A Theoretical Study of the Addition Mechanism of Carbon Dioxide to Methylamine. Modelling CO_2–Biotin Fixation

Juan Andrés,* Vicente Moliner, Jiri Krechl† and Estanislao Silla‡
Department of Experimental Sciences, Universitat Jaume I, Apartat 242, 12080 Castelló, Spain

The addition reaction of carbon dioxide to methylamine, which can be considered as a first step for the modelling of CO_2–biotin fixation, is investigated using an *ab initio* MO method at HF/6-31G*, MP2/6-31G* levels and CISD calculations. The complete potential energy hypersurface has been explored and the stationary points representing reactants, transition state and product localized and characterized. Analysis of the structural evolution of the system along its reaction path proves that the reaction mechanism is an asynchronous process and the transition state can be described as a four-membered ring where a C–N bond is formed and one proton is transferred.

Theoretical studies of reaction mechanisms provide a powerful tool in physical organic chemistry to check transition state (TS) structures, their location and characterization in the region of the potential energy hypersurface that determines both the direction and the rate of chemical transformation of reactants to products.[1] The development of efficient computational techniques for *ab initio* molecular orbital theory, particularly for analytical methods of determining the gradients and curvatures of potential energy hypersurfaces,[2,3] has now provided geometries and relative energies for stable molecules and also for transition state structures. A variety of efficient algorithms are now available for transition state structure searches,[4,5] thus providing a range of powerful tools for studies of reactivity.[6–8] This paper uses theoretical methods for checking the location, analysis and characterization of stationary points in the reaction mechanism of addition of carbon dioxide to methylamine. The emphasis is on the investigation of structures and energy status of stationary points. From the mechanistic point of view, CO_2 addition to CH_3NH_2 can be considered as a simple model of the reaction that takes place on the active site of biotin.[9] Unfortunately, there are no suitable experimental results about the active centre and its surroundings.

Method of Calculation

The exact determination of the properties of the TS was achieved by utilization of a simple algorithm.[5] The coordinates describing the system are separated in two sets: (q_i) and (q_j), where (q_i) is the control space set which is responsible for the unique negative eigenvalue in the respective force constant matrix connected with variables that form the transition vector.[10] The remaining coordinates, (q_j), are called the complementary space set. First, the transition state was located with the VA05 subroutine,[11] restricted to the control space, and the transition vector was determined by diagonalizing the force constant matrix. As a second step we optimized the complementary space utilizing the OC method.[12] Finally, a complete optimization using the VA05 method was carried out for the complete space of all variables. The optimizations were terminated after the overall average gradient length had been reduced to $< 5 \times 10^{-4}$ mdyn.§

The 6-31G* basis set, which includes polarization functions for the second-row elements, has been chosen. The HF/6-31G* calculations were carried out using the MONSTERGAUSS program[13] on an IBM 3090/150 computer at the *Centre d'Informàtica de la Universitat de Valencia*, while the correlation energy, considered at the second MP2 perturbation calculation routine,[14] and the CISD calculations[15] were performed using the GAUSSIAN 90 program[16] on the Hewlett Packard HP9000/720 workstation computers of the *Centre d'Informàtica de la Universitat Jaume I.* The TS was calculated analytically utilizing the facilities of GAUSSIAN 90 and we did not find important differences from the values resulting from the VA05 formalism.

Results and Discussion

Chemical reactions can be studied theoretically using different strategies. The common way is to study changes of geometrical structure and electron distribution that accompany changes of the total energy along the reaction pathway. In this study we have determined and characterized stationary points. Then we obtained a detailed analysis of the energy, transition vector, force constants and electron distribution that represent those particular points. This enabled us to describe the evolution of the electronic properties of the system during the reaction course.

The optimized values for selected bond lengths and bond angles for stationary points of CO_2 to CH_3NH_2 addition *in vacuo*, are presented in Table 1, with the total and relative energies of reactants (R), TS and product (P). From these results a four-centred structure is found for TS. The structures of stationary points are illustrated in Fig. 1.

