Transannular Interactions in Difunctional Medium Rings – Modelling Bimolecular Reactions

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1 Introduction

A bimolecular reaction is conveniently characterized by an energy diagram which summarizes mechanistic, structural, and energetic aspects (Figure 1). While educts (starting materials) and products as stable compounds can be analysed precisely, it is difficult to obtain information on the transition state and all other points.

Alicyclic molecules of medium ring size (8—12 membered rings) are puckered, and in some conformations certain ring atoms may be quite close to each other. This may cause transannular interactions and reactions of functional groups.[1] In such compounds it is possible to study the properties of these functional groups and their mutual interactions at distances close to those found in the transition state of the analogous bimolecular reaction (Figure 2).

Since in a chemical reaction bonds are broken and new bonds are formed (*i.e.* structural changes occur which imply electronic changes), the electronic interactions of the reactants are of major interest. The importance and the capacity of MO methods and the use of orbital interactions and correlation diagrams in analysing and describing reactions does not need to be emphasized.[2–4] Information on the orbital energies associated with the interaction of molecules at different distances and orientations – from their mutual polarization to repulsion or bonding – is necessary to understand a chemical reaction. Ultraviolet photoelectron (PE) spectroscopy provides a direct means of obtaining the energies of valence orbitals involved in reactions and orbital interactions can thus be determined experimentally.[5] This method is generally used in combination with the results of MO calculations. From perturbation theory, the interaction of two orbitals ϕ_i and ϕ_j can be expressed as the element $H_{ij} = \int \phi_i^* H' \phi_j d\tau$ of the Hamiltonian. The energies of the perturbed orbitals are $\epsilon_i = \epsilon_{i0} + |H'_{ij}|/(\epsilon_{i0} - \epsilon_{j0})$ and $\epsilon_j = \epsilon_{j0} + |H'_{ij}|/(\epsilon_{i0} - \epsilon_{j0})$ where ϵ_{i0} and ϵ_{j0} are the energies of the unperturbed orbitals. By direct through-space interaction, the perturbation energy is dependent on their overlap, *i.e.* on their relative orientation.

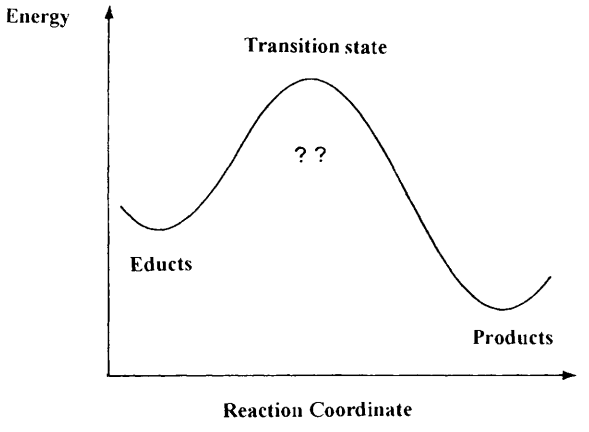

Figure 1 Two-dimensional energy diagram for a bimolecular reaction.

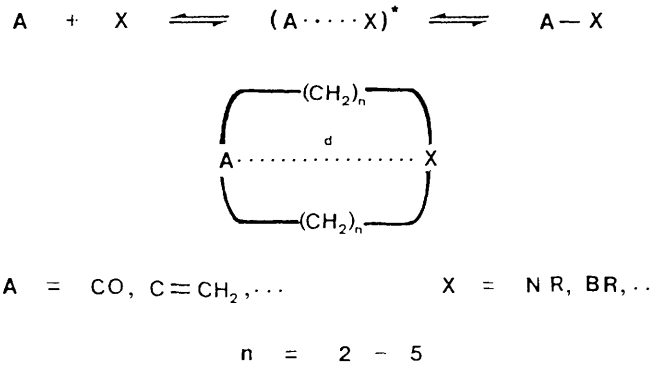

Figure 2 A bimolecular reaction and an analogous transannular interaction.

2 Methods

Details of reaction mechanisms – including the transition state – can be studied by quantum mechanical methods.[2,3] However, experimental information is also desirable. In recent years detailed investigations have been carried out on the electronic structures and bonding properties of molecular complexes in the vapour phase by employing UV PE spectroscopy.[6] Strong complexes can be directly studied by this method. In the case of weak interactions, such as in hydrogen bonded dimers or van der Waals complexes, molecular beams are used to produce sufficiently high concentrations of the species in the spectrometer. This technique might be used to investigate a reacting system on the product side of the transition state. Only very few systems with direct relevance for organic reactions have, however, been studied until now.

Transannular interactions have been discovered in alkaloids and were investigated by chemical, spectroscopic (IR, UV, ORD) and other physical methods by Leonard and co-workers[7] in the 1950's. The well known structure correlation method of Bürgi and Dunitz[8] is also based on non-bonded interactions but

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considers mainly the geometrical effects NMR spectroscopy (mainly ^{13}C) has also been used to study such interactions [9]

We have investigated several difunctional cyclic and bicyclic compounds in which the functional groups occupy opposite ring positions but because of the puckering of the ring may have a rather short transannular distance To determine the mutual interactions of the functional groups we need trios of compounds the difunctional and two monofunctional ones in which the functional groups have the same 'environment' as in the difunctional molecules, *i e* three compounds with the same ring size Interactions can be measured by any method If a given property found for the difunctional compound is the same as in the corresponding monofunctional compounds, there is no interaction Deviations from additivity indicate interaction In analysing such interactions, the indirect *through-bond* interactions have to be differentiated from the direct *through-space* interactions, only the latter are relevant for analogies to bimolecular systems

We have studied transannular electronic interactions by photoelectron spectroscopy (PES) and quantum chemical calculations The main purpose of this investigation was to find suitable compounds which might serve as models for analogous bimolecular systems These compounds should have transannular distances between the functional groups which are shorter than the van der Waals distance and which enable direct contact by orbital overlap On the other hand, the functional groups should be constitutionally well separated in order to limit their mutual inductive and through-bond interactions This implies that the structural and conformational properties of the molecules should be known Of course, rigid conformations which are well separated by high energy barriers would be most adequate for this purpose

