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Theoretical Investigations of the Influence of Pressure on the Selectivity of the Michael Addition of Diphenylmethaneamine to Stereogenic Crotonates

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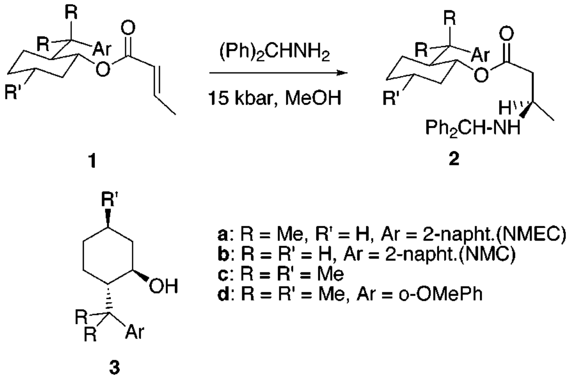
SIBFA (sum of interactions between fragments ab initio computed) molecular mechanics systematics has been modified to take into account the effect of pressure on intra- and intermolecular energies. The van der Waals radii are related to the pressure, using Bridgman results on the variation of crystal volume, on one hand, and the relation between the volume of an atom and its van der Waals radius on the other. This procedure produces a decrease of the volume of the systems considered. The modified systematics is used for the study of the conformation at 1 atm and 15 kbar of two stereogenic crotonates and of the complexes formed by these two molecules with the diphenylmethaneamine and the three solvent molecules present in the experiment. The results obtained show that in the case of NMECC **1a** the diastereoselectivity induced by high pressure and by the presence of methanol proceeds from an important stabilization of the *pro-R* reactive complex in which the crotonate has a *stacked-transoid* conformation. This stabilization is mainly due to intermolecular interactions. In the case of the second crotonate considered, NMCC **1b**, our results indicate that pressure induces a stabilization of the *pro-R* and *pro-S* complexes having the *axial* conformation for which the reaction exhibits little diastereoselectivity in qualitative agreement with experimental data. This study tends to show that it is possible to account theoretically for the influence of pressure on molecular conformation and/or complex structure, using a molecular mechanics method that is able to take into account the variation of volumes of the different entities present in the system studied.

Introduction

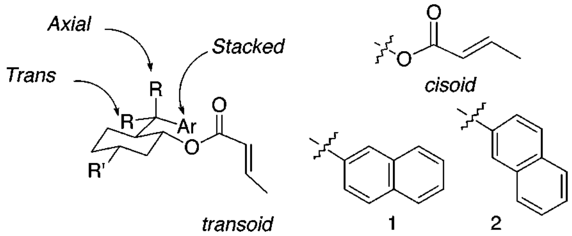
A previous molecular mechanics study[1] has found a close relationship between the theoretical stability of the *stacked* conformation of 8-arylmenthol crotonates **1** and the efficiency as a chiral auxiliary of the corresponding alcohols **3c** for the diastereoselective addition of diphenylmethaneamine, leading to β-aminoesters (Chart 1), under high pressure (15 kbar).[2] These calculations have even been able to propose a new chiral auxiliary, 8-*o*-methoxyphenylmenthol (**3d**), the efficiency of which has been experimentally confirmed.[3] However, recent experimental results suggest that the agreement between theory and experiment could seem partially fortuitous and require a need to take into account some additional features to be fulfilled in all cases.[4] Thus, the computations have considered only the *transoid* conformation (Chart 2) of the crotonate moiety since the stereochemical outcome of this reaction is consistent with the addition of the amine to the transoid conformation of the crotonate reactant.[2,3] Quite unexpectedly, the X-ray study of the related *trans*-2-[1-(2-naphthyl)-1-methylethyl]cyclohexyl-(*E*)-crotonate (NMECC, **1a**) has shown that, in the crystal, the crotonate moiety adopts a *cisoid* conformation.[4] More recent computations carried out on four chiral cyclohexyl-based crotonates bearing a β-naphthyl group have shown that the energy of their *cisoid* and transoid

Chart 1



a: R = Me, R' = H, Ar = 2-napht.(NMEC)
b: R = R' = H, Ar = 2-napht.(NMC)
c: R = R' = Me
d: R = R' = Me, Ar = o-OMePh

Chart 2



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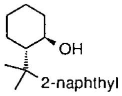
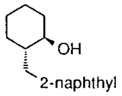
10.1021/jo9825308 CCC: $18.00

Table 1. Diastereoselectivities in the Michael Addition of Ph_2CHNH_2 to NMEC- and NMC-based Chiral Crotonates as a Function of Experimental Conditions (values from Ref 3)

	de in the Michael addition of Ph_2CHNH_2 to chiral crotonates derived from alcohols:	
conditions	**NMEC**  	**NMC** 
MeOH, 15 kbar	98	18
MeOH, 1 atm	10	7
CH_3CN-Et_2O, 15 kbar	8	5
CH_3CN-Et_2O, 1 atm	*a*	*a*

[a] No reaction in these conditions.

conformations differs by 0.1−0.6 kcal/mol.[5] These values are not large enough to justify some of the selectivities obtained experimentally (Table 1).[3] Furthermore, the diastereoisomeric excess (de) appears to be very sensitive to the solvent; it decreases considerably when going from CH_3OH to CH_3CN/Et_2O.[2,3] Finally, under atmospheric pressure, the reaction is not only considerably slower even in CH_3OH (5 days at 40 °C) but also much less diastereoselective as can be seen from the values reported in Table 1.[3]