To distinguish which variables control the addition process, the transition vector components for TS can be used. Both procedures, the numerical (VA05) as well as the analytical (GAUSSIAN 90) one, show that six variables (q_i coordinates) only, contribute more than 10% to the transition vector: the forming C1–N2, breaking N2–H3 and C1–O6 (double to single) bonds are predominant, together with the angles describing the H3 position, H3–N2–C1, C4–N2–H3 and H5–N2–H3. It must be noted that the force constant of the N2–H3 stretching mode is negative in the TS. This is the key variable and is responsible for the single negative value in the force constant matrix.

In order to get a deeper insight into the electronic reorganization taking place during the reaction, the bond orders of the reactants, product and transition state have been analysed. In the TS, the N2–C1 and H3–O6 bond orders reach the values 0.729 and 0.324, respectively, while the N2–H3 and C1–O6 decrease to 0.372 and 1.289, respectively. These results

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† *Permanent Address:* Department of Organic Chemistry, Institute of Chemical Technology, 166 28 Prague 6, Czechoslovakia.

‡ *Permanent Address:* Departament de Química Física, Universitat de Valencia, 46100 Burjassot, Valencia, Spain.

§ 1 dyn = 1×10^{-5} N.

Table 1 (*a*) Optimized HF/6-31G* and MP2/6-31G* structures of reactants, transition states and products. Energy given in Hartree. In parentheses are energies relative to R in kcal mol$^{-1\,a}$ (*b*) Bond distances in Å and bond angles in degrees

(*a*)	Reactants	Transition state	Product
HF/6-31G*			
Energy	−282.849 417	−282.755 630	−282.836 131
Relative	(0.0)	(58.85)	(−8.34)
MP2/6-31G*			
Energy	−283.640 354	−283.569 243	−283.622 461
Relative	(0.0)	(44.62)	(−11.23)
CISD			
Energy	−283.644 246	−283.571 271	−283.631 759
Relative	(0.0)	(45.79)	(−7.84)

	Reactants		Transition state		Product	
(*b*)	HF	MP2	HF	MP2	HF	MP2
Bond distances						
C1–N2	2.9409	2.7964	1.5188	1.5559	1.3649	1.3815
N2–H3	1.0017	1.0180	1.2656	1.2978	2.3039	2.3014
H3–O6	3.2588	3.4223	1.2739	1.2870	0.9480	0.9736
C1–O6	1.1441	1.1785	1.2650	1.2962	1.3387	1.3692
C1–O7	1.1439	1.1794	1.2650	1.2084	1.1859	1.2138
N2–H5	1.0019	1.0180	1.0056	1.0235	0.9956	1.0133
N2–C4	1.4556	1.4656	1.4654	1.4687	1.4504	1.4567
C4–H8	1.0838	1.0914	1.0822	1.0929	1.0850	1.0946
Bond angles						
H3–N2–C1	106.29	112.07	70.29	69.67	55.89	56.69
C4–N2–H3	110.84	109.87	126.14	127.57	174.79	173.64
O6–C1–N2	91.35	93.73	98.18	97.97	114.33	113.90
O7–C1–O6	176.66	175.69	137.45	137.43	121.23	121.41
H8–C5–N2	109.20	108.79	110.21	109.89	112.39	112.54
H5–N2–H3	106.83	105.83	115.57	115.90	69.60	70.54

[a] 1 cal = 4.184 J.

