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CORRELATION OF ENDO/EXO SELECTIVITY IN (4 + 2) CYCLOADDITIONS OF CYCLIC DIENES WITH SOLVENT EFFECTS. A SELF-CONSISTENT REACTION FIELD STUDY.

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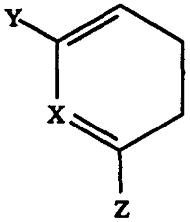
Abstract: MNDO-PM3 calculations on endo and exo transition structures (TS) of cycloadditions of six-membered carbo- and heterocyclic dienes with acrylic acid and acrylamide are reported. The comparison of calculation with experiments which were described for methyl acrylate and (N,N-dimethyl)acrylamide as dienophiles shows that no correlation exists under "gas-phase conditions", but that self-consistent reaction field (SCRF) calculations using benzene or dichloromethane as solvents lead to satisfactory agreement. The polar character of the TS, as expressed by their dipole moments, is responsible for the differing stabilizations of endo and exo TS by the solvent.

The observation of endo/exo selectivities has fascinated organic chemists ever since Alder and Stein formulated the rule of maximum accumulation of double bonds in the endo transition state (Alder's rule).[1] Numerous attempts have been made to find convincing explanations. Among these the concept of secondary orbital overlap in the endo transition structure (TS) has played a major role.[2] When this explanation was unsatisfactory, other influences, e.g., steric effects[3] were made responsible. A change in mechanism may also be involved.[4] The importance of solvent effects was recognized by Berson and led him to develop a solvent polarity scale.[5] More recently, Breslow[6] has noticed a strong increase in endo selectivity in water as solvent. The small $\Delta\Delta G^{\neq}$ values involved in this selectivity problem which should be due to $\Delta\Delta H^{\neq}$ rather than to $\Delta\Delta S^{\neq}$ is the result of cooperativity of several factors.

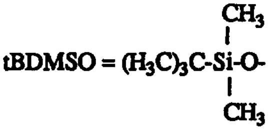
Experimental studies on cycloadditions of six-membered carbo- and heterocyclic dienes **1** to **6** to methyl acrylate and (N,N-dimethyl)acrylamide revealed a picture in which a strong preference for endo addition (**1**) is shifted to an almost exclusive formation of exo adduct (**6**) (see Table 2).[7] These systematic studies lent themselves for a theoretical investigation. Results on one of these cycloadditions have already been reported.[8]

Results

RHF MNDO-PM3 determinations of TS for endo and exo addition were carried out.[9,10] In order to simplify the computational problem we reduced methyl acrylate to acrylic acid (AA) and (N,N-dimethyl)acrylamide to acrylamide (AM). Likewise the substituents at the silyl groups were replaced by hydrogen atoms. The



1 X = CH, Y = Z = H
2 X = CH, Y = Z = OCH_3
3 X = CH, Y = tBDMSO, Z = H
4 X = CH, Y = TMSO, Z = CH_3
5 X = CH, Y = Z = tBDMSO
6 X = N, Y = Z = tBDMSO



$\text{tBDMSO} = (H_3C)_3C\text{-}\underset{CH_3}{\overset{CH_3}{Si}}\text{-}O\text{-}$

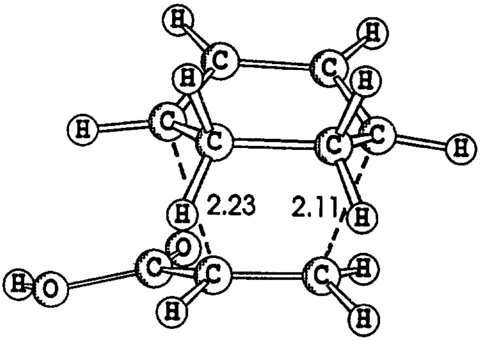
TMSO = $(H_3C)_3Si\text{-}O$

conformation chosen for acrylic acid corresponds to the minimum energy structure[11], that of acrylamide was assumed analogously. All TS are true saddle points as shown by one negative vibrational frequency.