In addition, other spectroscopic methods were used (mainly NMR) For conformational analysis, molecular mechanics investigations were also performed

3 Results

3.1 Nucleophilic Addition

3 1 1 Aminoketones

Nucleophilic addition to carbonyl compounds is one of the most important reactions in organic chemistry and biochemistry and has been studied in many examples by experimental and theoretical methods [2 3 8] The analysis of the stereochemistry of this reaction was of fundamental consequence in other important fields of organic chemistry, *e g* Baldwin's rules for ring closure[10] and asymmetric induction [2 11] The nucleophilic approach trajectory may be described in terms of the attack angle α between the developing C–Nu bond and the C=O bond A simple model based upon the analysis of the first-order interactions between the HOMO of the nucleophile and the MOs of the substrate has been proposed for qualitatively predicting the trajectory [12] Crystal structures of molecules containing amino and carbonyl groups in close proximity suggested that α is close to the tetrahedral angle (109 5°) [8] Since the reaction imples a $sp^2 \rightarrow sp^3$ transformation of the carbonyl carbon atom, the carbonyl compound becomes pyramidal and a correlation of the partial pyramidalization, measured by the distance of the C atom from the plane defined by its three bonded neighbours, and the incipient bond distance d was found [8] Similarly, there is a correlation between d and the length of the CO bond which increases as d decreases since the double bond is converted into a single bond Accordingly, an approximately linear correlation between carbonyl absorption frequency and d has been found and transannular nitrogen–carbonyl interactions have been studied systematically and extensively in medium ring compounds mainly by IR spectroscopy [7]

The addition of a neutral nucleophile to a carbonyl compound in the gas-phase is endothermic because the zwitterionic adduct is not stabilized by solvation as in a polar solvent, or by protonation as in acidic solution [13] A simple example of such a reaction which can be used as a model in our study is the addition of trimethylamine to acetone

$$Me_2C{=}O + NMe_3 \rightarrow Me_3N^+{-}CMe_2{-}O$$

The electronic implications of this reaction are shown in Figure 3 At all distances two n orbitals are the two highest occupied MOs (HOMO and NHOMO) of the system However, in the bonded complex there are two orthogonal n(O) orbitals on the sp^3 hybridized O atom, while in the isolated molecules there is an n(N) and an n(O) orbital of different symmetry The two π MOs (π and π^*) of the C=O group correlate with a σ and a σ^* orbital of the new C–N bond That π(C=O) does not correlate with an n(O) orbital and n(N) does not correlate with σ(C–N) is the reult of an 'avoided crossing' since all these orbitals have the same symmetry (C_s) in the supermolecule Already at approach distances d of around 500 pm distinct energy changes occur in these orbitals For the PE spectroscopic investigation it is important to note that in the interesting range of d (below the van der Waals distance of *ca* 300 pm) there is a crossing of the two highest occupied MOs which might result in difficulties in the identification of the corresponding IP values and their assignments The ionizations of electrons from the π(C=O) are expected at energies above 12 eV in the spectra In this region as well strong and broad σ ionizations are found which prevent proper assignments, so that this orbital cannot be used for our purposes From Figure 3 it is already obvious that the n(O) ionization might provide the best quantitative evidence for the interaction of the two molecules or functional groups since it shows a homogenous energy variation as a function of d which can be described by an exponential function, or at large d values approximately by a linear function

The intramolecular interaction (homoconjugation) in aminoketones has been interpreted as transannular amide resonance

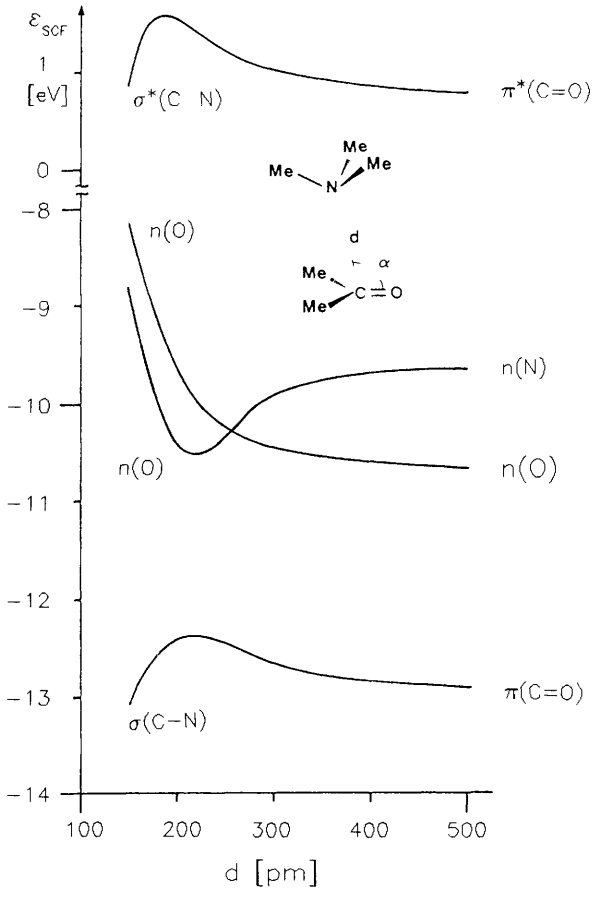


Figure 3 Course of orbital energies for the nucleophilic addition of trimethylamine to acetone

(Leonard,[7] in 1956) which leads to the atypical chemical and physical properties of these compounds Many medium ring aminoketones including several alkaloids have been studied in order to analyse transannular interactions [7 8] However, not all these compounds can be used for gas-phase spectroscopic investigations The PE spectra of some alkaloids like methadone[14 15] and cryptopine[15] have been measured, but the spectra are far too complex for a detailed analysis

