31. Steric Effects in Nucleophilic Aromatic Substitution Reactions with Aromatic Amines

12th Communication on Nucleophilic Aromatic Substitution Reactions[1])

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Summary. The kinetics of the S_NAr reactions of aniline and N-methylaniline with a variety of substituted nitrochlorobenzenes in acetonitrile demonstrate that the formation of the intermediate σ-complex is rate determining. The ratio of the rate constants of the aniline and the N-methylaniline reactions (k_A/k_M) increases with increasing size of the 6-substituent; with picryl chloride k_A/k_M reaches a value of over 20000. The reaction of aniline with 4-X-2,6-dinitrochlorobenzenes is subject to considerably larger *para*-substituent effects than the corresponding reactions with N-methylaniline. These results are interpreted in terms of two effects: (i) A primary steric effect, which renders the approach of N-methylaniline to the substrate difficult. (ii) A shift towards earlier, more reactant-like transition state structures caused by the primary steric effect. In early transition states the activating power of the electron-withdrawing substituents in the substrate is expected to be relatively small. An early transition state for the slow N-methylaniline reaction and a late transition state for the fast aniline reaction is in apparent contradiction to what would be expected on the basis of the *Hammond* postulate.

1. Introduction. – Secondary amines are usually considerably stronger nucleophiles in nucleophilic aromatic substitution reactions than primary amines of comparable basicity. However, this generalization holds only for aliphatic and alicyclic amines[2]). In the aromatic series primary amines react faster than their secondary counterparts. The reactivity difference seems to be astonishingly large when the substrate contains two nitro groups in the positions *ortho* to the leaving group. Table 1 shows a compilation of some literature data for reactions of aromatic amines with nitroaromatic substrates. All these reactions probably proceed by the addition-elimination mechanism (AE, S_NAr) originally suggested by *Bunnett & Zahler* [5] in 1951[3]).

Rheinlander [6], who in 1923 studied reactions of aniline and N-methylaniline with nitrochlorobenzenes, was unable to determine the rate constant of the anilinodechlorination of picryl chloride using his experimental technique. He resorted to determining the rate constant of the reaction of aniline hydrochloride with picryl chloride, which turned out to be some 38 times larger than the rate constant of the corresponding reaction with N-methylaniline. It seems likely that not aniline hydrochloride, but the small amounts of free aniline present at equilibrium acted as nucleophile in the reaction studied by *Rheinlander*. This, of course, leads to a considerably higher rate constant for the aniline reaction and, in turn, to a ratio of the rate constants of the two reactions k_A/k_M of the order of several thousand.

[1]) 11th Communication: *P. Rys, A. Schmitz & H. Zollinger* [1].
[2]) For a recent summary and discussion see [2]; see also [3].
[3]) For recent reviews see [2–4].

Table 1. *Rate constants of some reactions of aromatic amines with nitrohalogenobenzenes (literature data)*

Substrate		Nucleophile	Solvent	T °C	k [l mol^{-1} s^{-1}]	k_A/k_M[a])	Ref.
position of nitro group(s)	leaving group						
2, 4, 6	Cl	$PhNH_3Cl$ ($PhNH_2$)	EtOH	50	1.9×10^{-2}	38.5	[6]
2, 4, 6	Cl	PhNHMe	EtOH	50	4.93×10^{-4}		[6]
2, 4	Cl	$PhNH_2$	EtOH	50	2.75×10^{-3}	9.4	[6]
2, 4	Cl	PhNHMe	EtOH	50	2.95×10^{-4}		[6]
2, 4	Cl	$PhNH_2$	EtOH	50	2.74×10^{-4}	10	[7]
2, 4	Cl	PhNHMe	EtOH	67	7.3×10^{-5}		[8]
2, 4	Cl	$PhNH_2$	EtOH	100	4.77×10^{-3}	8.6	[9]
2, 4	Cl	PhNHMe	EtOH	100	5.49×10^{-4}		[9]
2, 4	Cl	*o*-toluidine	EtOH	100	4.92×10^{-4}		[9]
4	F	*p*-anisidine	DMSO	50	9.3×10^{-6}	58	[10]
4	F	N-Me-*p*-anisidine	DMSO	50	1.6×10^{-7}		[11]

[a]) Ratio of rate constants of reaction with aniline and N-methylaniline, resp.