Some representative TS are shown in **7** to **10**. The most symmetrical TS results for 1,3-cyclohexadiene (**7**), the incipient bond lengths being 2.2 Å and 2.1 Å. A silyloxy group at C-2 leads to a slightly less symmetrical TS (2.3 Å and 2.04 Å) which is displayed for acrylamide as dienophile in **8**. Acrylamide leads to results comparable to those obtained for acrylic acid. Two silyloxy groups at C-1 and C-3 produce a TS with separations of 1.8 Å and 3.4 Å, shown in **9** for the endo TS and being very similar for the exo TS. Both lead to intermediates with one bond-length of 1.6 Å and a distance of 3.4 Å for the second incipient bond. The intermediate is energetically 2.53 kcal mol^{-1} (endo addition) and 1.27 kcal mol^{-1} (exo addition) below the energy level of the TS. The structures of the intermediates are otherwise very similar to those of the TS. A related situation (**10**) exists for **6**, the 2-azadiene system. The cycloadditions of **2** to acrylic acid and acrylamide constitute interesting cases. According to the calculation the exo adducts are formed via concerted pathways with separations of the reacting centers of 2.46 and 1.99 Å for AA, respectively 2.39 and 2.02 Å for AM. Endo addition, conversely, is found to take place via two-step processes showing similar asymmetrical bond formation as the cycloadditions of **5** and **6**.

Ring closure of the intermediates required no activation energy within the limits of the gradient norm preset in the program. A similar situation had been encountered earlier for the cycloaddition of methylsulfonyl azide to a ketene aminal.[12] There it was shown that reduction of the gradient norm to < 1 led to a barrier for ring closure of ca. 0.1 kcal mol^{-1}. It is interesting to note that the X-ray structure of the intermediate isolated in the latter case corresponded closely to the calculated structure, thus lending credit to the reliability of the MNDO-PM3 calculation.

Unsymmetrical TS and intermediates are obtained in those cases where a zwitterionic structure is rationalized most easily by chemical intuition. Two silyloxy or alkoxy groups at the end positions of the allylic cation can stabilize a positive charge and the carboxy group a negative charge. One silyloxy group as in **8** is not sufficient to produce a highly unsymmetrical TS. It may be discussed, however, whether the cycloadditions of **5** and **6** should be considered as true two-step processes or whether they might rather be two-stage reactions.[13] The results for **2** where different mechanistic conclusions are reached for exo and endo addition indicate that concerted and two-step process are very close to each other. It is justified to ask



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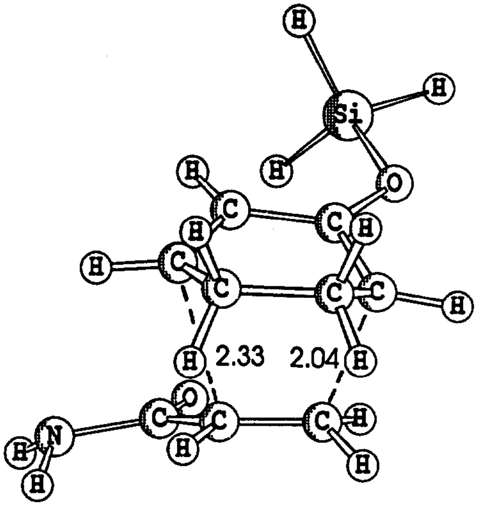

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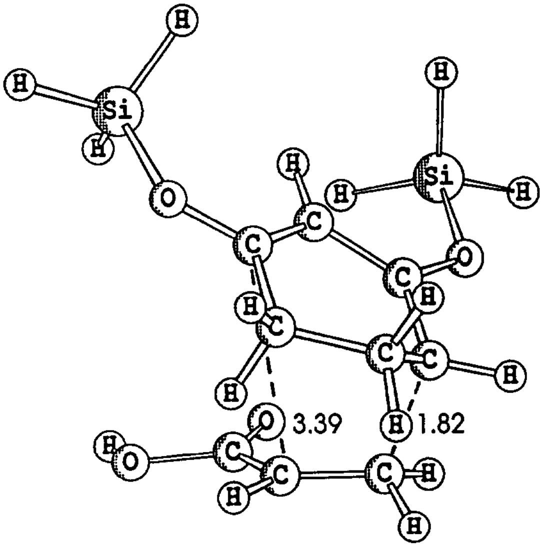