This set of data tends to show that the stability of the stacked conformers with respect to the other possible conformations (Chart 2) of such chiral crotonates is only one (even if it is the leading as suggested by previous results)[1,3] of the factors at work in such high-pressure diastereoselective Michael additions. Because of the importance of activation volumes in high-pressure chemistry[6] and the pressure dependence of the stereoselectivity that is assumed to originate from a difference in the activation volume of the possible diastereomeric transition states, the volumes of the different conformers of chiral crotonates under experimental study have been calculated. The results obtained show, provided that under high-pressure conditions the conformers with the smallest volumes and relative energies up to 1−2 kcal/mol are favored, a good correlation between the conformational molecular volume and their π-facial discrimation in the high-pressure-induced Michael addition of diphenylmethaneamine.[5] However, if these results can explain the influence of the pressure on the de, they do not provide any explanation for the role of the solvent on the selectivity. At this point, we underline that the role of the solvent on the kinetics of such a reaction is not considered in the present work since previous studies have provided satisfactory accounts of the contribution of protic solvents to related Michael additions.[7]

To get some insight into the different factors that could contribute to the diastereoselectivity of this particular reaction, we undertook a molecular mechanics study using a version of the SIBFA (sum of interactions between fragments ab initio computed) method[8] modified to take into account pressure. Previous studies concerned by modeling molecular conformation/interactions under high pressure have been carried out using Monte Carlo[9] or molecular dynamics[10] methods. Because of the size of the systems to be studied (98 atoms in the largest ones), we could not consider the use of an ab initio method.[11] Furthermore, the number of conformational domains (12), depicted in Chart 2, to be explored for the different situations to be considered would require computing facilities beyond thoses currently in use in organic chemistry modeling if molecular dynamics computations were undertaken. On the other hand, SIBFA, which has given good results not only for the correlation stacked conformer energy/diastereoselectivity of the high-pressure-induced Michael addition in these systems[1] but also for precursors of the transition states of an intramolecular Diels−Alder reaction,[12] can be expected to give a reasonable first estimate of the influence of pressure on the arrangement of the reactants as well as their relative energies.

The calculations will be carried out at 15 kbar, as in the experiments, and at atmospheric pressure. The largest systems considered will include a β-naphthylmethylethylcyclohexyl crotonate (NMECC, **1a**), the diphenylmethaneamine, and the number (three) of methanol molecules corresponding to the experimental conditions. The search of the most stable geometrical arrangement of such complexes, carried out under both conditions, will provide indications on the conformational changes induced by high pressure. These computations will unfortunately be dealing not with the transition state itself but only with what can be considered as the "pretransition state" (PTS) or the "near attack conformation " (NAC) as proposed by Lightstone and Bruice.[13] But under high pressure, the possibilities of conformational equilibrium and of diffusion are considerably reduced; the stability of the PTS should, therefore, be able to reflect to some extent that of the transition state. These computations are carried out for two auxiliaries, *trans*-2-[1-(2-naphthyl)-1-methylethyl]cyclohexanol (NMEC, **3a**) and *trans*-2-(2-naphthylmethyl)cyclohexanol (NMC, **3b**), which give significantly different π-facial differentiation of the corresponding crotonates (Table 1). A delineation of the role of the different forces at work in the reaction will be obtained from the variation, with the pressure, of the intra-/intermolecular energies (and of their different contributions). Furthermore, similar calculations carried out on the isolated chiral crotonates on one hand and on a model of the "reacting" system on the other will

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provide information of the role of the methanols in the reaction through the hydrogen bonding chart found in the complex. This analysis is possible since molecular mechanics computations give separately the inter- and intramolecular contributions to the energy as well as their different components (electrostatic, dispersion, etc.).

The first part of this study is concerned by the cisoid–transoid energy difference in methyl crotonate, a small enough molecule to be studied by sophisticated methods. Such calculations are necessary to validate the corresponding molecular mechanics results. This quantity is of prime importance for the problem studied since no de is expected for isoenergetic cisoid and transoid conformers.

Methodology

With SIBFA systematics, the total energy is calculated as the sum of inter- and intramolecular contributions

$$E = E_{\mathrm{Inter}} + \sum E_{\mathrm{Intra}}$$

the summation running the different molecules of the system considered. E_{inter} is calculated as the sum of 5 terms[8]

$$E_{\mathrm{Inter}} = E_{\mathrm{MTP}} + E_{\mathrm{Rep}} + E_{\mathrm{Disp}} + E_{\mathrm{Pol}} + E_{\mathrm{CT}}$$

In the case of E_{Intra}, there is no charge-transfer term but a torsion contribution, E_{Tor}, is taken into account, and we have

$$E_{\mathrm{Intra}} = E_{\mathrm{MTP}} + E_{\mathrm{Rep}} + E_{\mathrm{Disp}} + E_{\mathrm{Pol}} + E_{\mathrm{Tor}}$$