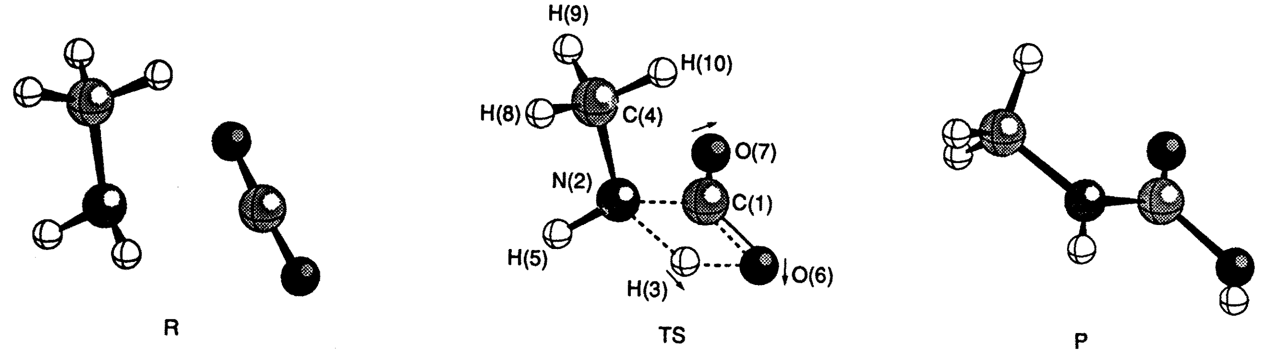

Fig. 1 Schematic representation of stationary points; R, TS and P for the addition of CO_2 to CH_3NH_2. The transition vector is represented schematically by arrows.

reveal the reaction mechanism as an asynchronous process.

The geometries of the stationary points obtained at HF and MP2 levels, respectively are almost invariant to the method used. The TS can be described as a four-membered ring where the transformations of C1–O6 (the double bond C1=O6 goes to a single one), N2–H_3 (the N2–H3 bond is broken) and the N2–C1 (the N2–C1 bond is formed) are *ca.* 70% completed, while the formation of the H3–O6 bond is only *ca.* 30%. This description shows the TS in an advanced stage of the reaction, closer to P than to the reactants, contrary to what is suggested by Hammond's postulate[17] for exothermic reactions.

Establishing a possible relationship between activation and reaction energy is achieved by using Miller's simplest relationship,[17] eqn. (1).

$$X^* = E_a/(2E_a - \Delta E) \qquad (1)$$

The values obtained for the TS parameter, X^*, by eqn. (1) are 0.47 (HF-631G*), 0.44 (MP2/6-31G*) and 0.46 (CISD). These differences, when the correlation energy is included, can be considered consistent with the idea that the step from R to TS followed by a step to P implies the breakdown and formation of chemical bonds and consequently a considerable electronic redistribution. So, even using this relationship, the Hammond postulate[17] does not seem to be fulfilled. These expressions were used because of their simplicity, but other equations[19,20] give the same trend.

The activation energy calculated from different models is high. This fact led us to conclude that the surroundings of the active site of the biotin must play a decisive role in the CO_2 fixation reaction in this enzyme.

MP2/6-31G* net atomic charges calculated with the help of Mulliken's population analysis are presented in Table 2; the other two methods offer results that differ from the presented ones by < 2%. Otto and Ladik[21] have shown that this method gives a qualitatively correct description of the charge-transfer

Table 2 Net atomic charge (a.u.) distribution in R, TS and P, calculated at MP2/6-31G* level (ΣCH_3 = C4 + H8 + H9 + H10)

	Reactants	Transition state	Product
C1	0.95	0.96	0.99
N2	−0.86	−0.91	−0.79
H3	0.34	0.55	0.46
O6	−0.48	−0.74	−0.72
O7	−0.48	−0.56	−0.58
H5	0.34	0.40	0.37
ΣCH_3	0.18	0.31	0.28

process. The most significant changes of charge distribution can be observed on the N2 and O6 atoms whose respective negative charges reach their maximum values along the reaction profile on the TS while the charge on H3 reaches its most positive value in the TS.

There are problems not yet solved concerning the ability of the one-determinant Hartree–Fock method to represent adequately homolytic bond-breaking and -forming processes. Recently, we have shown that the TS structure for the addition reaction of carbon dioxide to methylamine is not sensitive to the basis set used in the HF–SCF schemes.[22] Although calculations of the second-order stability test show that the single determinant RHF wave function of the TS is stable,[23] further studies, MC–SCF or atomic pair natural orbital analysis,[24] need to be done in order to represent correctly the possible biradical character in the TS.

In summary, all the results of the present study show the reaction mechanism for the addition mechanism of carbon dioxide to methylamine as an asynchronous process where one proton is transferred from the amine group and a C–N bond is formed.