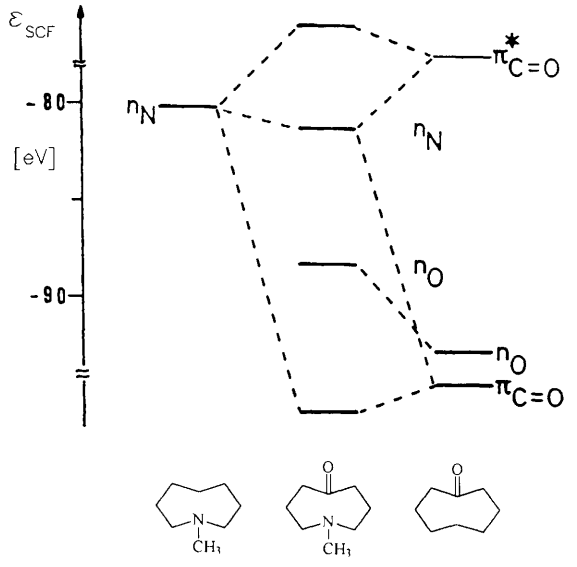


Figure 4 Orbital correlation diagram for a cyclic aminoketone

In Figure 4 an orbital correlation diagram is depicted for a cyclic aminoketone This figure confirms that the orbital n(O) is well suited to monitor the transannular interaction of the two functional groups, although it is orthogonal to both the n(N) and the π(CO) orbital In Figure 5, as an example, the low energy region of the PE spectra of 1-methyloctahydroazocin-5-one (2),

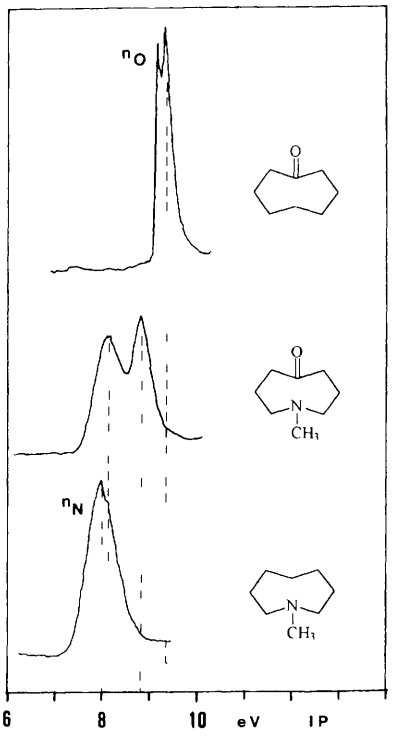
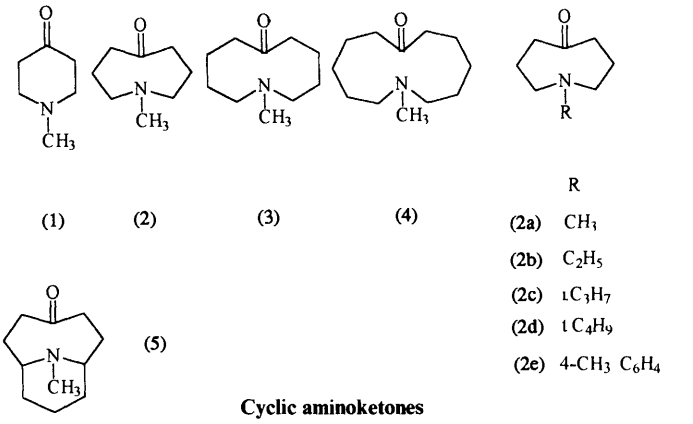


Figure 5 PE spectra of cyclooctanone, 1-methylhexahydroazocin-5-one (2) and 1-methyloctahydroazocine

cyclooctanone, and 1-methyloctahydroazecin is depicted It is evident that the n(N) and n(O) ionizations of the difunctional compound are shifted – as expected – to a different extent relative to their positions in the monofunctional molecules While n(N) is slightly stabilized, n(O) is destabilized to a larger extent According to first-order perturbation theory (*vide supra*) the n(N) orbital should also be destabilized, and by the same amount as π(CO) would be stabilized The different behaviour of the n(N) orbital can be ascribed to its simultaneous interaction with π^* (CO)



Cyclic aminoketones

Figure 6 summarizes the PES results for the investigated compounds The corresponding NMR results are shown in Figure 7 In the series of cyclic aminoketones (1)—(4) the PE spectroscopic investigation indicates that the eight-membered ring system (2) has the largest transannular interaction [16] For the ten-membered ring system (3) a significantly lower value was found, and for the twelve-membered analogue (4) no sizeable transannular interaction was observed These findings are consistent with certain conformations known for the respective ring system [17] The prevailing conformation of saturated eight-membered rings is the boat–chair (BC) form *X*-Ray analyses of the *N*-t-butyl and the *N*-*p*-tolyl derivatives (2d)[18] and (2e)[19] revealed the ring to possess this conformation with transannular N—CO distances *d* of 270 and 276 pm, respectively According to molecular mechanics calculations[20] the analogous ten- and twelve-membered ring compounds (3) and (4) prefer a boat–chair–boat (BCB) or [2323] and a [3333] conformation with *d* values of about 330 and 460 pm, respectively For (3) also, a crown-like TCCC form might be possible Stereoplots of some of these conformers are shown in Figure 8

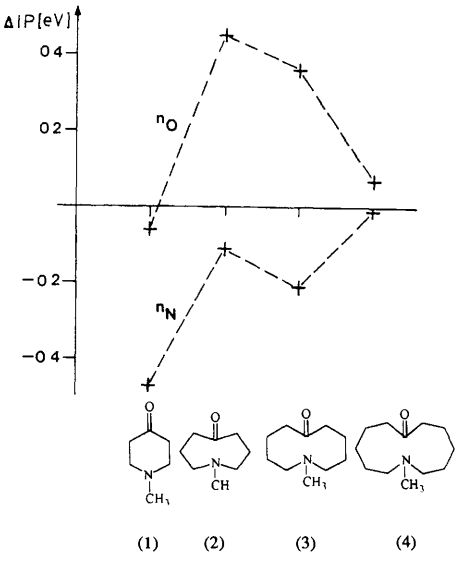


Figure 6 ΔIP values of aminoketones (1)—(4)