Since *Rheinlander's* work [6], 'steric effects' have been offered as an explanation for the lower reactivity of secondary aromatic amines as compared to their primary counterparts. In spite of their remarkable magnitude, however, these effects have never been the subject of a thorough investigation. We have therefore undertaken a study of the reactions of aniline and N-methylaniline with a variety of suitably substituted aromatic substrates in acetonitrile.

2. Results. – We determined the specific rates of the reactions of aniline and N-methylaniline with various substituted nitrochlorobenzenes in acetonitrile at 50 °C. All the reactions were found to be second-order overall, first-order with respect to each reactant. No base catalysis was detected. The spectrophotometric procedure used to determine the kinetics is described in the experimental section. The measured rate constants are given in Tables 2 and 3.

The data can be summarized as follows: (i) The rates of the reactions with aniline increase as the electron-withdrawing power of the substituent in the substrate increases. The substituent effect is of the order of magnitude expected on the basis of the inductive and resonance effects of the substituents. (ii) In the corresponding reactions with N-methylaniline only a small rate enhancement is observed. A cyano group in the position *ortho* to the leaving group causes a larger rate increase than a nitro group. For the *para*-position the opposite is true. (iii) In all but one case aniline reacts faster than N-methylaniline, although the latter is slightly more basic (pK_a = 4.60 and 4.84 resp.)[4]).

These data are consistent with the hypothesis that some kind of steric effect is operative. In order to elucidate further the nature of such an effect we determined the activation parameters of the reactions of aniline and N-methylaniline with 6-substituted 2,4-dinitrochlorobenzenes. A compilation of these results is given in Table 4.

[4]) From ref. [2], p. 40.

Table 2. *Rate constants of the reactions of 6-substituted 2,4-dinitrochlorobenzenes with aniline and N-methylaniline in acetonitrile at 50°C*

6-substituent	Aniline k_A[a] [l mol^{-1} s^{-1}]	k_{rel}[b]	N-methylaniline k_M[a] [l mol^{-1} s^{-1}]	k_{rel}[b]	k_A/k_M
H	2.86×10^{-5}	1	1.59×10^{-5}	1	1.8
CN	1.35×10^{-2}	470	1.94×10^{-4}	12	70
NO_2	5.95×10^{-1} [d]	20800	2.91×10^{-5}	1.8	20450
Me	1.80×10^{-6}	0.063	0.9×10^{-8} [c]	0.00057	200
aza-N[c]	1.68×10^{-1}	5874	2.78×10^{-1}	17480	0.6

a) Average of 3 to 6 kinetic runs; estimated error ± 3%.
b) Rate constant relative to the value for the reaction with 2,4-dinitrochlorobenzene.
c) 2-Chloro-3,5-dinitropyridine.
d) Cf. *Hirst & Rahman* [12]: $k_A = 0.527$ l mol^{-1} s^{-1} at 48.5°.
e) Reaction monitored to 9% conversion, corresponding to an elapsed time of 16 weeks; $[substrate]_0 = 0.1$ mol/l, $[amine]_0 = 1$ mol/l.

Table 3. *Rate constants of the reactions of 4-substituted 2,6-dinitrochlorobenzenes with aniline and N-methylaniline in acetonitrile at 50°C*

4-substituent	Aniline k_A[a] [l mol^{-1} s^{-1}]	k_{rel}[b]	N-methylaniline k_M[a] [l mol^{-1} s^{-1}]	k_{rel}[b]	k_A/k_M
H	5.03×10^{-5}	1	2.1×10^{-6} [c]	1	2515
CN	1.22×10^{-1}	2430	1.07×10^{-5}	535	11400
NO_2	5.95×10^{-1} [d]	11830	2.91×10^{-5}	1445	20450

a) Average of 3 to 6 kinetic runs; estimated error ± 3%.
b) Rate constant relative to the value for the reaction with 2,6-dinitrochlorobenzene.
c) Reaction monitored to 23% conversion, corresponding to an elapsed time of 22 weeks; $[substrate]_0 = 0.1$ mol/l, $[amine]_0 = 1$ mol/l.
d) Cf. *Hirst & Rahman* [12]: $k_A = 0.527$ l mol^{-1} s^{-1} at 48.5°.