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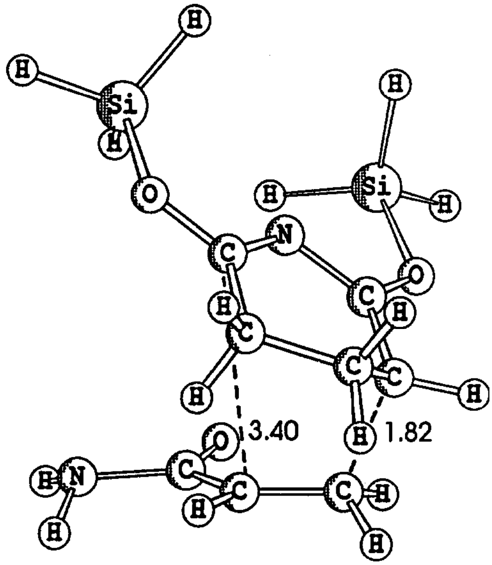

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whether the reliability of MNDO PM3 or generally semiempirical procedures might be overrated at this point? In the delicate balance between a true concerted and a two-step cycloaddition MNDO PM3 seems to have a tendency to favor the nonconcerted pathway. In calculations on cycloadditions of thioformaldehyde to diazomethane it was shown that ab-initio and MNDO PM3 led to opposing results for the formation of one of the regioisomers.[14] On the other hand, in the case of the 1,3-dipolar cycloaddition[12] mentioned above MNDO PM3 confirmed the X-ray structure of the intermediate. In any case, the substitution pattern of dienes **2**, **5**, and **6** will facilitate two-step processes.

Activation energies were determined as differences of the ground-state heats of formation of geometry-optimized reactants and TS. The values (Table 1) seem to be rather high if compared with the conditions under which the experiments were carried out. However, no kinetic data are available. An overestimation of activation energies is observed in other cases including ab-initio calculations.[15] More information, however, can be derived from relative energies. The highest activation energy is found for cyclohexadiene (**1**), the lowest for the bissilyloxy substituted diene **6**. This is in line with expectation, i.e. the more electron-rich the diene, the higher its reactivity in normal Diels-Alder reactions.[16] In those cases where two-step reactions are encountered the activation energies refer to the formation of the intermediate.

Table 1: Activation energies (kcal mol^{-1}) for cycloaddition of **1** - **6** to acrylic acid (AA) and acrylic amide (AM).

compound		1	2	3	4	5	6
AA	endo	34.31	30.81	31.66	30.90	26.60	26.22
	exo	35.00	32.60	32.05	32.46	27.98	26.52
AM	endo	34.60	31.15	32.56	-	27.64	27.35
	exo	35.19	33.12	32.90	-	29.17	27.50

In Table 2 we have collected the heats of formation of TS and intermediates for "gas-phase conditions", in "benzene", and in "dichloromethane". The calculations in "solution" are carried out with the GEOMOS program of Rivail and Rinaldi[17] which is based on the dielectric continuum model for the solvent. This is incorporated in the SCRF formalism.[18] We reoptimized the structures of the intermediates in solution whereas for the TS this could not be done because the program does not offer this possibility. Therefore, a single SCRF calculation in "solution" was performed on the "gas-phase" TS. The comparison of the reoptimized structures for the intermediates in the "gas-phase" and in "solution" tells that the solvent alters the structures only marginally.

The experimental results in benzene show that endo preference decreases for **1** to **3** from 86 to 50%, **4** yields a 50 : 50 mixture, and **5** and **6** give increasing amounts of exo addition (60 - 92%).[7] The calculation under "gas-phase" conditions favors endo addition in all cases, although to variable extent (0.3 - 2.0 kcal mol^{-1}). The calculations, therefore, are at variance with experiment, particularly for **5** and **6**. Not too much weight should be attributed to the numerical results for dienes **3** and **4**. It is daring to assume that quantum-chemical calculations of this type can reproduce reliably selectivities within a range of 50 ± 15 %. The trend analysis is to us the most important indicator.

