an adapted expression, which is suitable for **7**.[21] Application of this formula indicates a marked preference for the syn conformation in C_6D_6, $CDCl_3$, $(CD_3)_2SO$, CD_3CN, CD_3OD, and D_2O (Table V). This illustrates the well-known fact that the syn ⇄ anti distribution is shifted in favor of syn for 2′,3′-bridged nucleosides and nucleotides, in comparison with their unmodified counterparts. It should be mentioned that the $C_{1'}$–N_1 conformation in **8** could not be determined by NOE measurements, due to a near coincidence of the resonances of $H_{1'}$ and H_5 in the high-resolution ^1H NMR spectra.

Concluding Remarks

A marked increase of the g^- population around the $C_{4'}$–$C_{5'}$ bond is found for the 5′-P^{IV} and 5′-P^V TBP models **1**, **2**, **4**, and **5**, and the 5′-P^{IV} modified nucleotides **7** and **8**, upon lowering the solvent polarity. This effect can be explained on the basis of an enhanced charge repulsion between $O_{5'}$ and the endocyclic oxygen(s) at lower polarities. This is strongly supported by the experimental finding that the model systems **4** and **6** do not show a $C_{4'}$–$C_{5'}$ conformational change when the polarity of the solvent is varied. The present results are in line with our earlier proposal that the enhanced repulsion between $O_{5'}$ and $O_{1'}$, triggered via a coordinational transition from 5′-P^{IV} into 5′-P^V TBP, drives a rotation around $C_{4'}$–$C_{5'}$ toward g^-. Extended conformational analyses on the 5′-P^{IV} modified nucleotides **7** and **8** indicate that the ribose conformation can be best described as a two-state equilibrium between two puckered ring forms. The distribution over these forms varies slightly with the solvent polarity. A pronounced preference for syn orientation of the adenine base in **7** is found.

Acknowledgment. This investigation has been supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO). ^1H NMR spectra (500 MHz) were run at the Dutch National 500/200 hf NMR facility at Nijmegen. We thank Dr. J. W. de Haan for valuable discussions and L.J.M. van de Ven and P. van Dael (Nijmegen) for technical assistance in recording the NMR spectra.

Registry No. 1, 91237-85-3; **2**, 96430-26-1; **3**, 91237-89-7; **4**, 91237-87-5; **5**, 96430-27-2; **6**, 91237-90-0; **7**, 96259-12-0; **8**, 96430-28-3; (1,3-dioxolan-2-ylmethyloxy)diphenylphosphine, 96430-29-4; chlorodiphenylphosphine, 1079-66-9; 2-(hydroxymethyl)-1,3-dioxolane, 5694-68-8; 2,3-butanedione, 431-03-8; dimethoxy (*N*,*N*-dimethylamino)phosphine, 20217-54-3; trimethyl phosphite, 121-45-9; dimethylamine, 124-40-3; 2′,3′-*O*-isopropylideneadenosine 5′-dimethylphosphite, 96259-13-1; 2′,3′-*O*-isopropylideneadenosine, 362-75-4; 2′,3′-*O*-isopropylideneuridine 5′-dimethylphosphite, 96430-30-7; 2′,3′-*O*-isopropylideneuridine, 362-43-6.

(21) This equation is based on the minimal distances between H_8 and $H_{1'}$, $H_{2'}$, and $H_{3'}$ in forms I and II. From $r_{H_8\text{-}H_{1'},min} = 2.58$ Å, $r_{H_8\text{-}H_{2'},min} = 1.84$ Å, $r_{H_8\text{-}H_{3'},min} = 1.94$ Å, it follows that $(r_{H_8\text{-}H_{2'},min})^6 \approx (r_{H_8\text{-}H_{3'},min})^6 \approx {}^1/_8(r_{H_8\text{-}H_{1'},min})^6$. This leads to $P_{syn} = 8f_8\{1'\}/(8f_8\{1'\} + f_8\{2'\} + f_8\{3'\})$.

Stereochemistry of the Carbon-Skeleton Rearrangements Dependent on Coenzyme B_{12}. MNDO Quantum Chemical Calculations

Ingrid I. Merkelbach,* Hanneke G. M. Becht, and Henk M. Buck

Contribution from the Department of Organic Chemistry, Eindhoven University of Technology, 5600 MB, Eindhoven, The Netherlands. *Received December 5, 1983*

Abstract: Vitamin B_{12} acts as a cofactor in the enzyme-catalyzed carbon-skeleton rearrangements of methylmalonyl-coenzyme A to succinyl-coenzyme A, methylaspartate to glutamate, and methylitaconate to methylene glutarate. The stereochemistry of these isomerizations will be discussed on the basis of anionic enzyme-stabilized cyclopropane intermediates. With the help of MNDO calculations, energy profiles are constructed for the three ring-closure reactions. Following the reaction path, charge distribution and migration in the substrates are monitored, as well as the evolution of the coefficients of the atomic orbitals in the HOMO of the cyclopropane intermediates. Large charge migration will force the electron density at the carbon that undergoes inversion of configuration in the methylaspartate isomerization, in a direction opposite to the glycyl group. Orbital inversion on the adjacent glycyl carbon prevents the electron density to flow back, which is reflected in the antibonding character of the bond between these two carbons in the HOMO. On the other hand, retention of configuration in the methylmalonyl-coenzyme A rearrangement is attended with a smaller charge migration and a bonding character of the corresponding bond in the HOMO. Inversion of configuration is suggested for the methylitaconate isomerization.