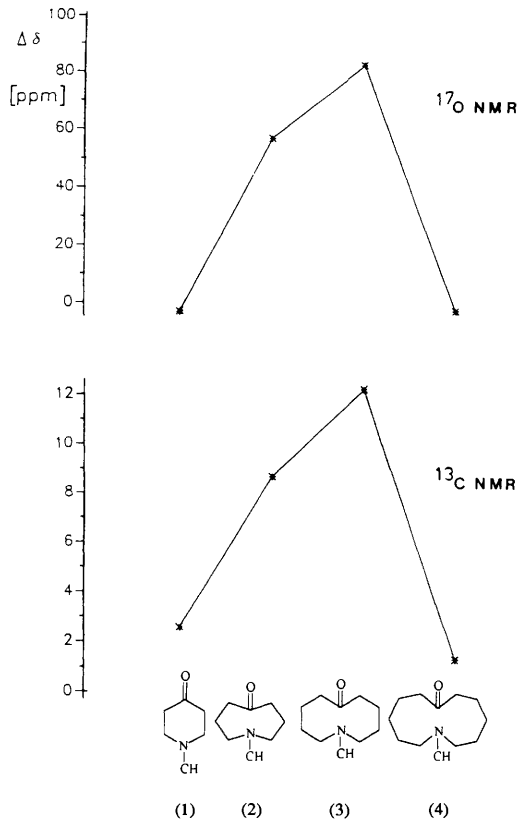


Figure 7 $\Delta\delta$ values of aminoketones (1)—(4)

^{13}C and ^{17}ONMR spectroscopic studies on the same cyclic aminoketones confirmed the PES and other earlier findings that there is essentially no interaction in the twelve-membered ring but considerable interaction in the eight- and the ten-membered systems [21] However, the relative size of interaction for the eight- and the ten-membered rings was found to differ According to the change of the chemical shifts relative to the corresponding cyclic ketones ($\Delta\delta$), the maximum value of transannular interaction is found in the larger ring compound (3) These differences may be explained, at least in part, by phase effects, *viz* solvation may alter the conformation in such a way that d is increased Infrared data indicate a large (*ca* 50 pm) change in the N—CO distance in 11-methyl-11-azabicyclo[5,3,1]undecane-4-one (5) when the solvent is shifted from chloroform to cyclohexane Also at variance are the findings of PE and NMR spectroscopy for the effect of substituent size in 1-alkyl-hexahydro-azocin-5-ones (2a)—(2d) [18] While the $\Delta IP(n_O)$ values are essentially independent on the alkyl substituent, the $\Delta\delta$-^{13}C-values decrease with increasing substituent size Most likely, these findings also are caused by solvation effects In addition, one has to consider that the chemical shift of a nucleus is a rather complex parameter which is not only dependent on ground-state properties of the molecule It might well be possible, therefore, that transannular interaction has different (quantitative) effects on $\Delta\delta$-^{13}C, $\Delta\delta$-^{17}O, and $\Delta IP(n_O)$ of the carbonyl group in a cyclic aminoketone

In summary, it can be stated that PES is an excellent method for studying transannular interaction in aminoketones and that the electronic changes of the carbonyl oxygen atom as a function of the distance between the functional groups can be quantitatively determined In Figure 9 the MNDO results for the bimolecular system acetone/trimethylamine and the PE spectroscopic results for cyclic aminoketones are compared It is obvious that the results obtained for the difunctional compounds can indeed be used as a model for the bimolecular reaction At distances $d > 250$ pm, the variation of $\Delta IP(n_O)$ as a function of d still can be well described by a linear function as expected from Figure 3