Table 2: Heats of formation (ΔH_f^0) in kcal mol^{-1} and dipole moments in D (in brackets) of TS and Intermediates in cycloadditions of **1** - **6** to acrylic acid (AA) and acrylamide (AM) and experimental endo : exo ratios.[a]

Trans. struc. (TS) or Interm. (IN)	exp. ratio endo : exo	gasphase conditions		SCRF in C_6H_6		SCRF in CH_2Cl_2	
		endo	exo	endo	exo	endo	exo
1 + AA **TS**	86:14	-20.51 (2.49)	-19.82 (1.86)	-22.72 (2.68)	-21.48 (1.98)	-23.31 (2.81)	-21.86 (2.07)
1 + AM **TS**	74:26	30.68 (3.50)	31.27 (2.89)	28.50 (3.77)	29.53 (3.11)	27.71 (3.95)	28.96 (3.25)
2 + AM **TS**	73:27	-49.32 (4.48)	-47.35 (5.27)	-51.77 (5.02)	-50.35 (5.88)	-52.69 (5.41)	-51.45 (6.25)
2 + AA **TS**	68:32	-100.24 (5.70)	-98.45 (4.46)	-103.27 (6.48)	-101.36 (5.03)	-104.60 (7.03)	-102.25 (5.39)
3 + AA **TS**	65:35	-77.08 (2.50)	-76.69 (3.70)	-78.84 (2.68)	-79.28 (4.20)	-79.26 (2.80)	-79.97 (4.52)
3 + AM **TS**	50:50	-25.60 (2.34)	-25.26 (4.26)	-27.37 (2.48)	-27.84 (4.76)	-27.84 (2.57)	-28.63 (5.05)
4 + AA **TS**	50:50	-87.68 (6.64)	-86.12 (8.47)	-90.50 (7.47)	-90.14 (9.94)	-91.79 (8.04)	-92.18 (10.94)
5 + AA **TS**	40:60	-139.70 (7.56)	-138.32 (9.47)	-142.85 (8.39)	-142.60 (10.78)	-144.31 (8.94)	-144.73 (11.63)
5 + AM **TS**	30:70	-88.07 (6.14)	-86.54 (8.93)	-90.56 (6.78)	-90.28 (10.07)	-91.57 (7.21)	-92.06 10.82)
6 + AM **TS**	15:85	-91.89 (6.22)	-91.74 (8.11)	-94.45 (6.79)	-95.41 (9.17)	-95.47 (7.19)	-97.05 (9.88)
6 +AA **TS**	8:92	-143.61 (7.49)	-143.26 (8.80)	-146.80 (8.25)	-147.46 (10.00)	-148.25 (8.77)	-149.44 (10.81)
2 + AM **IN**	73:27	-50.01 (5.67)	-	-53.04 (6.86)	-	-54.56 (7.75)	-
2 + AA **IN**	68:32	-100.91 (6.93)	-	-104.93 (8.63)	-	-107.73 (10.45)	-
4 + AA **IN**	50:50	-88.09 (8.31)	-86.16 (9.44)	-92.09 (9.76)	-91.26 (11.84)	-94.51 (10.83)	-95.34 (14.39)
5 + AA **IN**	40:60	-142.23 (9.79)	-139.59 (12.58)	-146.86 (11.07)	-147.11 (15.31)	-149.53 (11.86)	-153.67 (18.72)
5 + AM **IN**	30:70	-90.39 (8.46)	-87.59 (11.86)	-94.04 (9.61)	-94.01 (14.37)	-95.95 (10.24)	-98.24 (16.02)
6 + AM **IN**	15:85	-94.63 (8.71)	-93.42 (10.90)	-98.41 (9.63)	-99.34 (12.84)	-100.30 (10.16)	-102.82 (14.05)
6 + AA **IN**	8:92	-146.07 (10.22)	-144.69 (12.21)	-151.26 (11.45)	-152.75 (14.68)	-154.24 (12.25)	-157.69 (16.02)

[a] calculations refer to **1** - **6** with hydrogen at O and Si, to acrylic acid and to acrylamide

The results of the calculation in "solution" are intriguing. The TS and the intermediates are stabilized in both solvents, more in dichloromethane (ϵ = 8.9) than in benzene (ϵ = 2.27). The solvent of greater dielectric constant has the greater effect. Of the two competing TS for endo and exo addition that one is stabilized more which has the higher dipole moment (given in table 2 in brackets). If the endo TS has the higher dipole moment the preference for endo addition is augmented, if the exo TS has the higher dipole moment then the endo preferenece, found in the "gas-phase" calculation, is diminished or reversed to exo addition. The results in benzene as solvent are in agreement with the experimental observations for dienes **1**, **2**, **5**, and **6**. Dienes **3** and **4** are border-line cases and should, therefore, be discussed only qualitatively, also in view of the approximations inherent in the dielectric continuum model. The solvent has a decisive influence on the selectivity.