Because E_{MTP}, E_{Rep}, and E_{Disp} are pair-wise additive terms, E can also be written

$$E = \sum_{i,j} E_{ij} + E_{\mathrm{Pol}} + E_{\mathrm{CT}} + E_{\mathrm{Tor}}$$

where E_{ij} is the interaction energy between nonbonded atoms i and j belonging to fragments F and F′ (belonging to the same or to two different molecules of the system studied), respectively. The van der Waals contribution to E_{ij} is given by

$$E_{ij}^{\mathrm{vw}} = E_{\mathrm{Disp}} + E_{\mathrm{Rep}} = A_{ij}/R_{ij}^{6} + B\exp(-\alpha_{ij}R_{ij})$$

where R_{ij} is the interatomic distance and B a constant, while A_{ij} and α_{ij} have values that depend on the atomic species of i and j. Following Kitaygorodski,[14] A_{ij} is taken as:

$$A_{ij} = A' r_{\mathrm{o}\,ij}^{6}$$

where A' is a universal constant and $r_{\mathrm{o}ij}$, corresponds to the best interatomic distance measured in reference crystals, such as graphite for carbon. Atoms i and j van der Waals radii, $r_{\mathrm{vw}i}$ and $r_{\mathrm{vw}j}$, are deduced from $r_{\mathrm{o}ij}$ using relation

$$r_{\mathrm{o}ij} = r_{\mathrm{vw}i} + r_{\mathrm{vw}j}$$

Similarly for α_{ij}, we can write

$$\alpha_{ij} = \alpha'/r_{\mathrm{o}ij}$$

The calculation of the van der Waals contribution ($E_{\mathrm{Disp}} + E_{\mathrm{Rep}}$) is carried out following Kitaygorodski's chart, which relates this quantity to equilibrium interatomic distances in crystals. This expression for E_{Disp} and E_{Rep} is of particular adequacy for taking into account the effect of pressure on intra- and intermolecular energy within the SIBFA framework. Isaacs[15] has suggested that the compressibility (molecular volume/interatomic distance decrease with pressure) proceeds from a reduction of the "effective" radius of atoms in solids and of the "void" between molecules in liquids. Following this suggestion, we have introduced the influence of pressure in the inter-/intramolecular energies by varying the van der Waals radii, using the above relations and Bridgman results. Bridgman[16] has determined, from measurements of volume change, due to pressure P, of isotropic crystals a pressure/volume relationship

$$\frac{-\Delta V}{V_0} = aP - bP^2$$

it is possible to take into account the pressure effects on the van der Waals radii, which are the "effective" radii of the atoms in the crystal. Following the definition of the compressibility β at temperature T

$$\beta = -\frac{1}{V_0}\left(\frac{\partial V}{\partial P}\right)_T$$

and taking into account that

$$\left(\frac{\partial V}{\partial P}\right)_T = \left(\frac{\partial \Delta V}{\partial P}\right)_T$$

it appears that the coefficients a and b are related to the compressibility by

$$\beta = a - 2bP$$

and

$$\left(\frac{\partial \beta}{\partial P}\right)_T = -2b$$

On the other hand, each atom can be considered as a sphere with a radius equal to its van der Waals radius. Thus, at atmospheric pressure its volume is equal to

$$V_{\mathrm{o}} = \frac{4}{3}\pi r_{\mathrm{o\,vw}}^{3}$$

and the volume variation with pressure is given by

$$\Delta V = V_{\mathrm{p}} - V_{\mathrm{o}} = \frac{4\pi}{3}(r_{\mathrm{p\,vw}}^{3} - r_{\mathrm{o\,vw}}^{3})$$

Therefore, the relation

$$\frac{\Delta V}{V_{\mathrm{o}}} = \frac{r_{\mathrm{p\,vw}}^{3} - r_{\mathrm{o\,vw}}^{3}}{r_{\mathrm{o\,vw}}^{3}} = \frac{r_{\mathrm{p\,vw}}^{3}}{r_{\mathrm{o\,vw}}^{3}} - 1$$

gives the van der Waals radius $r_{p\mathrm{vw}}$ at pressure P provided the volume variation ΔV be known for that pressure. Bridgman has tabulated for a number of atoms either the coefficients a and b which relate ΔV to the pressure or ΔV at different pressures. In this last case, the a and b coefficients are obtained from a least-squares treatment.[16]

As precedingly,[5,17] the computation of the molecular volume Ω is based on van der Waals volume and not on electron density envelopes.[18] With that approximation, it can be obtained using Ostrogradski's formula from a surface integration where Σ is the volume Ω integration boundary, that is

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[14] Kitaygorodsky, A. I. *Tetrahedron* **1961**, *14*, 230.

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Chart 3

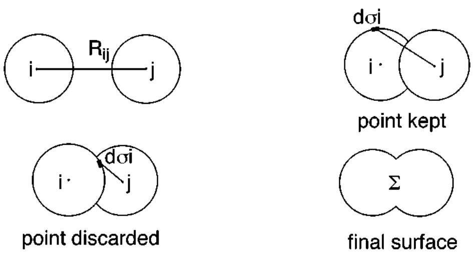


Chart 4

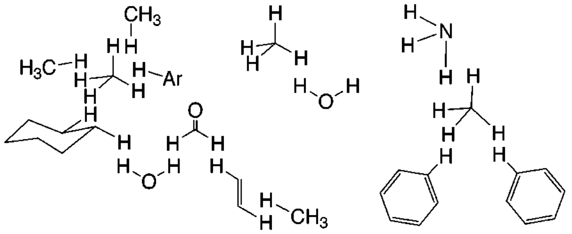
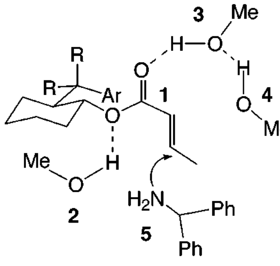


Chart 5



the molecular surface and $\vec{n}_e$ is the normal vector to Σ directed toward the outside of Ω.

$$\Omega = \int_{\Omega}\int\int \mathrm{d}v = \int_{\Sigma}\frac{1}{3}\,\vec{r}\;\vec{n}_e(\Omega)\;\mathrm{d}\sigma$$

The integration surface Σ is obtained from the summation of (parts of) spheres centered on each atom i of the molecule (Chart 3). For atoms i and j, if the interatomic distance R_{ij} is larger than the sum of their van der Waals radii, the surface of both spheres is included in Σ. If the interatomic distance R_{ij} is smaller than the sum of the van der Waals radii, part of the spheres have to be skipped. The surface element $\mathrm{d}\sigma_i$ is kept if and only if the distance between $\mathrm{d}\sigma_i$ and atom j is larger than atom j's van der Waals radius by running over sphere i using a Korobov grid.[17] Points $\mathrm{d}\sigma_j$ of sphere j are kept according to the same criteria. The values of the van der Waals radii used for the volumes computations take into account the pressure. Therefore, it is possible to have an estimation of the pressure on this quantity for the different possible conformers.