Vitamin B_{12} has been shown to act as an obligatory enzyme cofactor, to effect a remarkable series of 11 rearrangement reactions. They consist of the carbon-skeleton rearrangements and the hydroxyl and the amine migrations, according to the bond that is broken during the reaction.[1] In this study special attention is given to the carbon-skeleton rearrangements, i.e., the isomerization of L-methylmalonyl-coenzyme A to succinyl-coenzyme A, *threo*-β-methylaspartate to L-glutamate, and β-methylitaconate to α-methyleneglutarate, where hydrogens (for the sake of clarity deuterons are used in Figure 1) and a carbon-centered group R migrate in an intramolecular [1,2] shift. Under enzymatic conditions the hydrogen (deuteron in Figure 1) is transferred via the 5′-methylene group of vitamin B_{12}[2] and migrates in methylmalonyl-coenzyme A with retention of configuration[3] (i.e., the incoming hydrogen and the leaving group R occupy the same position). The migration in methylaspartate occurs with inversion

(1) (a) Dolphin, D. "B_{12}"; John Wiley and Sons: New York, 1982; Vol. 1, p 328. (b) Zagalak, B.; Friedrich, W. "Vitamin B_{12}"; W. de Gruyter: Berlin, 1979; p 557.

(2) (a) Rétey, J.; Arigoni, D. *Experientia* **1966**, *22*, 783–784. (b) Cardinale, G. J.; Abeles, R. H. *Biochim. Biophys. Acta* **1967**, *132*, 517–518. (c) Switzer, R. L.; Baltimore, B. G.; Barker, H. A. *J. Biol. Chem.* **1969**, *244*, 5263–5268. (d) Kung, H. F.; Tsai, L. *J. Biol. Chem.* **1971**, *246*, 6436–6443.

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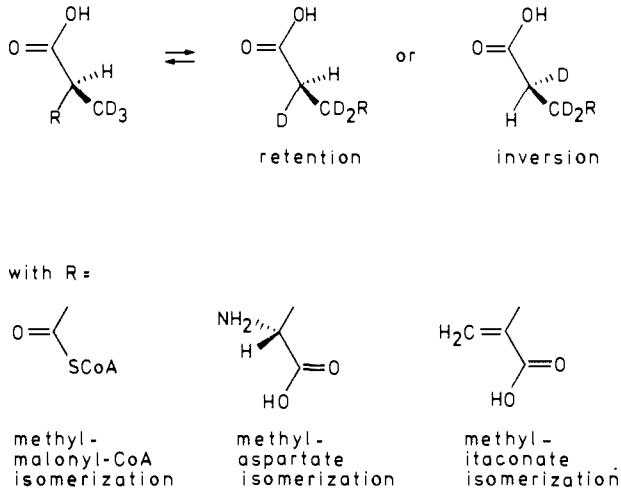

Figure 1. The three carbon-skeleton rearrangements dependent on coenzyme B_{12}.

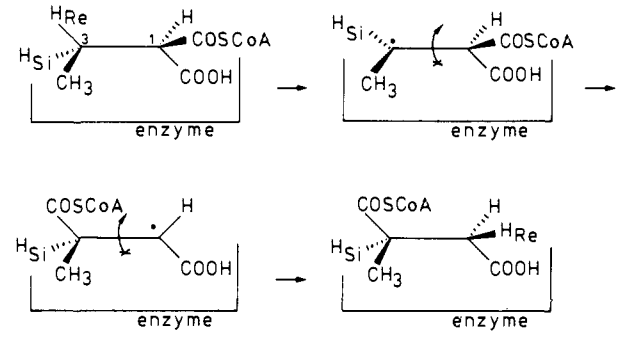

Figure 2. Retention of configuration in the radical mechanism for the methylmalonyl-coenzyme A rearrangement as proposed by Rêtey.

of configuration,[4] and the stereochemistry of the methylitaconate isomerization is unknown. In general for the coenzyme B_{12} dependent rearrangements a radical mechanism is proposed, as was recently summarized by Rêtey,[5] based upon data arising from isotope labeling,[6] electron paramagnetic resonance,[7] and UV spectroscopic measurements.[8] As Rêtey describes in his article,[5] this radical mechanism is put forward independently of the stereochemical results published, while in particular the steric course of a reaction is extremely useful to draw conclusions as to the mechanism. In order to integrate the stereochemical results in the radical mechanism, he[5,9] assumes a very intimate and unambiguous interaction between enzyme and substrate that prevents rotation around the C_1–C_3 bond (see Figure 2). While the Rêtey model emphasizes the role of the enzyme, it does not take into account the intrinsic properties of the substrates; moreover, no explanation is given of the modifications of the enzyme, needed to achieve inversion in the methylaspartate isomerization.