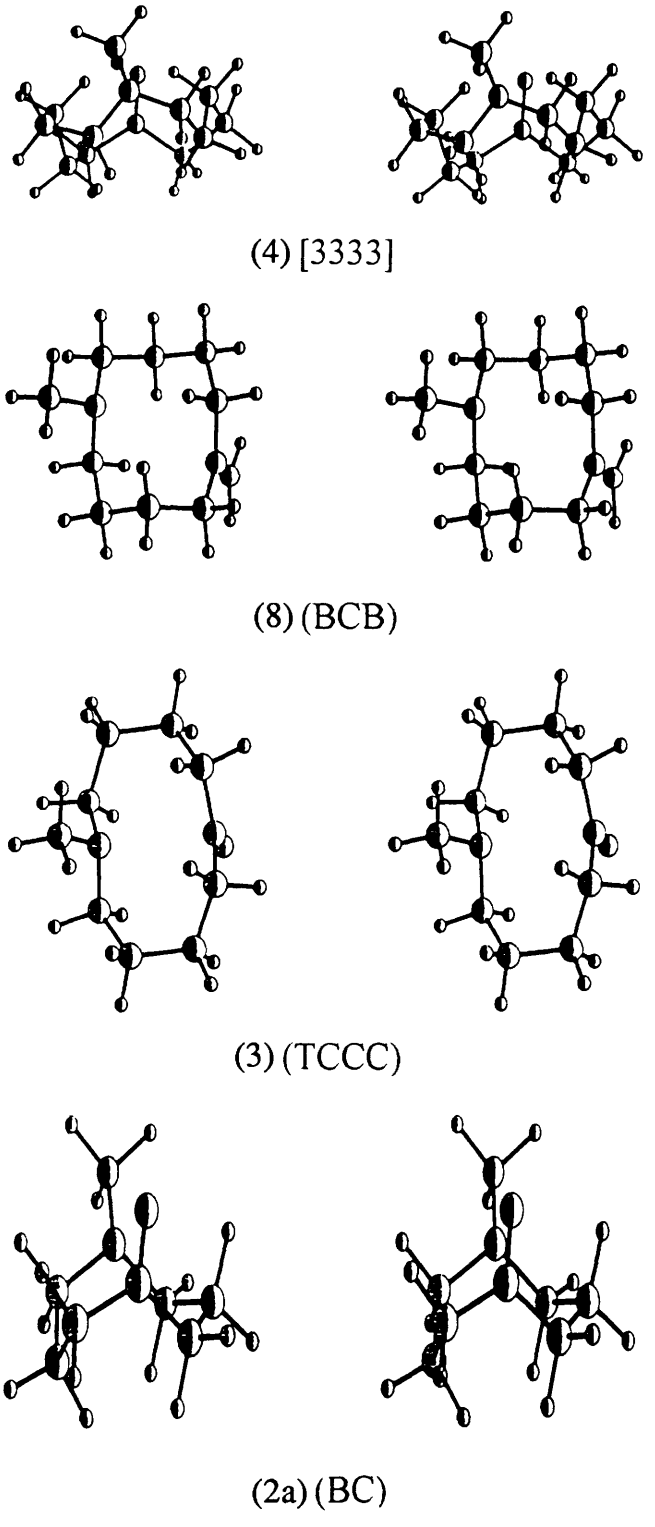


Figure 8 Stereoplots of some difunctional medium ring compounds

3 1 2 Aminoalkenes

The stereochemistry of the addition of nucleophiles to alkenes is of practical importance for asymmetric syntheses Theoretical studies revealed approach angles of *ca* 120° This may easily be rationalized in terms of simple orbital interaction arguments The preferred trajectory of the entering nucleophile will be that which maximizes the overlap between the centres involved in bond formation while keeping the overlap involving the other end of the double bond to a minimum

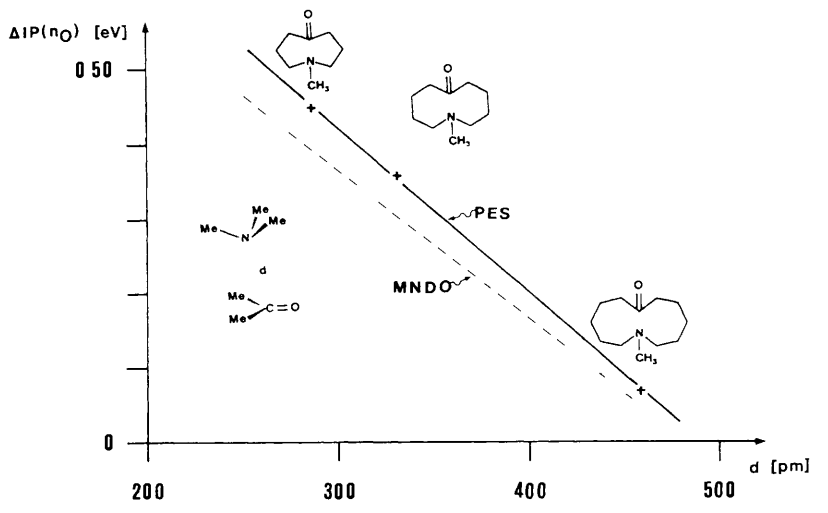


Figure 9 ΔIP (n_O) values calculated for the nucleophilic addition of trimethylamine to acetone and observed for cyclic aminoketones

We have studied the relevant MOs for the model system isobutene/trimethylamine with the MNDO method

$$Me_2C{=}CH_2 + NMe_3 \rightarrow Me_3N^+{-}CMe_2{-}CH_2^-$$

The results are depicted in Figure 10 The amine lone-pair is converted into the N–C σ bond during the addition reaction while the C=C π bond becomes the lone-pair centred on the methylene group of the former alkene However, owing to the 'avoided crossing' of orbitals of the same symmetry, the n(N) orbital of the free amine is correlated with the n(C) orbital of the addition complex and the π(C=C) MO is correlated with the σ(CN) orbital The same holds for the antibonding orbitals (LUMO of the system) π^* (C=C) and σ^* (CN) The approach angle α has a value of 104° For the PE spectroscopic investigation it is important that at a N–C distance d of about 300 pm (*i e* near the van der Waals distance) already a substantial destabilization of the HOMO and a sizeable stabilization of the NHOMO can be noticed A transannular reaction of this type has indeed been studied in a tetrahydroazecin derivative [22]

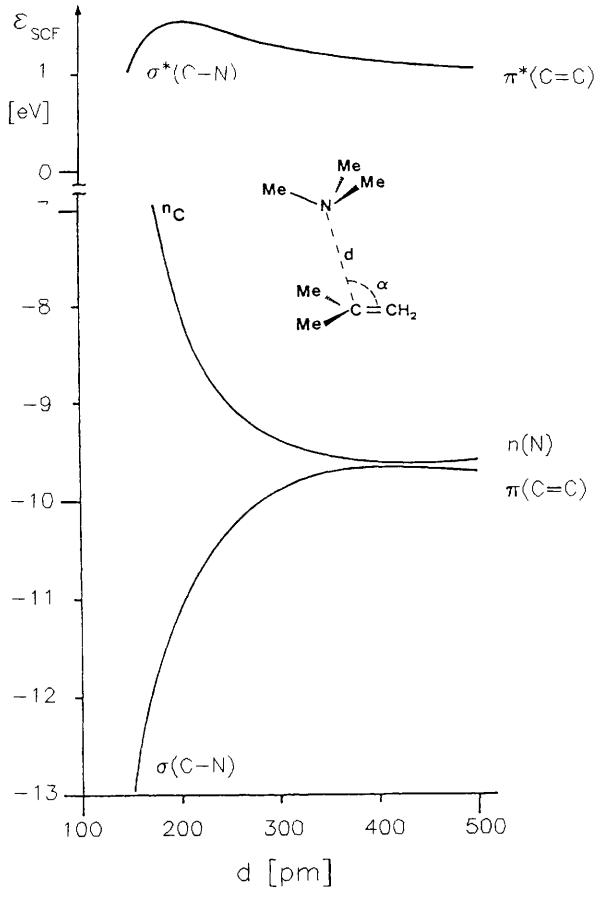


Figure 10 Course of orbital energies for the nucleophilic addition of trimethylamine to isobutene

An orbital correlation diagram for aminoalkenes is shown in Figure 11 We have investigated several methyleneazacycloalkanes (6)—(9) The results of PE and NMR spectroscopy are shown in Figures 12 and 13, respectively By PE spectroscopy a transannular interaction energy of *ca* 0 2 eV between the two functional groups in the eight-membered ring compound 1-methyl-5-methyleneoctahydroazocine (7) has been found, while for the corresponding compound with a ten-membered ring (8) there is essentially no such interaction because of an unfavourable conformation [16] In the homologue with a twelve-membered ring (9), both the π(C–C) and the n(N) orbital are slightly destabilized which is evidence against their direct interaction

