction between the $2p\pi$ cyano carbon orbital and the approach $2p\pi$ orbital of the nearest terminal nitron atom can occur. In fact, if standard bond distances and angles are employed and the dipole is projected onto the plane of cyanoacetylene, then the distance from the nearest terminal atom of the nitron to the cyano carbon ($r = 0.86$ Å) is only

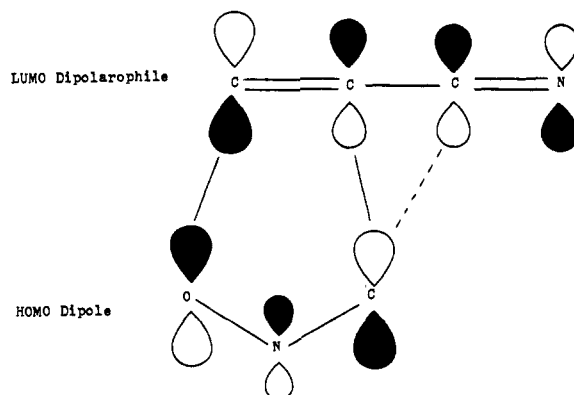


Figure 2. The HOMO dipole-LUMO dipolarophile interaction in the concerted addition of *N*-methylnitron to cyanoacetylene.

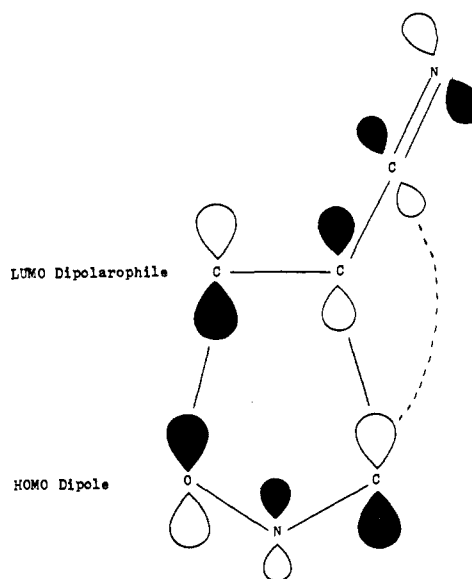


Figure 3. The HOMO dipole-LUMO dipolarophile interaction in the concerted addition of *N*-methylnitron to acrylonitrile.

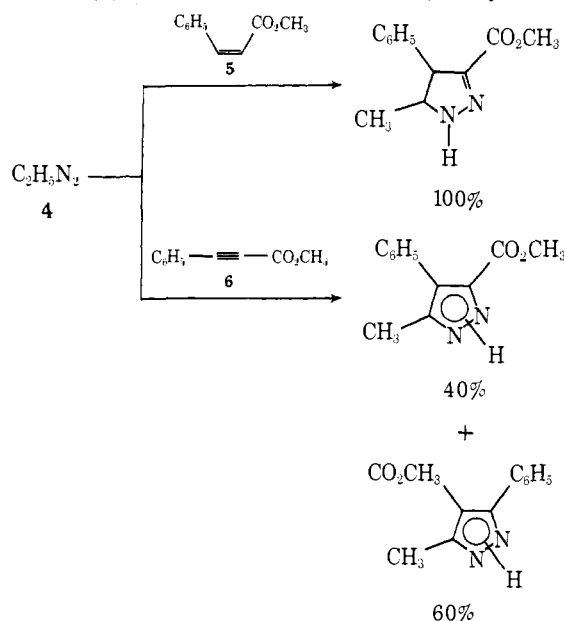
slightly greater than that to the adjacent acetylene carbon ($r = 0.52$ Å). A similar operation for acrylonitrile yields considerably greater asymmetric values (1.29 and 0.45 Å) for the primary-secondary and primary-primary distances, respectively.

Regiochemical Implications. It is necessary to include the primary-secondary attraction in addition to standard primary-primary in an electron-deficient triple-bonded compound. In general when the dipole has the same atom as its primary centers, the primary-secondary orbital interaction will have nearly the same degree of added stabilization for each concerted attack and thus will not alter regiochemistry compared to alkene behavior, significantly. However, as a result of differing long-range bond characteristics of heteroatoms (e.g., $\gamma_{CC} > \gamma_{CN} > \gamma_{CO}$), the primary-secondary interaction can contribute to the transition state energies in a disproportionate fashion for 1,3-dipoles which have asymmetric primary centers. Therefore in the cycloaddition reactions involving nitrones and electron-poor acetylenes, we attribute the observed loss in regioselectivity to the fact that the C-C primary-secondary attraction will be substantially larger than the C-O contribution since at long distance $\gamma_{CC} > \gamma_{CO}$,³² thereby counterbalancing the primary-primary orbital preferences which dominate in the corresponding olefins.