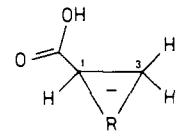

Figure 3. The anionic cyclopropane intermediate which accounts for the stereochemistry of the carbon-skeleton rearrangements.

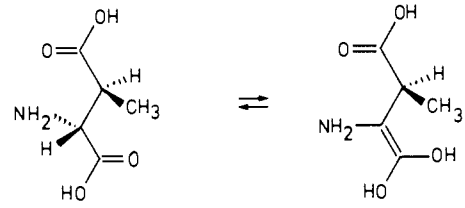

Figure 4. The keto–enol tautomerization in methylaspartate, resulting in a structure which accommodates the negative charge after ring closure.

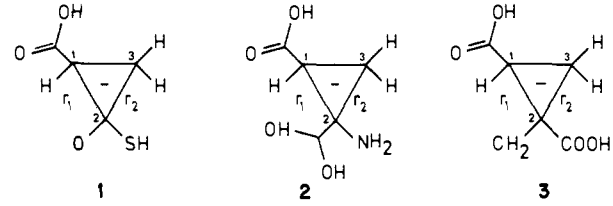

Figure 5. The three intermediates of which the ring closure has been studied.

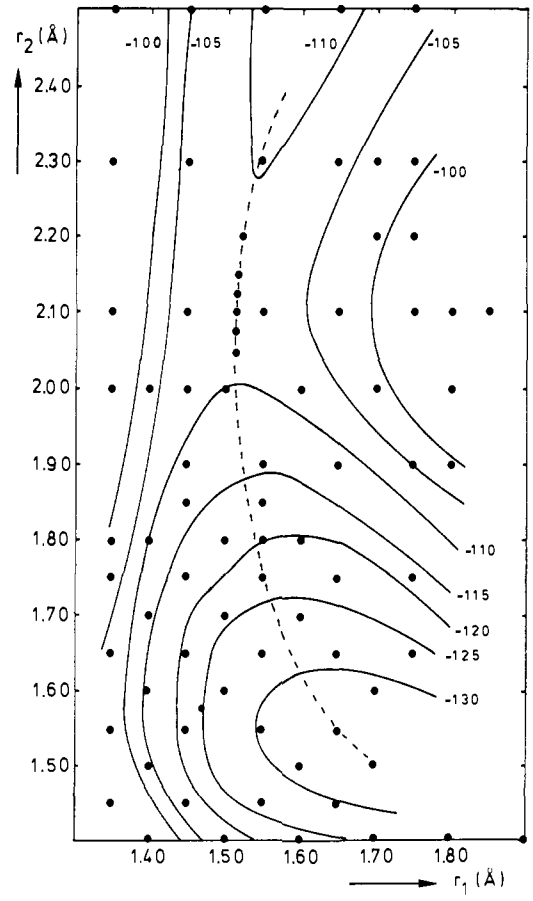

Figure 6. Heat of formation (kcal/mol) as a function of r_1 and r_2 for intermediates during ring closure for the methylmalonyl-coenzyme A isomerization.

From enzymatic data it has been shown by Pratt[10] that the three groups of rearrangements demonstrate some remarkable distinct features. The enzymes of the carbon-skeleton rearrangements

(3) (a) Sprecher, M.; Clark, M. J.; Sprinson, D. B. *Biochem. Biophys. Res. Commun.* **1964**, *15*, 581–587. (b) Sprecher, M.; Clark, M. J.; Sprinson, D. B. *J. Biol. Chem.* **1966**, *241*, 872–877. (c) Rêtey, J.; Zagalak, B. *Angew. Chem.* **1973**, *85*, 721–722.

(4) (a) Sprecher, M.; Sprinson, D. B. *Ann. N.Y. Acad. Sci.* **1964**, *112*, 655–660. (b) Sprecher, M.; Switzer, R. L.; Sprinson, D. B. *J. Biol. Chem.* **1966**, *241*, 864–867.