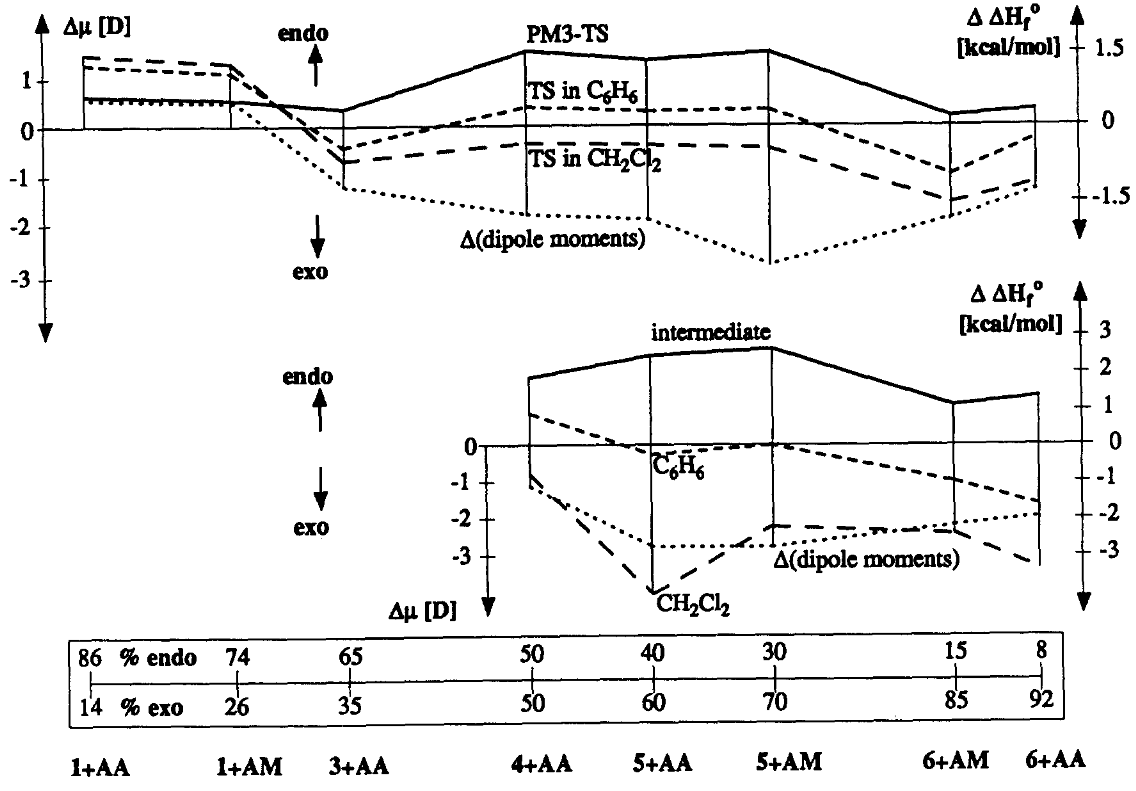
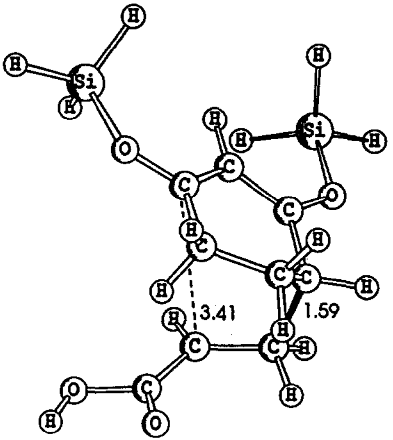


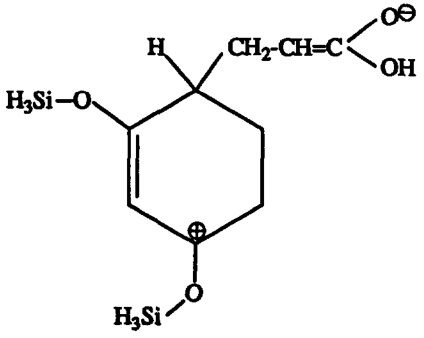
Fig. 1: $\Delta H^o_{f(endo)} - \Delta H^o_{f(exo)}$ ($\Delta\Delta H^o_f$) (right scale) in kcal mol^{-1} and $\mu_{endo} - \mu_{exo}$ (D) (left scale) for endo and exo TS and intermediates.