Primary-secondary orbital interactions can be expected to affect the orientation preference of other asymmetric oxy-

gen-containing 1,3-dipoles such as nitrile oxides. Experimental data on formonitrile oxide reacting with methyl propiolate and methyl acrylate^{2b} are in agreement with this concept. However, the alternative argument, that the influence of dipole LU-dipolarophile HO control causes the isomer distributional changes, appears highly consistent with estimated orbital energies and experimental results for a wide variety of reactions.^{2b} Thus in this class of dipoles it is not necessary to contribute any unique role to primary-secondary orbital interactions.

Similarly regiochemical differences have been observed frequently between diazoalkanes reacting with disubstituted electron-poor alkenes and alkynes.^{8c} For example, methyl cinnamate (5) combines with diazoethane (4) to yield solely



the 3-substituted species whereas β -phenylmethyl propiolate (6) produces a 40:60 mixture of the two possible isomers. Primary-secondary orbital interactions offer a consistent rationale for these reversals in which dipole HO-dipolarophile LU control would be expected.³³

The fact that no regiochemical reversals have been found between diazoalkanes and monosubstituted electron-deficient double- and triple-bonded compounds can be attributed to the larger difference in the magnitude of the primary orbital coefficients of the monosubstituted dienophiles as compared to the 1,2-disubstituted dienophiles. This larger difference in coefficient magnitudes allows the primary orbital interactions to dominate in the monosubstituted cases. Furthermore, the lack of reversal in these cases as compared to the nitrones can also be attributed to the enhanced differential in the primary orbital coefficients of the diazoalkanes.⁵

These findings suggest that similar interactions could be important in determining regioselectivities for Diels-Alder cycloadditions involving electron-deficient alkynes and alkenes reacting with dienes which contain a primary heteroatom. Little experimental data of this nature are known; it has been reported that crotonic acid and the corresponding ethyl ester of α,β -acetylenic acid form cycloadducts with the α,β -unsaturated carbonyl *o*-methide quinone but the structures of the products were not established.³⁴ One problem we envision in assessing the importance of the primary-secondary interactions in Diels-Alder cycloadditions is the need to ensure dienophile LU-diene HO control. This is a nontrivial consideration since standard dienes which contain a desirable heteroatom such as oxygen display high ionization potentials and high electron affinities (e.g., IP acrolein ~ 11 eV; EA acrolein ~ 1.3 eV).^{2a} Thus, reactions involving heterodienes which are substituted

with electron donors appear to offer the best opportunity to test the significance of these proposed interactions in Diels-Alder cycloadditions.

Conclusion

Extension of FMO principles reveals long-range bonding interactions between primary and secondary orbitals in cycloaddition reactions. These forces will stabilize one of the two possible transition states by a disproportionate amount when a primary heteroatom is involved. This difference becomes substantial when the heteroatom has very short-range bonding characteristics such as oxygen. When this is combined with the finding that electron-deficient alkynes have highly delocalized LUMOs, it is possible to understand the unexpected product distributions observed in a number of 1,3-dipolar cycloadditions involving electron-poor acetylenes. Furthermore, the effect of the primary-secondary interactions is most significant when the difference in the primary orbital coefficients on either of the reaction species is small.