Other procedures have been proposed to calculate molecular volumes.[18] The one retained herein presents the advantage of being fully consistent with the method used to take into account the effect of the pressure.

The fragments (Chart 4) used as input for the chiral crotonates are the same as those discussed in ref 1 except for the crotonate entity. In the present work, the crotonaldehyde is made of three fragments: formaldehyde, ethylene, and methane in order to allow the cisoid−transoid conformational variation. Diphenylmethaneamine is made of ammonia, methane, and two benzene fragments, while water and methane are those of the methanols. The multipoles (monopoles, dipoles, and quadrupoles) are calculated from the MP2 density matrixes in order to take into account the contribution of electron correlation to the molecular electron distribution. Optimizations for the "reacting" systems were carried out through the hydrogen bonding chart depicted in Chart 5 since the critical role of methanol might be interpreted in terms of hydrogen-bond formation between this solvent and the crotonate moiety, a phenomenon favored under high-pressure, because of the decrease in atomic distance and suppression of thermal motions.[3]

Table 2. Conformational Energy Minima (kcal/mol) and Conformational Molecular Volume (mL) of NMEC-based Chiral Crotonate[a]

	1 atm				15 kbar			
conf.	*E*	Δ*E*	*V*	Δ*V*	*E*	Δ*E*	*V*	Δ*V*
Sc	606.4	0.0	190.7	4.1	412.7	0.0	161.9	2.4
St	606.6	0.2	186.6	0.0	413.0	0.3	159.5	0.0
Tc	607.4	1.0	194.1	7.5	414.9	2.2	168.4	8.9
Tt	607.6	1.2	194.3	7.7	415.2	2.5	168.0	8.5
Ac	610.0	3.6	192.4	5.8	413.6	0.9	166.3	6.8
At	610.3	3.9	191.8	5.2	413.8	1.1	166.1	6.6

[a] Under its threshold "*Stacked*" (S), "*Trans*" (T) and "*Axial*" (A) (position of the aryl group), as well as *transoid* (t) and *cisoid* (c) [only the most stable of the two orientations of the naphthyl group (1 or 2, Chart 2) are given] conformation.

The ab initio calculations have been carried out using the Gaussian94[19] series of programs. The geometry optimizations were performed with the 6-31G** basis and the B3P86[20] functional.

Results and Discussion

Methyl Crotonate. The ab initio complete optimization of the cisoid and transoid conformations, using the B3P86 hybrid functional, gives a 0.7 kcal/mol energy difference in favor of the cisoid form. This value is close to those reported by Houk et al.[21] on one hand and Ruiz-Lopez et al.[22] on the other for methyl acrylate at the SCF level (0−1.8 kcal/mol depending on the basis set and computational level used). SIBFA gives a cisoid conformer more stable than the transoid one by 0.4 kcal/mol. This result shows that SIBFA is not only able to give the correct order of stabilities but also reasonable values of energy differences between quasi-isoenergetic conformations. This systematics should, therefore, account correctly, in the case of the compounds under study, for the energy variation with this particular conformational parameter.

***trans*-2-[1-(2-Naphthyl)-1-methylethyl]cyclohexyl-(*E*)-crotonate (NMECC) 1a.** This compound corresponds to the case of an excellent de (98%) when the addition takes place at 15 kbar in methanol and a poor one in other conditions as can be seen from Table 1. The values of Table 2, which concern the isolated NMEC-derived chiral crotonate at 1 atm, and Figure 1a show that the SIBFA computations give results in excellent agreement with experiment since the most stable conformation is the *stacked cisoid* (Sc) form with orientation 1 (Chart 2) of the naphthyl group as observed in the crystal.[4] We see also from Table 2 that the energy

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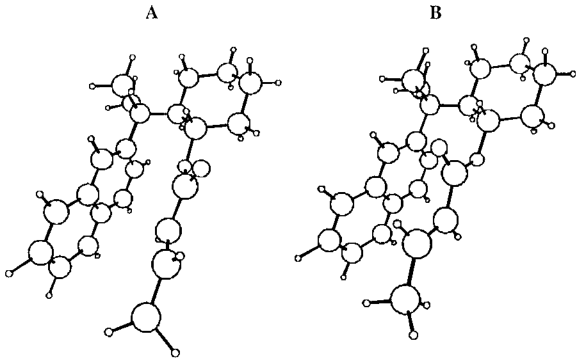

Figure 1. Most stable geometrical arrangement of the cisoid form of NMECC at 1 atm (A) and under 15 kbar (B).

difference between the cisoid and transoid conformations is very small (0.2−0.3 kcal/mol) and of the same order of magnitude for the stacked, trans, and axial conformers. This feature, which is not modified by a pressure of 15 kbar as can be seen from the corresponding values of Table 2, is in agreement with the low de obtained in absence of protic solvent since the stacked cisoid (Sc) and transoid (St) conformers, the most stable ones, give opposite diastereoisomers.