Compound (7) most likely has a similar conformation to the aminoketone of the same ring-size (2) The same probably holds for the compounds with a twelve-membered ring [(4) and (9)] However, in the case of the ten-membered ring compounds (3) and (8) there must be different conformations (see Figure 8) – either the ring has changed its conformation with the replacement of the O atom by a CH_2 group or the functional groups are at different positions in the ring For (9), according to force field calculations,[20] a BCB or [2323] form seems to be most probable

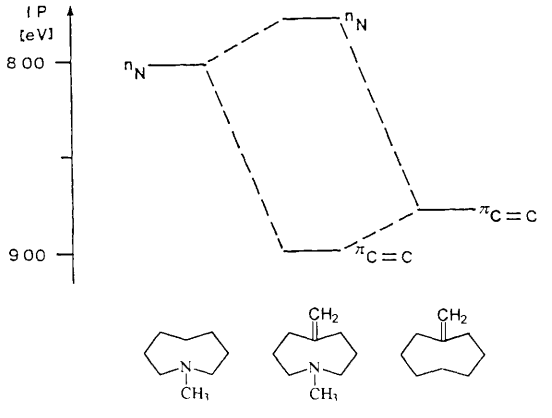


Figure 11 Orbital correlation diagram for a cyclic aminoalkene

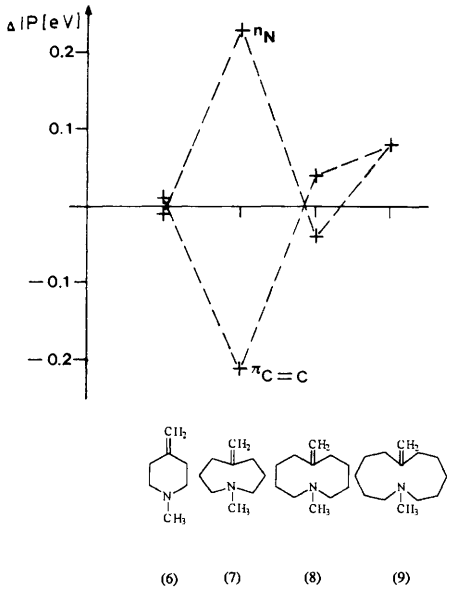


Figure 12 ΔIP values of aminoalkenes (6)—(9).

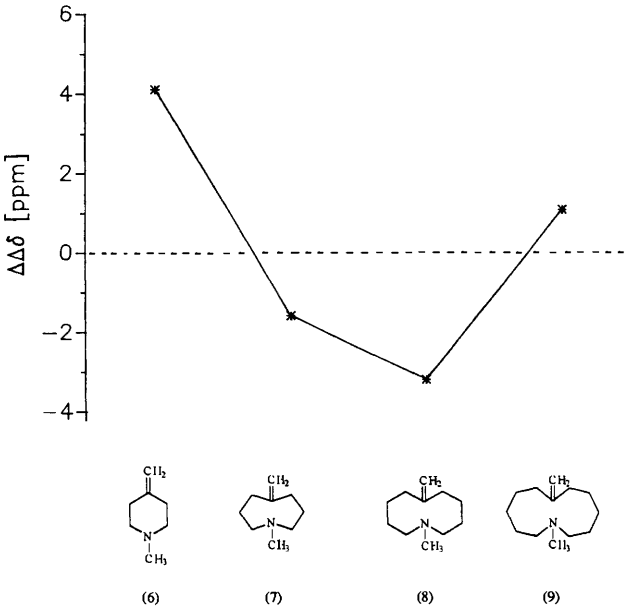
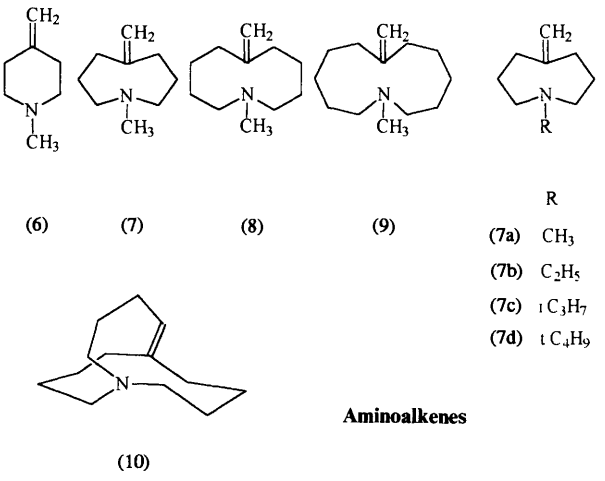


Figure 13 $\Delta\delta$ values of aminoalkenes (6)—(9).

From ^{13}CNMR spectroscopy (Figure 13), for compounds (7) and (8) an increased polarity of the C=C bond, as measured by the difference of the chemical shifts $\Delta\delta$ of the two carbon atoms of the CC double bond relative to the corresponding methylenecycloalkane, is found compared to the corresponding methylenecycloalkanes; the effect for the ten-membered ring compound is even larger than that for the eight-membered analogue.[20] As in the case of the aminoketones, this result differs from the findings by PE spectrosopy and the same arguments are offered for explanation: since the interaction of the functional groups is accompanied by substantial polarization, solvation will be of considerable importance and therefore the NMR results (solution) may well be different from the PE results (gas phase). Again these findings should caution against too simple an explanation of experimental data.

In compound (7) the distance d between the functional groups is about 285 pm.[20] An even shorter distance $d \approx 273$ pm has been found in 1-azabicyclo[4.4.4]tetradec-5-ene and the through-space interaction amounts to 0.64 eV.[23] For compound (8) a value of 335 pm is estimated by MM2 calculations for d.[20]



Combining these data, functions for the variation of n(N) and π(C=C) with d, as shown in Figure 14, can be constructed. Obviously the interaction of these orbitals increases exponentially as their distance decreases.