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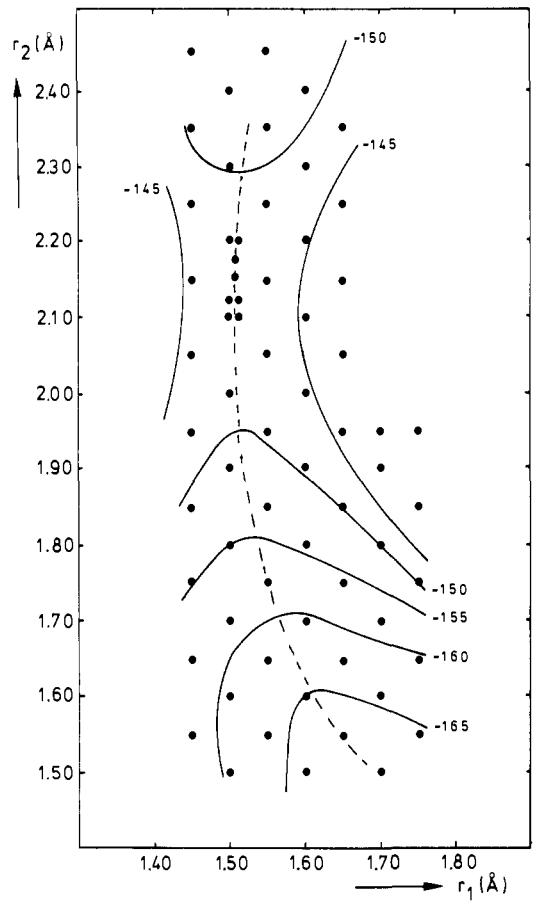

Figure 7. Heat of formation (kcal/mol) as a function of r_1 and r_2 for intermediates during ring closure for the methylaspartate isomerization.

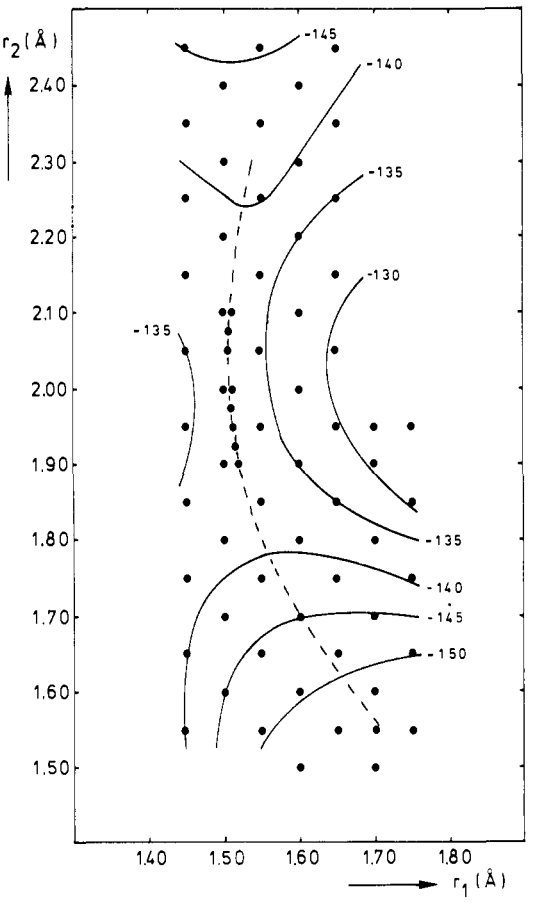

Figure 8. Heat of formation (kcal/mol) as a function of r_1 and r_2 for intermediates during ring closure for the methylitaconate isomerization.

require no other cofactors,[10] while those of amine migrations all apparently require pyridoxal phosphate and sometimes other cofactors such as K^+, Mg^{2+}, and ATP. The enzymes of the hydroxyl migrations all require simple ions such as K^+. Although the role of some of these factors, e.g., pyridoxal phosphate, is uncertain, the question is raised *if* there is a common denominator to the mechanism of reaction of the different groups of substrates. This is emphasized by the fact that enzymes that catalyze the isomerization of diols, glycerol, and ethanolamine give very unusual and characteristic ESR spectra in the presence of substrates. In all cases, the ESR spectrum consists of two components, one due to the Co(II) ion and a narrow doublet due to an organic radical, the splitting being explained by interaction with the Co(II) ion. No such signal could, however, be observed with methylmalonyl-coenzyme A mutase.[11] Though a radical mechanism might be appropriate for hydroxyl or amine migrations, the probability of such a mechanism with respect to the carbon-skeleton rearrangements becomes less. Moreover, model studies suggest[12] that in methylmalonyl-coenzyme A mutase reactions the coenzyme–C bond assists in the formation of a substrate carbanion in the rearrangement step. In order to test this model description for the stereochemistry of the carbon-skeleton rearrangements in general, we selected the anionic cyclopropane intermediates as given in Figure 3 for the quantum chemical calculations.