The values of Table 2 show also that pressure decreases the difference of volume between the cisoid and transoid forms of the stacked conformers, the St conformer remaining, however, by far the more compact. In addition, pressure inverts the stability of the trans and axial conformations. At 15 kbar, the latters have an energy that differs by less than 1 kcal/mol from that of the stacked conformations. This variation, to be related to the molecular volumes at 1 atm of the different conformers (the axial being more compact than the trans), confirms our hypothesis on the importance of this factor for their stabilization under high pressure since the volume of the axial arrangement is more compact than the trans one.

From Figure 1, which shows the optimized geometries of the Sc conformation at both pressures, we see that the only significant variation concerns the orientation of the crotonate moiety that rotates about the C−O bond, getting closer to the naphthyl rings upon pressure increase. The same variation takes place for the St conformer (not shown).

Table 3. Conformational Energy Minima (kcal/mol) and Conformational Molecular Volume (mL) of the Reactive Complex[a]

	1 atm (de = 18%)				15 kbar (de = 98%)			
conf.	E	ΔE	V	ΔV	E	ΔE	V	ΔV
Sc	1254.0	0.4	382.2	5.9	864.8	2.5	314.7	0.1
St	1253.6	0.0	376.3	0.0	862.3	0.0	314.6	0.0
Tc	1256.1	2.5	386.4	10.1	868.5	6.2	325.9	11.3
Tt	1254.8	1.2	383.6	7.3	865.0	2.3	326.9	12.3
Ac	1258.7	5.1	379.8	3.5	865.6	3.3	322.1	7.5
At	1256.6	3.0	381.0	4.7	864.1	1.7	321.6	7.0

[a] Including the NMEC based chiral crotonate under relevant conformations (see Table 2), diphenylmethaneamine, and three methanol molecules.

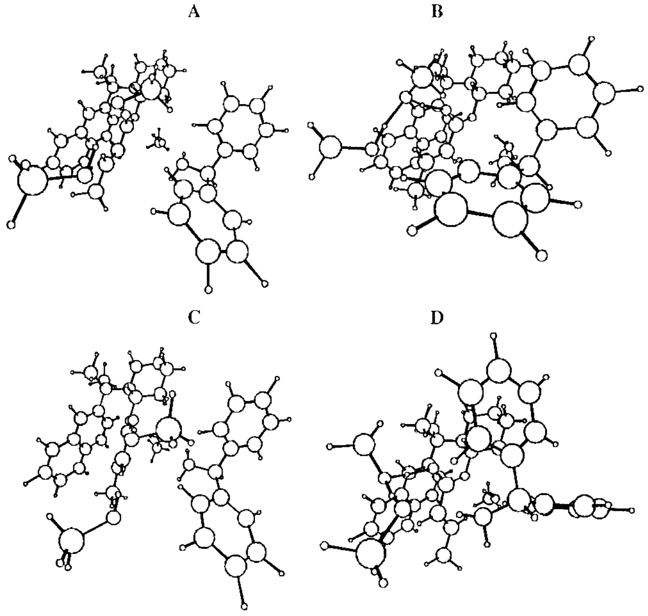

Figure 2. Most stable geometrical arrangements of the cisoid (A & B) and transoid (C & D) of the complex formed by NMECC, three methanols and the diphenylmethaneamine at 1 atm (A & C) and under 15 kbar (B & D).

When the "complex", including the diphenylmethaneamine and three methanols in addition to NMECC **1a** (Chart 5) which can reasonably be considered as the entity that undergoes the chemical reaction, is optimized, the results obtained at 1 atm and 15 kbar differ significantly. From Table 3, we see that under both conditions the St conformation of NMECC **1a** is the most stable. However, the tabulated values show clearly that at 1 atm the energy difference between the cisoid and the transoid forms (0.4 kcal/mol) is not large enough to give rise to a large de. Under a pressure of 15 kbar, we find that the St conformation is more stable by 2.5 and 1.7 kcal/mol than the Sc and axial-transoid (At) conformers, a result able to account correctly for the large de (98%), which is obtained in these conditions.[3] This last value, which shows that the energy difference between the stacked and At conformers is considerably reduced by the pressure (1.7 kcal/mol instead of 3.0 kcal/mol), *suggests that under high pressure the second diastereoisomer formed would not be due to the cisoid/transoid equilibrium but to the stacked/axial one.* The values of Table 2 concerning the volume of the complex (Figure 2) show that the geometrical arrangement of the "complex" is significantly less modified when going from 1 atm to 15 kbar in the case of the Sc conformer than in the case of the St form. The examination of the different contributions to the energy of the complex for the Sc and St conformations of NMECC **1a** shows that the intramolecular energy is in favor of the cisoid form (1279.4/1279.8 kcal/mol at 1 atm and 901.3/905.1 (Table 4) under 15 kbar), while the intermolecular contribution is larger for the transoid conformation of the crotonate (−25.3/−26.3 kcal/mol at 1 atm and −35.7/−42.8 kcal/mol under 15 kbar). From the values of Table 4, we see that the larger value of E_{Inter} in the system with the St crotonate is mainly due to the electrostatic forces (E_{MTP}), while the van der Waals contribution ($E_{\mathrm{Disp}} + E_{\mathrm{Rep}}$) is in favor of the Sc form. From the values of the interaction energies (and of their contributions) of the different "dimers" of the complex, we see that the interactions of NMECC **1a** with the methanol 3 (hydrogen bonded to the carbonyl) on one hand and methanol 4 with the amine on the other are responsible for the greater stability of the complex with St conformation (see Chart 5 for the molecules numbering). The values of Table 4 show also that the interaction