References and Notes

- (1) (a) E. I. du Pont de Nemours and Co.; (b) University of Connecticut.
- (2) (a) K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozler, and J. K. George, *J. Am. Chem. Soc.*, **95**, 7287 (1973); (b) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *ibid.*, **95**, 7301 (1973); (c) K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975).
- (3) R. Huisgen, *J. Org. Chem.*, **41**, 403 (1976).
- (4) R. Sustmann, E. Wenning; and R. Huisgen, *Tetrahedron Lett.*, 877 (1977), and references cited therein.
- (5) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, New York, N.Y., 1976.
- (6) N. D. Epiotis, *Angew. Chem., Int. Ed. Engl.*, **13**, 751 (1974).
- (7) T. Minato, S. Yamabe, S. Inajiki, H. Fujimoto, and K. Fukui, *Bull. Chem. Soc. Jpn.*, **47**, 1619 (1974).
- (8) (a) J. Bastide, N. El Ghandour, and O. Henri-Rousseau, *Bull. Soc. Chim. Fr.*, 2290 (1973); (b) J. Bastide and O. Henri-Rousseau, *ibid.*, 2294 (1973); (c) J. Bastide, O. Henri-Rousseau, and L. Aspart-Pascot, *Tetrahedron*, **30**, 3355 (1974).
- (9) R. E. Townshend, G. Ramunni, G. Segal, W. J. Hehre, and L. Salem, *J. Am. Chem. Soc.*, **98**, 2190 (1976).
- (10) (a) G. Leroy and M. Sana, *Tetrahedron*, **31**, 2091 (1975); (b) *ibid.*, **32**, 709 (1976); (c) D. Poppinger, *J. Am. Chem. Soc.*, **97**, 7486 (1975).
- (11) (a) P. V. Alston, R. M. Ottenbrite, and D. D. Shillady, *J. Org. Chem.*, **38**, 4075 (1973); (b) P. V. Alston and R. M. Ottenbrite, *ibid.*, **40**, 1111 (1975).
- (12) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).
- (13) (a) M. D. Gordon, T. Fukunaga, and H. E. Simmons, *J. Am. Chem. Soc.*, **98**, 8401 (1976); (b) A. Streitwieser, Jr., R. W. Boerth, and M. D. Gordon, *ibid.*, submitted for publication.
- (14) K. Tamaru and M. Ickikawa, "Catalysis by Electron Donor-Acceptor Complexes, Their General Behavior and Biological Roles", Halsted Press, New York, N.Y., 1975.
- (15) (a) H. Seidl, R. Huisgen, and R. Knorr, *Chem. Ber.*, **102**, 904 (1969); (b) R. Huisgen, H. Seidl, and J. Wulff, *ibid.*, **102**, 915 (1969).
- (16) (a) H. Seidl, R. Sustmann, and G. Wallbillich, *Chem. Ber.*, **100**, 1786 (1967); (b) M. Chlisl and R. Huisgen, *Tetrahedron Lett.*, 5209 (1969); (c) C. Grundmann and P. Grunanger, "The Nitrile Oxides", Springer-Verlag, Heidelberg, 1971.
- (17) J. Sims and K. N. Houk, *J. Am. Chem. Soc.*, **95**, 5798 (1973).
- (18) R. A. Firestone, *J. Org. Chem.*, **41**, 2212 (1976).
- (19) W. J. Hehre, R. Stewart, and J. A. Pople, *J. Chem. Phys.*, **51**, 2652 (1969).
- (20) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, N.Y., 1970.
- (21) R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.*, **97**, 1285 (1975).
- (22) J. A. Pople and M. S. Gordon, *J. Am. Chem. Soc.*, **89**, 4253 (1967).
- (23) K. N. Houk and L. L. Munchausen, *J. Am. Chem. Soc.*, **98**, 937 (1976).
- (24) H. Stafast and H. Bock, *Tetrahedron*, **32**, 855 (1976).
- (25) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967).
- (26) J. Geltner, R. Huisgen, and R. Sustmann, *Tetrahedron Lett.*, 881 (1977).
- (27) H. O. House, L. E. Huber, and M. J. Umen, *J. Am. Chem. Soc.*, **94**, 8471 (1972).
- (28) R. Ditchfield, W. J. Hehre, and J. A. Pople, *J. Chem. Phys.*, **54**, 724 (1971).
- (29) For 4-31G calculations, $\epsilon_{\text{LUMO}}^{\text{acrylonitrile}} = 2.68$; $\epsilon_{\text{LUMO}}^{\text{cyanoacetylene}} = 2.79$.
- (30) FMO ab initio coefficients were "normalized" via a Mulliken population analysis as is standardly done for atomic charges in order to offer a meaningful comparison with the valence-electron data. The results are displayed in Table II.
- (31) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).
- (32) Although it was assumed in Figures 2 and 3 that no molecular changes have occurred at the transition state, ab initio potential energy calculations on diazomethane cycloaddition reactions¹⁰ reveal geometrical movements which already favor primary-primary interactions and diminish primary-secondary terms. Thus the primary-secondary core resonance integrals

will be substantially less than suggested in Figures 2 and 3 and will be much longer ranged in character than the primary-primary transition state interactions. For example,

$$\frac{\gamma_{cc}(3.00 \text{ \AA})}{\gamma_{cc}(1.75 \text{ \AA})} = 0.24 \quad \frac{\gamma_{cn}(3.00 \text{ \AA})}{\gamma_{cn}(1.75 \text{ \AA})} = 0.18 \quad \frac{\gamma_{co}(3.00 \text{ \AA})}{\gamma_{co}(1.75 \text{ \AA})} = 0.14^{2b}$$

(33) The LUMO secondary orbital coefficients are similar in magnitudes in β -phenylmethyl propiolate. However, the secondary orbital coefficients in the next LUMO are large and only the primary-secondary interaction involving the carbomethoxy group will be bonding in the interaction of this MO with the HOMO of the dipole. No reversals are predicted in these cases if only the primary orbital coefficients are considered.