The way in which these anions can be generated is subject to a lot of speculation. Three possible ways are summarized below. All three should obey the observation of Miller et al.,[13] showing the hydrogen which migrates during the isomerization of methylmalonyl-coenzyme A to succinyl-coenzyme A becomes one of three equivalent hydrogens on C_5' of coenzyme B_{12}, before a hydrogen is returned to the substrate. The first two, suggested by those who hold to initial radical generation for all the coenzyme B_{12} dependent rearrangements, consist of radical generation in the substrate, followed by either electron transfer from cobalt to the substrate ($R\cdot + Co(II)\cdot \rightarrow Co(III)^+ + R^-$) or charge transfer from protein basic and acidic sites to the substrate radical, a suggestion put forward by Prof. Finke.[14] A third possibility is proton loss from the substrate to C_5' of the coenzyme, whereby one of the three hydrogens of the C_5' methyl group becomes covalently bonded to cobalt via an agostic M(H)C interaction, as proposed by Brookhart et al.[15] Then substrate–enzyme interaction can accommodate for the charge buildup in the substrate at the various stages of the rearrangement.

For the sake of simplicity, the calculations were confined to the substrate system without introducing enzyme or coenzyme

(10) Pratt, J. M. "B_{12}"; Dolphin, D., Ed.; John Wiley and Sons: New York, 1982; Vol 1, p 331.
(11) Pratt, J. M. "B_{12}"; Dolphin, D., Ed.; John Wiley and Sons: New York, 1982; Vol. 1, p 381.
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(14) (a) Personal communication of R. G. Finke. (b) Finke, R. G.; Schiraldi, D. A.; Mayer, B. J. *Coord. Chem. Rev.* **1984**, *54*, 1–22.
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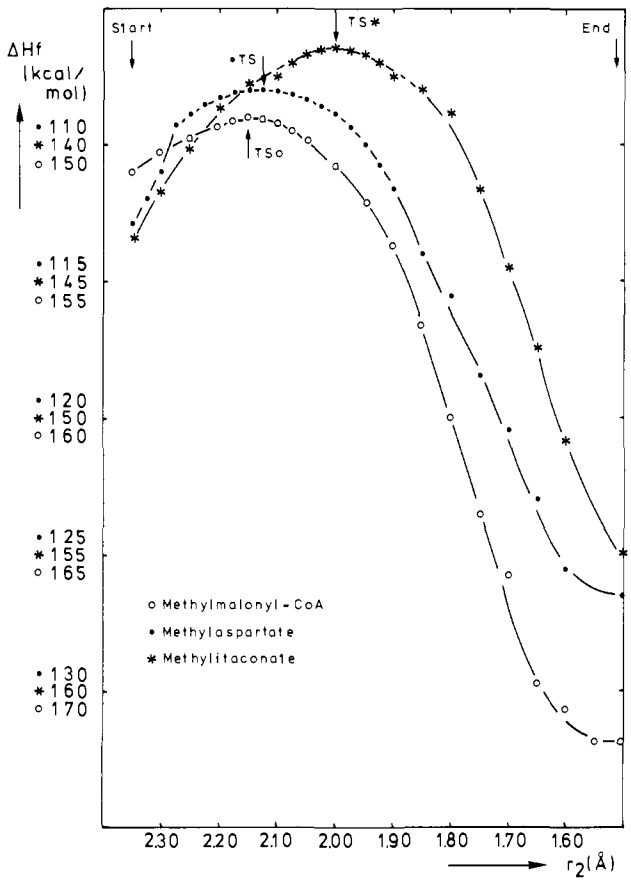

Figure 9. Heat of formation (kcal/mol) as a function of the reaction coordinate r_2 for the three carbon-skeleton rearrangements.

specific sites. The key intermediate as illustrated in Figure 3 is formed by proton abstraction from the methyl group (C_3) followed by an approach of group R (see Figure 1) and the now negatively charged methylene group. The intermediate ring closure during the isomerization of methylmalonyl-coenzyme A and methylitaconate is facilitated by polarization of the C=O and C=C bond in group R, respectively. In the isomerization of methylaspartate a keto–enol tautomerization can provide an analogue structure, able to accommodate negative charge (see Figure 4). Instead of one enzyme essential for the isomerization of methylmalonyl-coenzyme A and methylitaconate, the enzyme complex for the isomerization of methylaspartate consists of two proteins.[16] The fully optimized MNDO structure of the enol form is only 2 kcal/mol higher in energy than the keto form, an energy difference which is smaller than the unpredictable error of the MNDO method.[17] The final rearrangement product is formed by proton addition at the acid-substituted C_1 and rupture of the C_1–R bond.