Table 4. Contributions (kcal/mol) to the Intermolecular Interaction Energy in the "Pretransition State" Complex and Between the Different Possible "Dimers" Present[b]

	intermolecular					intramolecular		
	E_{Disp}	E_{Rep}	E_{Pol}	E_{CT}	E_{MTP}	E_{Inter}	E^{a}_{Intra}	E_{tot}
Sc	−19.3	41.4	−9.9	−5.6	−42.5	−35.7	901.3	864.8
1−2	−3.5	3.1	−1.4	−0.8	−8.1	−10.7	539.6	528.9
1−3	−4.5	9.4	−2.2	−2.1	−9.1	−8.4	539.6	531.2
1−4	−1.0	0.2	−0.2	−0.0	−0.5	−1.6	539.7	538.1
1−5	−3.2	1.9	−0.1	−0.1	−0.9	−2.3	521.7	519.4
2−3	0.0	0.0	0.0	0.0	0.1	0.1	230.8	230.9
2−4	0.0	0.0	0.0	0.0	0.1	0.1	230.9	231.0
2−5	−1.1	1.9	−0.4	−0.2	−4.4	−4.4	212.9	208.5
3−4	−4.1	10.5	−3.2	−2.3	−16.5	−15.4	230.9	215.5
3−5	−1.0	0.4	−0.1	0.0	−1.0	−1.7	212.9	211.2
4−5	−0.9	1.0	−0.4	−0.1	−2.3	−2.6	212.9	210.3
St	−24.1	56.7	−14.2	−7.9	−53.5	−42.8	905.1	862.3
1−2	−4.3	3.6	−1.3	−0.7	−7.3	−9.9	540.0	530.1
1−3	−7.0	18.8	−4.2	−4.0	−15.2	−11.4	540.0	528.6
1−4	−0.5	0.0	−0.1	−0.0	−0.4	−1.0	540.0	539.0
1−5	−4.2	2.5	−0.4	−0.1	−1.0	−3.2	522.6	519.4
2−3	0.0	0.0	0.0	0.0	0.3	0.2	231.0	231.2
2−4	0.0	0.0	0.0	0.0	0.1	0.1	230.9	231.0
2−5	−0.7	0.5	−0.3	0.0	−1.7	−2.2	215.4	213.2
3−4	−4.4	11.8	−3.5	−2.5	−17.5	−15.9	230.9	215.0
3−5	−0.7	0.2	−0.1	0.0	−2.0	−2.6	215.5	212.9
4−5	−2.3	5.3	−1.4	−0.6	−8.9	−7.9	215.4	207.5

[a] E_{Intra} is the sum of the five intramolecular energies or of those of the two monomers when dealing with dimers. [b] For the Sc and St conformations of NMECC under a pressure of 15 kbar (see Chart 5 for the molecule numbering).

Table 5. Conformational Energy Minima (kcal/mol) and Conformational Molecular Volume (mL) of NMC Based Chiral Crotonate under Relevant Conformations[a]

	1 atm (de = 7%)				15 kbar (de = 18%)			
conf.	E	ΔE	V	ΔV	E	ΔE	V	ΔV
Sc	503.5	1.4	180.8	2.0	364.3	0.5	151.0	0.0
St	502.1	0.0	178.8	0.0	363.8	0.0	153.9	2.9
Tc	504.8	2.7	184.4	5.6	365.8	2.0	159.5	8.5
Tt	504.4	2.3	184.2	5.4	365.5	1.7	159.4	8.4
Ac	504.0	1.9	180.2	1.4	364.5	0.7	157.1	6.1
At	503.7	1.6	180.1	1.3	364.2	0.4	157.8	6.8

[a] (See Table 2.)

energy between methanols 3 and 4 is larger than that between NMECC **1a** and methanol 3; this feature explains the preference for the methanol-methanol hydrogen bond over the methanol NMECC **1a** one in the case of methanol 4.

***trans*-2-(2-Naphthylmethyl)cyclohexyl-(*E*)-crotonate (NMCC) 1b.** For this compound, the values of Table 5 show that at 1 atm the St conformation is the most stable by 1.4 kcal/mol and that the axial arrangements have the same energy as the Sc form. At this point, we have to notice that the energy difference between the St conformer on one hand and the Sc and axial arrangements on the other does not appear in complete agreement with NMR[3] results concerning this compounds. These data, obtained in solution, tend to show that the NMCC stacked conformations are significantly less populated than in the case of NMECC **1a**, while the present computations give for both compounds similar populations of the stacked forms. However, our results give the correct overall trend when going from **1a** to **1b** since the average energy difference between the stacked and nonstacked conformers is 2.7 kcal/mol for the former and 1.7 kcal/mol for the latter. Moreover, our calculations do not take into account the solvent effect on the stability of the different conformers in solution, a contribution that can destabilize the stacked conformations with respect to axial and trans arrangements. In addition, the Thorpe−Ingold[23] effect, which produces variations of the valence angles at the tethering carbon between the cyclohexyl ring and the naphthyl group, is not taken into account in the present computations since with the version of SIBFA used in this study, only the torsion angles are varied. Since it has been shown[24] that these variations can be of some importance, we carried out some computations, at 1 atm, to get an estimation of the (de)stabilizing contribution of such variations on the energy difference between the St and At conformers. In a first step, we carried out a complete optimization, using AM1, of 2,3-dimethyl-2-phenylbutane (**4**) to model compound **1a** and of 1-phenyl-2-methylpropane (**5**), to model compound **1b** (Chart 6). These computations show that replacing the methyl groups of **4** by hydrogens produces an increase of 3° of the angle between the plane of the phenyl and isopropyl C−C bond. The calculations carried out for the transoid stacked and axial conformations of NMCC with an angle of 112.5° instead of 109.5° for the C−C−C valence angle concerned by the Thorpe-Ingold effect, the energy difference between the St and At conformations is of 1.1 kcal/mol instead of 1.6 kcal/mol as reported in Table 5. This result shows that, for NMCC, the difference between the theoretical and experimental results concerning the most stable conformation in solution, as deduced from NMR, is not due to inacuracy of SIBFA method/parametrization.