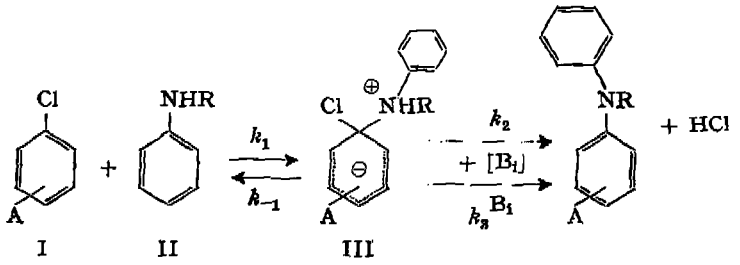
Table 4. *Rate constants and activation parameters of the reactions of aniline and N-methylaniline with 6-substituted 2,4-dinitrochlorobenzenes in acetonitrile at 50°C*

6-substituent	nucleophile	k [l mol^{-1} s^{-1}]	E_a[a] [b] kJ mol^{-1}	$\Delta H^{\neq}$ [b] [d] kJ mol^{-1}	$\Delta S^{\neq}$ [c] [e] JK^{-1} mol^{-1}	$\Delta G^{\neq}$ [b] kJ mol^{-1}
H	$PhNH_2$	2.86×10^{-5}	58.1 (13.9)	55.2 (13.2)	−161.5 (38.6)	107.5 (25.7)
CN	$PhNH_2$	1.35×10^{-2}	43.1 (10.3)	40.2 (9.6)	−157.0 (37.5)	90.6 (21.7)
NO_2	$PhNH_2$	0.595	32.2 (7.7) [f]	29.7 (7.1)	−158.5 (37.9)	80.6 (19.3)
H	$PhNHCH_3$	1.59×10^{-5}	55.2 (13.2)	52.3 (12.5)	−175.0 (41.8)	109.2 (26.1)
CN	$PhNHCH_3$	1.94×10^{-5}	49.0 (11.7)	46.0 (11.0)	−174.3 (41.6)	102.1 (24.4)
NO_2	$PhNHCH_3$	2.91×10^{-5}	54.0 (12.9)	51.0 (12.2)	−174.5 (41.7)	107.5 (25.7)

a) *Arrhenius* activation energy.
b) Number in parentheses is the corresponding value in kcal mol^{-1}.
c) Number in parentheses is the corresponding value in cal K^{-1} mol^{-1}.
d) Estimated error ± 2.1 (0.5) kJ mol^{-1}.
e) Estimated error ± 5.9 (1.4) JK^{-1} mol^{-1}.
f) Cf. *Hirst & Rahman* [12]: $E_a = 7.9 \pm 0.27$ kcal mol^{-1}.

We notice that the entropies of activation for all the six reactions are very similar and that the differences in the rate constants are essentially due to an effect on the activation enthalpies.

3. Discussion. – A large body of evidence[5]) suggests that all of the reactions studied most probably occur by the addition-elimination (*AE*, S_NAr) mechanism of nucleophilic aromatic substitution (1):



(1)

The symbol A represents activating (*i.e.* electron-withdrawing) substituents, B is a base and R stands for either hydrogen or a methyl group. The rate expression for this system (2) can be derived by applying the *Bodenstein* [14] approximation[6]):

$$\frac{\text{rate}}{[\text{ArCl}]\,[\text{ArNHR}]} = \frac{k_1k_2 + k_1\sum_i k_3^{B_i}[B_i]}{k_{-1} + k_2 + \sum_i k_3^{B_i}[B_i]} \qquad (2)$$

A salient feature of this mechanism is the fact that the intermediate (III) can proceed to products by two distinct pathways: (i) spontaneously (k_2), and (ii) through general base catalysis ($k_3^{B_i}$). If no base catalysis is observed the inference can be made that the formation of the intermediate (k_1) is the rate determining step and that $k_2 \gg k_{-1}$[7]). In this case the measured overall rate constant, k_{obs}, is equal to k_1.