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References

1 Z. Havlas and R. Zahradník, *Int. J. Quant. Chem.*, 1984, **26**, 607.
2 P. Pulay, in *Modern Theoretical Chemistry, Vol. 4, Applications of Electronic Structure Theory*, ed., H. F. Schaefer, Plenum Press, New York, 1977.
3 J. A. Pople, R. Krishnan, H. B. Schlegel and J. S. Binkley, *Int. J. Quant. Chem., Symp.*, 1979, **13**, 225.
4 H. B. Schlegel, in *New Theoretical Concepts for Understanding Organic Reactions*, eds., J. Bertrán and I. G. Czismadia, Kluwer Academic Publishers, The Netherlands, 1989.
5 O. Tapia and J. Andrés, *Chem. Phys. Lett.*, 1984, **109**, 471.
6 S. S. Shaik, in *New Theoretical Concepts for Understanding Organic Reactions*, eds., J. Bertrán and I. G. Czismadia, Kluwer Academic Publishers, The Netherlands, 1989.
7 J. Andrés, R. Cárdenas, E. Silla and O. Tapia, *J. Am. Chem. Soc.*, 1988, **110**, 666.
8 J. Andrés, J. Krechl and E. Silla, *Chem. Phys. Lett.*, 1990, **169**, 509.
9 (*a*) Chien H. Fung, Albert S. Mildvan and John S. Leigh, Jr., *Biochemistry*, 1974, **13**, 1160; (*b*) Chien H. Fung, Raj K. Gupta and Albert S. Mildvan, *Biochemistry*, 1976, **15**, 85.
10 J. W. McIver, Jr., *Acc. Chem. Res.*, 1974, **7**, 72.
11 (*a*) M. J. D. Powell, VA05 program, Harwell Subroutine Library, Atomic Energy Research Establishment, Harwell, UK. (*b*) H. B. Schlegel, program FORCE, Ph.D. Thesis, Queens University, Kingston, Canada, 1975.
12 N. C. Davidson, *Math. Prog.*, 1975, **9**, 1; S. Bell, J. Crighton and R. Fletcher, *Chem. Phys. Lett.*, 1981, **122**, 82.
13 M. R. Peterson and R. A. Poirier, Program MONSTERGAUSS, University of Toronto, 1988.
14 C. Moller and M. S. Plesset, *Phys. Rev.*, 1934, **46**, 618.
15 J. A. Pople, J. S. Binkley and R. Seeger, *Int. J. Quant. Chem. Symp.*, 1976, **1**, 10.
16 GAUSSIAN 90, M. J. Frisch, M. Head-Gordon, G. W. Trucks, J. B. Foresman, H. B. Schlegel, K. Raghavachari, M. Robb, J. S. Binkley, C. Gonzalez, D. J. Defrees, D. J. Fox, R. A. Whiteside, R. Seeger, C. F. Melius, J. Baker, R. L. Martin, L. R. Kahn, J. J. P. Stewart, S. Topiol and J. A. Pople, GAUSSIAN, Inc., Pittsburgh PA, 1990.
17 G. S. Hammond, *J. Am. Chem. Soc.*, 1955, **77**, 334.
18 A. R. Miller, *J. Chem. Soc.*, 1978, **100**, 1984.
19 (*a*) S. J. Formosinho, *J. Chem. Soc., Perkin Trans. 2*, 1987, 261; (*b*) 1988, 839; (*c*) A. J. C. Varandas and S. J. F. Formosinho, *J. Chem. Soc., Faraday Trans. 2*, 1986, 282.
20 (*a*) G. Lendvay, *J. Mol. Struct., THEOCHEM*, 1988, **167**, 331; (*b*) G. Lendvay, *J. Phys. Chem.*, 1989, **93**, 4422.
21 P. Otto and J. Ladik, *Int. J. Quant. Chem.*, 1980, **18**, 1143.
22 J. Andrés, V. Moliner, J. Krechl and E. Silla, *Int. J. Quant. Chem.*, 1992, to be published.
23 R. Seeger and J. A. Pople, *J. Chem. Phys.*, 1977, **7**, 66.
24 G. A. Petersson, T. G. Tensfeldt and J. A. Montgomery, Jr., *J. Am. Chem. Soc.*, 1992, **114**, 6133.

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