Quantum Chemical Calculations

The formation of the cyclopropane intermediates **1–3** has been studied with MNDO calculations.[18] Of course MNDO results cannot give the final proof of the assumed reaction mechanism, but a detailed understanding of the dynamics and stereochemistry of organic reactions requires, above all, a knowledge of the potential energy surface.[18] The energy profile of all three ring-closure reactions is calculated by optimization of all distances, angles, and torsion angles to minimal heat of formation at a number of fixed values of r_1 and r_2 (see Figure 5), ranging between 1.35 and 1.80 Å for r_1 and between 1.40 and 2.50 Å for r_2. In this way the angle C_3–C_1–C_2 changes from tetrahedral (in the linear molecule direct after proton abstraction) to triangular (at the end of the ring closure). As initial values for distances and bond angles, those optimized by Dewar et al.[19] for the MNDO program are used. The reaction path is drawn along the line of minimal energy. The results of these calculations are given in Figures 6–8. Following the reaction path, the heat of formation as a function of the reaction coordinate r_2 is given for all three ring-closure reactions in Figure 9. The graphs are closely related, except that the transition state of the methylitaconate ring closure is situated later on the reaction coordinate. A minimum in energy is reached for values of r_2 between 1.60 and 1.50 Å. The calculations are not extended beyond this value because in our model the proton addition to C_1 takes place before this minimum in energy is reached. The charge density accumulated on the various groups of the intermediate structures varies with the reaction coordinate r_2 in a quite similar way for the three rearrangements, with the exception of the charge density on the group which stabilizes the negative charge by polarization of a double bond, i.e., C=O, C=C(OH)$_2$, and C=CH$_2$ (C=X in Figure 10). In the isomerizations of methylaspartate and methylitaconate, the charge accommodated by this group in the beginning of the reaction coordinate is high in comparison with the isomerization

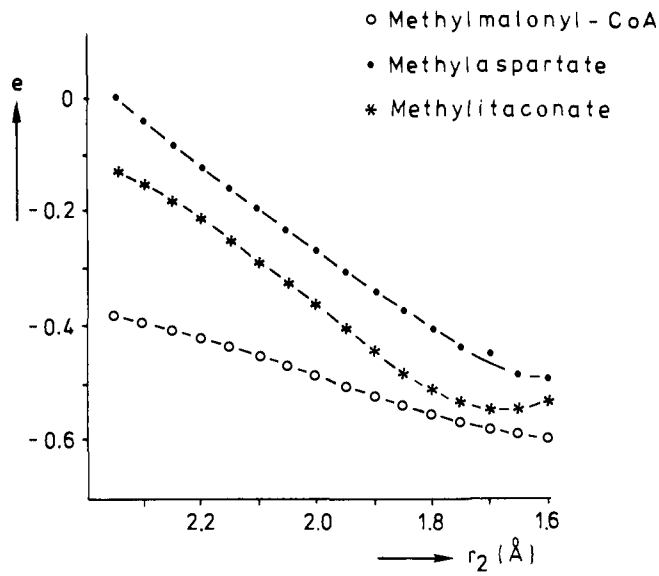

Figure 10. Charge on group =X as a function of r_2 for the carbon-skeleton rearrangements.

Table I. The Coefficients of the Atomic Orbitals of the Ring Carbons at the Moment of Proton Addition to the Cyclopropane Intermediates

	methylmalonyl-coenzyme A	methyl-aspartate	methyl-itaconate
C_1			
s	−0.15	−0.12	−0.14
x	+0.08	+0.03	+0.04
y	+0.50	+0.31	+0.38
z	−0.30	−0.20	−0.25
C_2			
s	+0.03	+0.04	+0.04
x	+0.01	+0.03	+0.03
y	−0.09	+0.07	+0.11
z	−0.21	+0.03	+0.03
C_3			
s	+0.11	+0.06	+0.06
x	+0.00	+0.00	+0.00
y	−0.31	−0.18	−0.22
z	+0.22	+0.08	+0.09

(16) Suzuki, F.; Barker, H. A. *J. Biol. Chem.* **1966**, *241*, 878–888.
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(19) Dewar, J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907–4917.