For a selection of dienes and dienophiles the results for "gas-phase", "benzene", and "dichloromethane" are compared with the dipole moments in fig. 1. The difference $\Delta\Delta H^o_f = \Delta H^o_{f(endo)} - \Delta H^o_{f(exo)}$ is plotted against the ratio endo : exo for the cycloadditions of dienes **1** to **6** to methyl acrylate and/or (N,N-dimethyl)acrylamide. The upper graph describes the difference in activation energies, the lower one the difference in stability of the intermediates for those cases where the calculations had indicated a two step cycloaddition. Where intermediates are suggested by the calculation the difference in activation energy refers to formation of the intermediate . The figure displays also the difference of the dipole moment ($\Delta\mu$ =

μ_{endo} - μ_{exo}). The solvent favors, both for the TS and the intermediates, the structure which exhibits the higher dipole moment. Due to the geometrical similarities in the dienes this series seems to be particularly suited to single out solvent effects while leaving other contributions to the selectivity constant. It should not be concluded that other effects are negligible for the problem of endo/exo selectivity. However, the results suggest that selectivities obtained even in solvents of low polarity cannot be compared directly with calculations which simulate "gas-phase" conditions.



11a



11b

One of the examples where the calculation led to an intermediate will be described in more detail (exo intermediate for **5** + acrylic acid). The structure of this species (**11a**) is such that in terms of valence bond theory a zwitterion can be written (**11b**). Two silyloxy groups stabilize a positive charge in the former diene subunit and the carboxy group a negative charge. The polar character of **11a** is underscored by the high dipole moment 12.6 D. It is expected that any solvent, even of low dielectric constant, will stabilize the intermediate. As the dipole moment decreases on the way from the intermediate to the product (μ = 3.46) it can be assumed that ring closure will be subject to a solvent induced barrier. In the "gas phase" no detectable barrier for ring closure was found within the given gradient norm. We determined the reaction coordinate for cyclization of **11a** in the "gas-phase" by systematically decreasing the distance of the bond forming atoms and reoptimising all other geometrical variables at each point. Then, this reaction coordinate was calculated by putting the "gas-phase" structures in "dichloromethane" as solvent. In fig. 2 the reaction coordinates in "dichloromethane" and under "gas-phase" conditions are plotted. The TS is lowered in energy in the dielectric continuum by 6.4 kcal mol^{-1}, the intermediate is stabilized by the solvent by 10.4 kcal mol^{-1}. If the geometry of the intermediate is recalculated in "dichloromethane" an additional stabilization of 3.7 kcal mol^{-1} is found. As anticipated, a barrier to ring closure is obtained when considering the solvent. Its magnitude of 1.8 kcal mol^{-1} is small. However, it is the observation of the barrier which is of interest. The dielectric continuum model of solvation is rather crude and one should not overestimate the numerical accuracy of the calculation. Qualitatively, however, the model behaves as expected. Reactants and product being less polar than the intermediate display smaller stabilization by the solvent.

The results are an indication that more attention should be paid to solvent effects when comparing quantum chemical calculations with experiments obtained in solution.

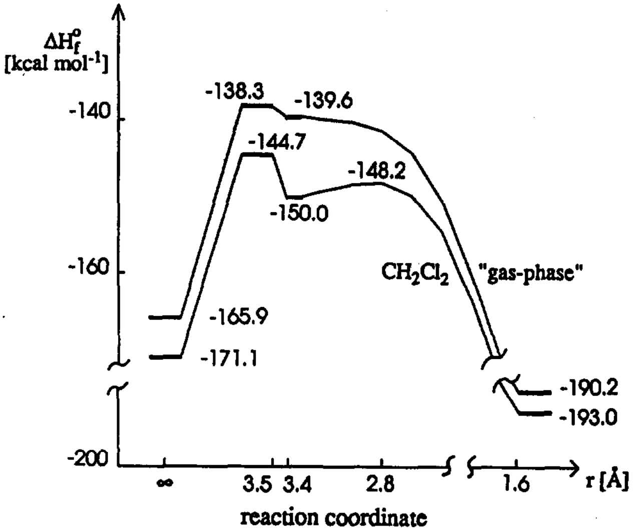


Fig. 2: Reaction coordinate for ring closure of intermediate **11a** under "gas-phase conditions" and in dichloromethane (kcal mol^{-1}).

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