(34) K. Hultsch, *Angew. Chem.*, **60**, 179 (1948).

Monte Carlo Studies on the Structure of a Dilute Aqueous Solution of Methane

S. Swaminathan, S. W. Harrison, and David L. Beveridge*

Contribution from the Chemistry Department, Hunter College of the City University of New York, New York, New York 10021. Received December 2, 1977

Abstract: Statistical thermodynamic computer simulations on the dilute aqueous solution of methane at 25 °C under canonical ensemble conditions are reported. The calculations employ the Monte Carlo-Metropolis method based on potential functions representative of ab initio quantum mechanical calculations. Calculated partial molar internal energies and radial distribution functions are presented. The results are analyzed for the statistical state of the system in terms of quasicomponent distribution functions for coordination numbers and binding energies and difference quasicomponent distribution functions. The local solution environment of methane is directly identified with a composite of distorted, defective pentagonal dodecahedral clathrate contributions. The structure of solvent water involves an increase in four-coordinate contributions as compared to pure water.

I. Introduction

The dilute aqueous solution of methane is a system of prominent interest in molecular liquids as the prototype of a nonpolar molecular solute dissolved in liquid water. Moreover, a detailed knowledge of the structure of the methane-water solution at the molecular level can provide leading information on the interaction of water with dissolved hydrocarbon chains in general and thereby contribute to the theoretical basis for understanding the role of water in maintaining the three-dimensional structural integrity of biological macromolecules in solution.

We report herein new theoretical studies of the methane-water intermolecular interaction and Monte Carlo computer simulations of the dilute aqueous solution of methane under canonical ensemble conditions, with temperature T , volume V , and number of particles N specified and constant. All simulations are based on pairwise potential functions representative of ab initio quantum mechanical calculations of the intermolecular interactions.

Our analysis of solution structure is developed in terms of quasicomponent distribution functions in a manner consistent with a previous analysis of liquid water structure contributed from this laboratory. Perturbations of water structure by dissolved methane are developed in terms of difference quasicomponent distribution functions. This study forms an integral part of a series of theoretical investigations on the solvation of prototype biomolecular functional groups and solvent effects on noncovalent biomolecular processes currently underway in this laboratory.

II. Background

General backgrounds on solutions of nonpolar solutes in water have been recently reviewed by Franks¹ and Ben-Naim.² Early important work on this system is due to Eley³ and Frank and Evans.⁴ Methane has been identified as a "structure maker" in aqueous solution in the language of Frank and Wen.⁵ The nature of structural changes in solvent water by dissolved hydrocarbons has for some time been discussed in

terms of water clathrate formation⁶ based on work by Glew⁷ and analogies drawn from a number of hydrate crystal structures of nonpolar species,⁸ known to involve water clathrate cages of order 20 and 24.

Early computer simulations of the methane-water system were reported by Dashevsky and Sarkisov.⁹ Recent important theoretical studies of the methane-water system are the ab initio molecular orbital calculations of the methane-water pairwise interaction energy by Ungemach and Schaefer¹⁰ and the Monte Carlo computer simulation on the dilute aqueous solution in the isothermal-isobaric ensemble by Owicki and Scheraga¹¹ (OS). The OS simulation was based on the water-water potential discussed below and a potential function representative of the Ungemach-Schaefer calculations for the methane-water interaction. Due to limitations in the potential functions, the density of the system in these calculations turned out to be somewhat lower than that observed at 25 °C; still analysis of the results gave the best quantitative theoretical evidence of structuration of vicinal water in the solution to date and the calculated average methane-water coordination number of 23 is consistent with water clathrate contributions to the solution structure.

Theoretical studies of the methane-water solution require an accurate description of the structure of the pure solvent, liquid water, as a point of departure. The structure of liquid water has been the subject of two recent Monte Carlo computer simulations, one from this laboratory using the canonical (T, V, N) ensemble¹² and the other by Owicki and Scheraga in the isothermal-isobaric (T, P, N) ensemble.¹³ Both calculations are based on the analytical pairwise potential function for the water-water interactions representative of ab initio quantum mechanical configuration interaction calculations,¹⁴ known to give reasonable agreement with experimental data on the oxygen-oxygen radial distribution function.¹⁵ The calculated radial distribution functions of liquid water are seen to be very sensitive to electron correlation effects in the intermolecular potential function.¹²

The individual papers contain considerable additional details on the structure of water from different but mutually com-