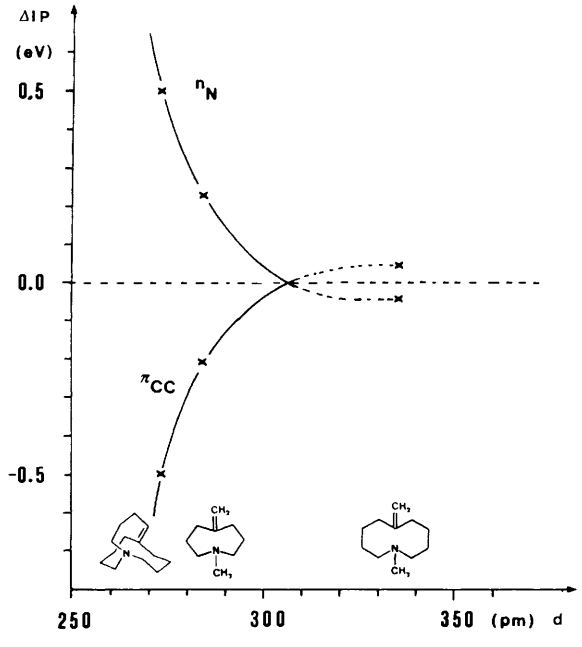
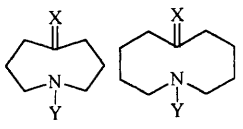


Figure 14 ΔIP values for aminoalkenes with differing transannular distances.

In summary, it can be stated that PE spectroscopy is an excellent method for studying transannular interactions in aminoalkenes and that the results can be used to model the bimolecular nucleophilic addition of an amine to an alkene.

3.1.2 Other Systems

In addition, we have studied several other disubstituted eight- and ten-membered medium ring compounds like (11) and (12) by the same techniques. However, in most cases transannular interactions are difficult to investigate because of transannular cyclization or hydrogen bonding. The situation is also complicated by the rather complex electronic structure of the compounds which cause PE spectra with superposition of several ionization bands, and this may prevent correct determination of IP values and assignments. In the same way, orbital interactions may become too difficult for a straightforward analysis.



(11) (12)

X = O NH $NNMe_2$ NOH NOMe

Y = OH OMe NH_2 NHMe NMe_2

Difunctional eight- and ten-membered ring compounds

3.2 Electrophilic Addition

This type of reaction has been studied on two examples addition of a borane to an alkene and addition of a borane to an amine The corresponding electronic interactions were determined on medium ring boraalkenes and aminoboranes

3 2 1 Boraalkenes

Houk *et al* [24] have investigated the hydroboration reaction by *ab initio* calculations and have also calculated the corresponding transition structures Egger and Keese[25] used the MNDO method to study the regio and the stereochemistry of this reaction All borane additions to an alkene occur with approach angles centring around 75° As a model reaction we have studied the interaction of trimethylborane and isobutene with the MNDO method

$$Me_2C{=}CH_2 + BMe_3 \rightarrow Me_2C^+{-}CH_2{-}[BMe_3]^-$$

The approach angle, $\alpha = B{-}C^2{-}C^1$, for this system was found to be *ca* 81° As is to be seen in Figure 15, interaction of the two molecules begins at B–C distances d smaller than *ca* 500 pm, significant changes in orbital energies (> 0 1 eV) are taking place at $d < 300$ pm The largest variation suffers the LUMO which is lowered by *ca* 1 4 eV from the isolated molecules to the bonded complex and changes from $2p_z$(B) to $2p_z$(C) Of greater relevance for the spectroscopic investigation (*vide infra*) is the course of the

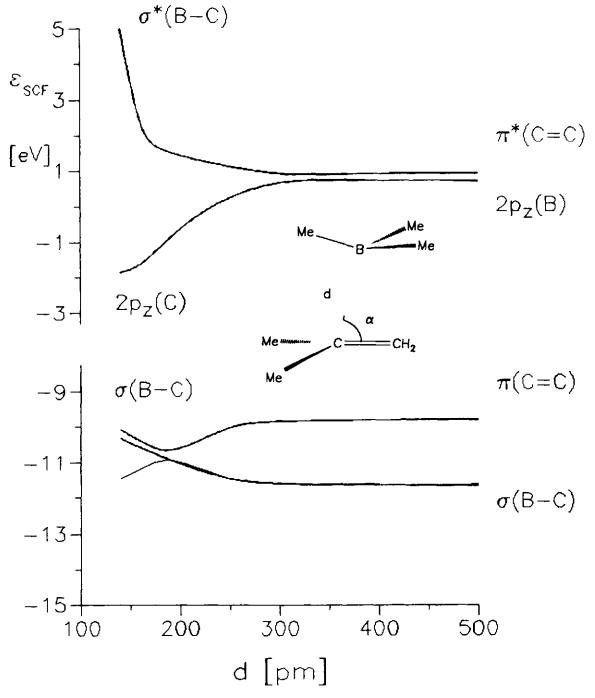
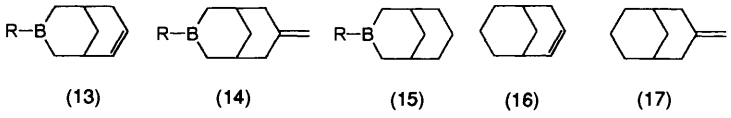


Figure 15 Course of orbital energies for the electrophilic addition of trimethylborane to isobutene

HOMO Here the π(C=C) MO is transformed to a σ(B–C) orbital which is accompanied by a stabilization of *ca* 0 8 eV passing through a minimum around the standard B–C bond length