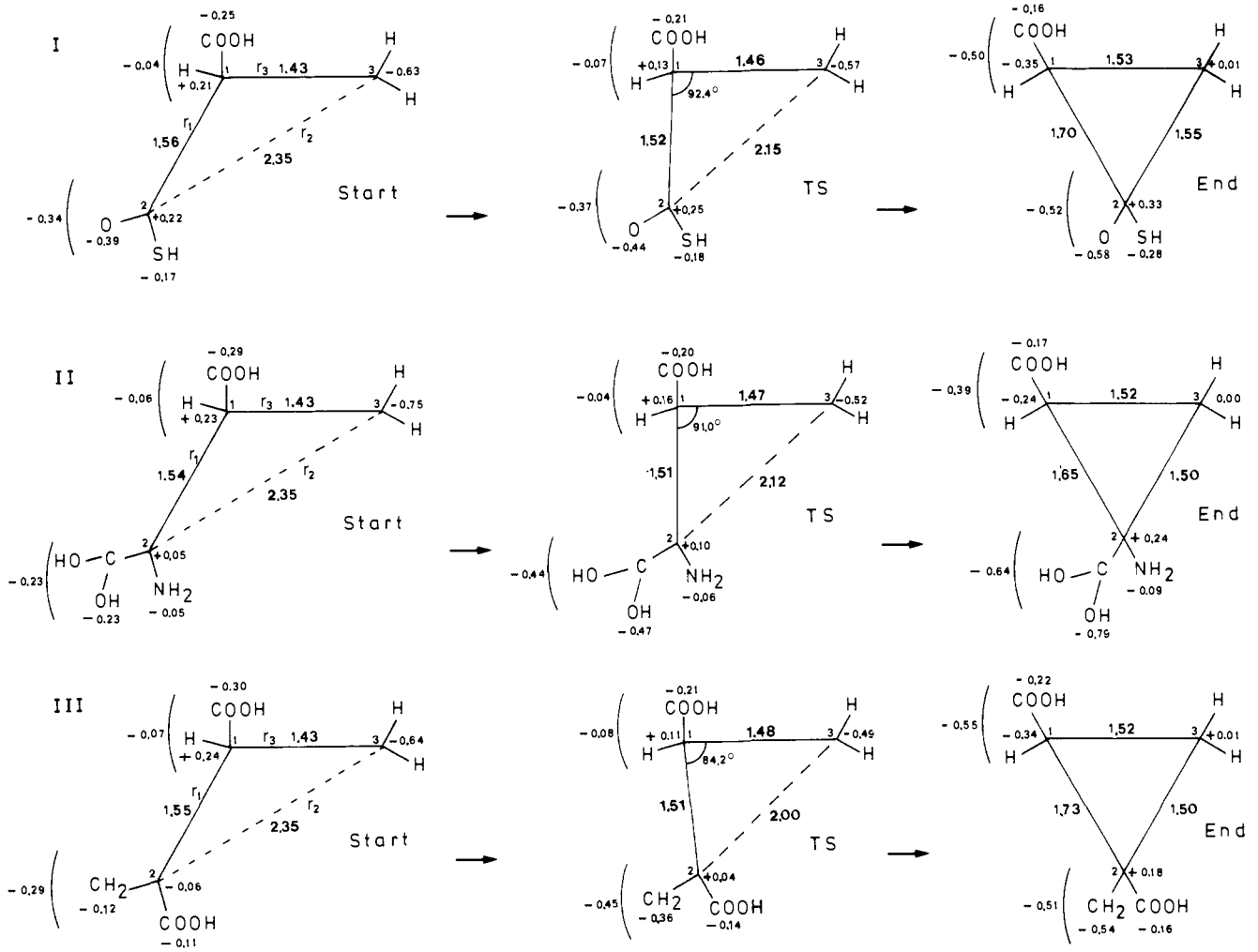

Figure 11. Charge delocalization over the cyclopropane intermediates at different stages of ring closure.

of methylmalonyl-coenzyme A, as can be seen in Figure 10.

The charge distribution over the intermediate structures at different stages of the ring closure is given in Figure 11. The definition of the intermediates Start, TS (transition state), and End is given in Figure 9.

The evolution of the coefficients of the atomic orbitals in the HOMO of the cyclopropane intermediates along the reaction coordinate is followed. The two atomic orbitals with the highest coefficient in the HOMO are given in Figure 12 as a function of r_1 and r_2.

In all three reactions the overall picture is the same. In the beginning of the ring closure the contribution of the atomic orbitals on C_3, the carbon from which the proton is abstracted, is dominant. After the transition state the atomic orbital on the formerly double bonded oxygen, respectively carbon, in the direction of C_3 becomes important. Near the end of the ring formation the orbital on C_1 in the direction of C_2 will have a large coefficient in the HOMO, as can be seen in Figure 12. A very important difference between the three reactions becomes clear, if also atomic orbitals with smaller coefficients in the HOMO are taken into account. If the intermediate is situated in the y–z plane, with the C_1–C_2 bond on the y axis, the contribution of the atomic orbitals of the three carbons constituting the ring is given in Table I for r_1 = 1.7 Å and r_2 = 1.6 Å.

The coefficients of the atomic orbitals of C_1 and C_2 are of opposite sign in the y direction and of equal sign in the z direction in the methylmalonyl-coenzyme A intermediate. Both indicate an overlap between the atomic orbitals on C_1 and C_2, as can be seen in Figure 13, i.e., the HOMO has a bonding character between C_1 and C_2, the electron density between C_1 and C_2 is high. In the methylaspartate and methylitaconate intermediates, the contributions of the atomic orbitals of C_1 and C_2 to the HOMO are of equal sign in the y direction and of opposite sign in the z direction, i.e., the HOMO has an antibonding character between C_1 and C_2. There is a node in electron density between C_1 and C_2. The two orbitals just below the HOMO in energy do not play an important role in the picture between C_1 and C_2.