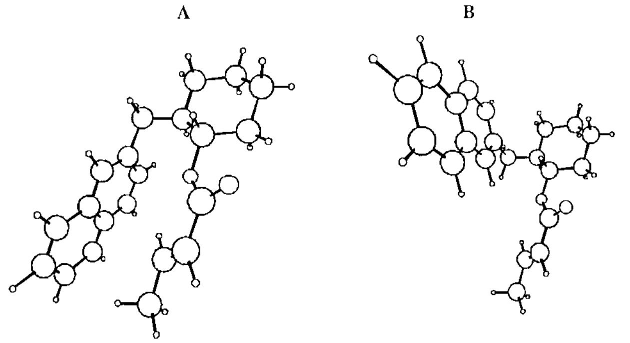

Figure 3. Most stable geometrical arrangements of stacked and axial conformations of the transoid form of NMCC under 15 kbar.

Chart 6

4 **5**

Under high pressure, the two axial and the two stacked conformations have energies which differ by 0.4−0.7 kcal/mol with again the St as the most stable. The stabilization by pressure of the axial conformers can be related to the smaller difference of volume between the axial and stacked conformers than in the case of the preceding compound. Figure 3 shows that with the At conformation the two *pro-R* and *pro-S* approaches of the crotonate

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[23] (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem Soc.* **1915**, *107*, 1080. (b) Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305.

[24] von R. Schleyer, P. *J. Am. Chem. Soc.* **1961**, *83*, 1368.

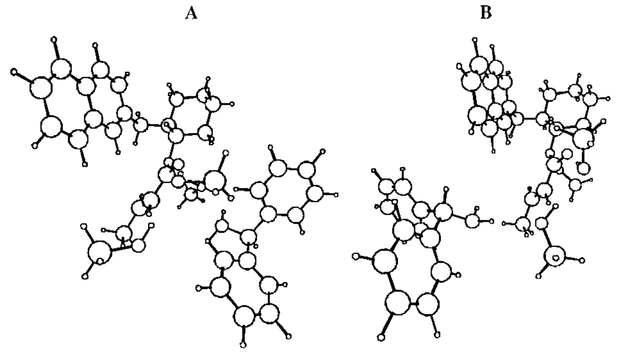

Figure 4. Most stable geometrical arrangements of *pro-R* (A) and *pro-S* (B) complexes formed by axial transoid NMCC, three methanols and diphenylmethaneamine under 15 kbar.

Table 6. Conformational Energy Minima (kcal/mol) and Conformational Molecular volume (mL) of the Reactive Complex[a]

	1 atm (de = 7%)				15 kbar (de = 18%)			
conf.	E	ΔE	V	ΔV	E	ΔE	V	ΔV
Sc *pro-S*	1133.8	0.7	372.5	4.3	800.6	3.9	309.3	0.0
St *pro-R*	1133.1	0.0	368.2	0.0	796.7	0.0	309.9	0.6
Tc *pro-S*	1137.4	4.3	374.9	2.4	804.4	7.7	316.3	7.0
Tt *pro-R*	1136.1	3.0	377.5	9.3	800.2	3.5	316.3	7.0
Ac *pro-S*	1137.0	3.9	369.7	1.5	802.1	5.4	312.3	3.0
At *pro-R*	1133.8	0.7	370.9	2.7	797.6	0.9	314.3	5.0
At *pro-S*	1135.0	1.9	372.5	4.3	798.1	1.4	314.3	5.0

[a] Including the NMC based chiral crotonate under relevant conformations (see Table 2), one diphenylmethaneamine and three methanol molecules.

moiety by the amine are possible. The values of Table 6, which concern the "pretransition state" complex, show that for this crotonate at 1 atm the At conformation corresponds to arrangements that have a stability close to that in which it adopts the St form and equal to that of the Sc one. However, one should notice that the most stable axial conformation is *pro-R* as is the St arrangement. The values corresponding to the complex under 15 kbar show that in this case the pressure tends to stabilize the axial-*pro-S* conformation that now has an energy differing only 0.5 kcal/mol from that of the axial-*pro-R* arrangement. The stabilization of the axial-*pro-S* form is in qualitative agreement with the low de increase induced by pressure in this case.[3] The values reported in Table 7 show that for the complex with the stacked conformation of the chiral crotonate the difference of stability between the cisoid and transoid conformation has the same origin as in the case of NMECC **1a** since the variation of the value of the different contributions follows the same trends. The values concerning the complex with an axial crotonate conformer show that the intramolecular energy is the factor responsible for the stabilization of the axial-*pro-S* complex.