We have studied transannular interactions in the 3-borabicyclo[3 3 1]nonene and nonane derivatives (13) and (14) with an endo or exocyclic CC double bond, respectively [26] The corresponding monofunctional reference compounds are bicyclo-[3 3 1]non-2-ene (16), 3-methylenebicyclo[3 3 1]nonane (17), and the 3-borabicyclo[3 3 1]nonanes (15) The compounds were investigated by PE, ^{13}C and ^{11}BNMR spectroscopy In addition, molecular mechanics and semi-empirical quantum chemical calculations have been performed Although the transannular distances in both groups of compounds vary little ($d \approx 300$ pm), the difunctional compounds with an exocyclic double bond (14) show distinct transannular interactions, the compounds with an endocyclic double bond (14) show distinct transannular interactions, whereas in the compounds with an endocyclic double bond (13) such effects are virtually absent Equivalent to a significant stabilization of the HOMO already at this distance an increase of 0 2—0 4 eV of the first IP of (14) relative to (15) is observed These results are substantiated by ^{11}B and ^{13}CNMR data of the difunctional compounds indicating an increase of the δ-^{11}B value and of the polarity of the C=C bond as a result of their interaction



(13) (14) (15) (16) (17)

R CH_3 C_2H_5 iC_3H_7 tC_4H_9 OCH_3

(13–15) a b c d e

Boraalkenes

3 2 2 Aminoboranes

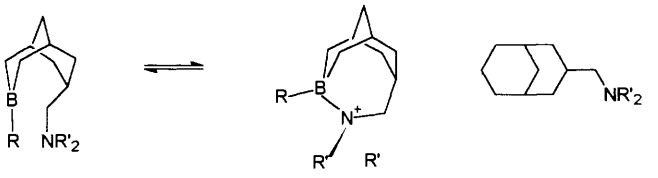
The direct interaction of a nucleophilic and an electrophilic reagent might be studied using the borane/amine system PE spectra of strong complexes like NH_3-BH_3 [27], pyridine boranes,[28] and BF_3-amine systems[29] have been measured We have studied the complex formation using the model reaction

$$Me_3N + BMe_3 \rightarrow [Me_3N]^+{-}[BMe_3]^-$$

In this reaction the nitrogen lone-pair is converted into the N–B σ bond However, in the complex a σ(BC) orbital is the HOMO which correlates with the n(N) of the amine in the separated molecules Calculations by the AM1 method indicate that the HOMO of the system is stabilized by *ca* 1 0 eV [30] and this should be reflected in the PE spectra of suitable compounds In addition, ^{15}N and ^{11}BNMR spectroscopy might be used for experimental studies

The intramolecular interaction of the donor–acceptor pair borane–amine has been investigated for the *endo*-7-(dialkylaminomethyl)-3-borabicyclo[3 3 1]nonane derivatives (18a–c,e) and (19a,e) The monofunctional reference compounds are the bicyclic boranes (22) and the *endo*-3-(dialkylaminomethyl)-bicyclo[3 3 1]nonanes (23) and (22) In particular, the intramolecular complex formation of the corresponding 2-azonia-1-boratricyclo[4 3 1 $1^{4\ 8}$]undecanes (20) and (21) has been studied in the gas phase by UVPE spectroscopy and in solution by ^{11}BNMR spectroscopy [31] The absence of an n_N ionization band in the PE spectra of the aminoboraalkanes (18a–c) leaves no doubt that in the gas phase the tricyclic adducts (20a–c) are formed The presence of this band in the spectra of (18e), (19a), and (19e) is consistent only with their bicyclic structures and excludes the adducts (20e), (21a), and (21e), respectively In $CDCl_3$ solution, B–N complex formation was noticed for (18a–c,e)(→20a–c,e) and (19a)(→21a) as well as a weak intramolecular interaction in compound (19e) from the δ-^{11}B chemical shift

data The observations for the gas phase and the solution are consistent for compounds (18a–c) and (19e), while for (18e) and (19a) a different behaviour is observed Obviously, the adducts (18e) and (19a) of the latter compounds are not stable in the gas phase under the conditions of PE spectral measurements (25 °C, *ca* 5 Pa) The observations may be roughly explained by steric and electronic effects enlargement of the dialkylamino group and of the substituent on the boron atom weakens the intramolecular tricyclic borane–amine complex The methoxy group reduces the acceptor strength of the boron atom and by this the complex is destabilized The difference in the properties of the two methoxy derivatives (18e) and (19e) in solution may be caused by the different size of the dialkylamino groups, but intermolecular effects may also be of importance



(18, 19) (20, 21) (22, 23)

R	(18, 20)	(19, 21)
CH_3	a	a
C_2H_5	b	
i C_3H_7	c	
t C_4H_9	d	
OCH_3	e	e

R'	CH_3	C_2H_5
	(18)	(19)
	(20)	(21)
	(22)	(23)

Aminoboranes

4 Discussion

Transannular interactions in difunctional medium rings have been studied by spectroscopic and theoretical methods Besides conformational analysis, the investigations centred on studying electronic interactions (through-space) as a function of the transannular distance These interactions and the implications for the characteristic molecular orbitals of the functional groups were determined by PE spectroscopy and theoretical methods (MMX, MNDO, AM1) The results were applied to bimolecular reactions of the analogous type to describe the reacting system close to the transition state

The investigations have shown that medium ring aminoketones, aminoalkenes, and boraalkenes are good models for the analogous bimolecular systems and allow the modelling of nucleophilic and electrophilic addition reactions The aminoboranes studied so far have not provided significant experimental insight into the orbital interactions involved in the reaction of an amine (nucleophile) with a borane (electrophile) since either strong intramolecular complexes could be formed or the interaction of the groups was too weak for clear spectroscopic evidence In general, difunctional compounds would be best suited for such studies when the direct interaction is attractive, but steric or conformational strain would prevent approach distances close to bonding distances

Using PE spectroscopy the through-space interaction of functional groups can be detected at a proximity below the van der Waals distance

However, there are also limitations to this method Only occupied orbitals can be detected by PE spectroscopy Since unoccupied MOs are also relevant for reactivity it would be very desirable to obtain their energies This can be accomplished by electron transmission spectroscopy The functional groups in the monofunctional reference compounds should have the same environment as in the difunctional compound This requirement cannot always be completely fulfilled because the molecules should also have the same conformation Only neutral reactants can be studied The investigations are done on the free molecules in the gas phase, while in reality most reactions are performed in solution

However, these shortcomings cannot conceal the experimental evidence for processes of highest chemical importance

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