Discussion

Further examination of the pattern given by the way charge delocalizes in the model anionic intermediate (intermediate Start in Figure 11) shows that the negative charge is best stabilized on the formerly double bonded oxygen in methylmalonyl-coenzyme A in comparison with the way the $-C(OH)_2$ group accommodates the negative charge in methylaspartate. The methylene group of methylitaconate behaves intermediate in accommodation of the negative charge. The relative small initial accommodation of negative charge by the diol group in methylaspartate can be considered as a prerequisite for a larger charge migration *during* ring closure. Such a large charge migration from C_3 over C_2 to C_1 might force the electron density to pass momentarily beyond C_1. Subsequent orbital inversion at C_2 will prevent the electron density to flow back via the C_1–C_2 bond and to delocalize over the cyclopropane ring. Proton addition at that moment on the reaction coordinate will lead to inversion of configuration on C_1, i.e., the proton comes in at the opposite side of the leaving glycyl group. The relative small charge migration *during* ring closure of methylmalonyl-coenzyme A will not be strong enough to force the electron density to pass C_1, resulting in retention of config-

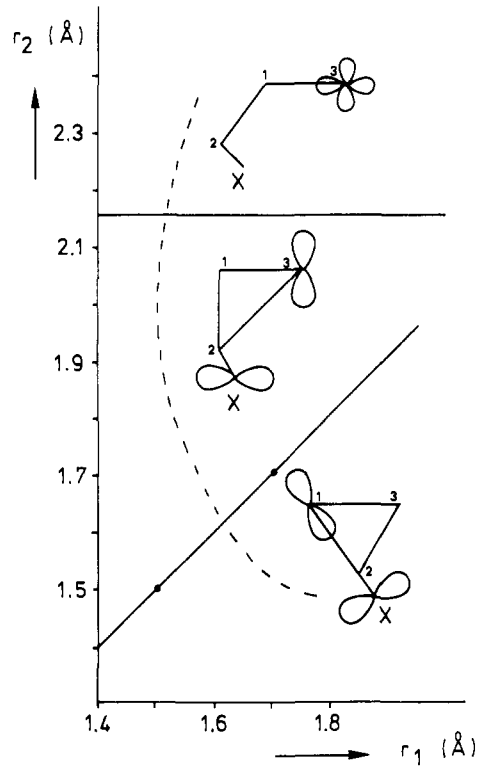

Figure 12. The two atomic orbitals with the largest coefficient in the HOMO for all three carbon-skeleton rearrangements.

uration at C_1. This rather new concept of orbital inversion to prevent electron back-donation to C_2 is strongly supported by the picture originating from the development of the coefficients of the atomic orbitals in the HOMO. Figure 12 shows charge migration via C_2 and not directly from C_3 to C_1. This direction of migration is necessary for the electron density to pass C_1 in line of the C_1–C_2 bond, which will lead to inversion of configuration on C_1. Figure 13 indicates an antibonding character for the C_1–C_2 bond of the methylaspartate intermediate, which prevents the electron density from flowing back to C_2 and the proton from adding to the C_1–C_2 bond. The bonding character of the C_1–C_2 bond in the methylmalonyl-coenzyme A intermediate will cause proton addition with retention of configuration at C_1, due to the high electron density between C_1 and C_2. The antibonding character of the C_1–C_2 bond in the HOMO of the methylitaconate intermediate suggests inversion of configuration in this rearrangement. Finally, it may be of interest to note that in the case of methylmalonyl-coenzyme A mutase with ethylmalonyl-coenzyme A as substrate instead of methylmalonyl-coenzyme A only partial inversion is observed.[20] Besides the role of the enzyme in the enzyme–substrate binding (ethylmalonyl reacts at only one thousandths the rate of the natural substrate), the loss of stereospecificity in the case of ethylmalonyl-coenzyme A may also be electronic in nature.

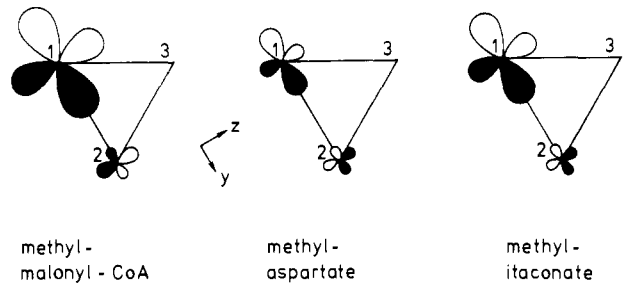

Figure 13. Bonding and antibonding character of the C_1–C_2 bond in the HOMO.

Conclusion

Energy profiles of the carbon-skeleton rearrangements with kationic or radical intermediates in the rearrangement step are required to discuss a possible preference for the anionic pathway. However, the fact that an anionic intermediate can declare the known stereochemistry can be considered as an extra indicator in addition to the chemical evidence suggesting a carbanion in the rearrangement step of the methylmalonyl-coenzyme A isomerization.

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