Conclusion

Using a relation between compressibility and atomic van der Waals radii, based on previous work by Bridgman[16] and Isaacs,[15] SIBFA systematics has been modified to take into account the influence of pressure on inter- and intramolecular energies. With such a procedure, the parametrization of the method is not modified. Therefore, it can reasonably be expected that the quality of the results[8] is the same at all pressures. The results obtained for two stereogenic crotonates show that the energy variation with pressure depends significantly upon molecular conformation. Thus, for one of the compounds studied, NMCC **1b**, the most stable conformation is different at 1 atm and 15 kbar. Our results show also that pressure modifies intermolecular interactions since for NMECC **1a** the complex with diphenylmethaneamine plus three methanols is more stabilized when the crotonate has a St conformation than when it has any of the other possible arrangements. In this case, it is a feature that broadens the range of energy of the different possible complexes. As a consequence, pressure makes the addition more diastereoselective in agreement with experiment.[3] In the second case, NMCC **1b**, this variation does not occur because several conformations undergo a stabilization of comparable magnitude. This result prevents the increased stereoselectivity obtained for NMECC **1a**, a feature in agreement with experiment.

Table 7. Contributions (kcal/mol) to the "Pretransition State" Complex Energy for the Sc, St, and At Conformations of NMCC[a,b]

	intermolecular					intramolecular		
	E_{Disp}	E_{Rep}	E_{Pol}	E_{CT}	E_{MTP}	E_{Inter}	E^{a}_{Intra}	E_{tot}
Sc	−18.8	41.3	−10.0	−5.6	−42.9	−35.9	836.5	800.6
St	−21.0	49.1	−12.0	−6.7	−49.7	−40.1	836.8	796.7
At *pro-R*	−20.8	49.9	−12.2	−6.7	−50.2	−40.1	837.7	797.6
1−2	−3.5	3.1	−1.3	−0.8	−7.6	−10.2	475.1	464.9
1−3	−5.2	13.8	−3.2	−3.1	−13.0	−10.7	475.1	464.4
1−4	−1.7	0.6	−0.5	−0.1	−3.9	−5.5	475.0	469.5
1−5	−2.5	1.5	−0.1	−0.1	−0.9	−2.0	457.2	455.1
2−3	0.0	0.0	0.0	0.0	0.0	0.0	231.1	231.1
2−4	0.0	0.0	0.0	0.0	0.0	0.0	231.2	231.2
2−5	−1.4	2.5	−0.7	−0.3	−5.0	−5.0	213.2	208.2
3−4	−4.4	11.8	−3.5	−2.5	−17.4	−15.8	231.1	215.3
3−5	−1.3	0.7	−0.2	0.0	−1.1	−1.9	213.2	211.3
4−5	−0.8	0.5	−0.3	0.0	−1.4	−1.9	213.5	211.3
At *pro-S*	−20.0	50.2	−12.5	−7.2	−49.7	−38.9	837.0	798.1
1−2	−3.7	3.2	−1.3	−0.8	−8.2	−10.8	474.8	463.9
1−3	−6.9	16.0	−3.8	−3.5	−15.1	−13.2	474.7	461.5
1−4	−1.4	0.5	−0.5	0.0	−3.7	−5.1	474.7	469.6
1−5	−2.2	1.0	−0.2	0.0	−0.7	−2.2	456.4	454.2
2−3	0.0	0.0	0.0	0.0	0.2	0.2	230.4	230.6
2−4	0.0	0.0	0.0	0.0	0.0	0.0	230.4	230.4
2−5	0.0	0.0	0.0	0.0	0.1	0.1	212.2	212.3
3−4	−4.7	13.4	−3.7	−2.5	−17.6	−14.9	230.5	215.6
3−5	−0.1	0.0	0.0	0.0	−0.2	−0.3	212.1	211.8
4−5	−1.6	3.1	−0.8	−0.4	−5.1	−4.7	212.1	207.4

[a] E_{Intra} is the sum of the five intramolecular energies or of the sum of those of the two monomers when dealing with dimers. [b] Under a pressure of 15 kbar and for the different possible dimers in the *pro-R* and *pro-S* at forms (see Chart 5 for the molecule numbering).

At a pressure of 15 kbar, the molecular and complexes volumes are calculated to be much smaller than at 1 atm but the variation of the molecular volumes with molecular conformation is not noticeably modified by pressure. On the other hand, our results show clearly that the Tc and Tt conformations with the largest volumes at 1 atm are those which have their energy less modified by pressure. This feature is also found but to a smaller extend in the case of the complexes. This finding is in line with those of Diedrich and Klärner[25] concerning the role of molecular volume and packing coefficients in the effect of pressure on pericyclic reactions. Our results tend to show that a computational method taking into account the compressibility of the system studied through the

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[25] Diedrich, M. K.; Klärner, F.-K. *J. Am. Chem. Soc.* **1998**, *120*, 6212.

volume variation appears to be able to give, at least at the qualitative level, structural modifications due to pressure. Since SIBFA has provided pertinent results for peptides and proteins,[8,26] it should, with the modifications that we have introduced, be able to account for the conformational changes taking place in pressure-denatured proteins.[27]

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(26) (a) Gresh, N.; Roques B.-P. *Biopolymers* **1997**, *41*, 145. (b) Garmer, D. R.; Gresh, N.; Roques, B.-P. *Proteins, Struct., Funct, Genet.* **1998**, *31*, 41.

(27) Hummer, G.; Garde, S.; Garcia, A. E.; Paulaitis, M. E.; Pratt, L. R. *Proc. Natl. Acad. Sci.* **1998**, *95*, 1552.