All the reactions investigated in the present study are not base catalyzed. This result is expected and consistent with many previous findings [2]. Chloride ion is a very good leaving group in nucleophilic aromatic substitution reactions. This means that $k_2 \gg k_{-1}$ and that $k_{obs} = k_1$. Base catalysis with chloride ion as leaving group has only been found in a few special cases where factors like the solvent and the entering amine contribute to a drastic lowering of the ratio k_2/k_{-1}[8]). The differences in the rate constants of the various reactions must therefore be explained in terms of differences in the free energy of activation of step k_1, the formation of the intermediate.

Let us first consider the entropies of activation listed in Table 4. The entropies of activation for all six reactions are very similar. Within each reaction series (with either aniline or N-methylaniline as nucleophile) they are constant, *i.e.* not influenced by the *ortho*-substituents. The fact that the values for the N-methylaniline series are slightly more negative can be readily understood either in terms of a steric effect exerted by the methyl group (which makes some internal motions in the transition state more difficult) or, alternatively, in terms of slight differences of solvation of the

5) See *e.g.* [2–4] and [13].
6) See also [15], p. 78.
7) For the *rationale* behind this reasoning see [2] [3].
8) See [2] and references mentioned therein.

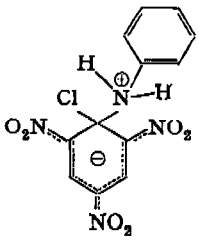
reactants or the transition states in the two series. The only conclusion which seems warranted is that all six reactions proceed *via* transition states of very similar structure.

It may be somewhat astonishing that the activation entropies are not influenced to any great extent by these steric effects. One might have expected a considerably lower (more negative) entropy of activation for the sterically hindered cases since various internal motions in the transition state should be stiffened. That this is not the case illustrates once again that our present state of knowledge does not appear to allow us to make predictions about the activation parameters of a reaction in solution with any certainty. No doubt, little understood solute-solvent interactions are of prime importance in determining these parameters.

Aniline reacts faster than N-methylaniline with all but one of the substrates investigated (see Tables 2 and 3). However, the ratio of the rate constants k_A/k_M only becomes large when both positions *ortho* to the leaving group in the substrate contain a substituent other than hydrogen. The magnitude of the ratio k_A/k_M appears to increase with increasing size of the 6-substituent. A methyl group in the 6-position has the same directional effect as a 6-nitro group. The only reaction in which the ratio of k_A/k_M is smaller than 1 is the reaction with 2-chloro-3,5-dinitropyridine. In this compound the pyridine nitrogen occupies one of the *ortho*-positions and its lone electron pair takes the place of the 6-substituent in other substrates. Apparently the lone electron pair is less bulky than even a hydrogen substituent[9]). All these observations are characteristic of the operation of a 'steric effect'[10]).

In the reactions of 2,6-dinitro-4-X-chlorobenzenes a change in the substituent X has no influence on the steric conditions at C(1), the reaction center. To a first approximation we would therefore expect a substituent effect of very similar magnitude on the reactions with aniline and N-methylaniline; in other words, a constant value for the ratio k_A/k_M. Table 3 shows, however, that this ratio is 2515 for X = H, 11400 for X = CN and 20450 for X = NO_2. Interestingly, and contrary to expectations, the fastest reaction shows the highest selectivity (*i.e.* the highest ratio k_A/k_M). The reaction with aniline as the nucleophile clearly is much more sensitive to *para*-substituent effects than the corresponding reaction with N-methylaniline (see Table 3).

This phenomenon may be understood if the structural differences in the transition states of the two reactions are considered. We may assume that the *Meisenheimer* complex (V) is a good model for the rate determining transition state of the aniline reaction[11]) [12]:



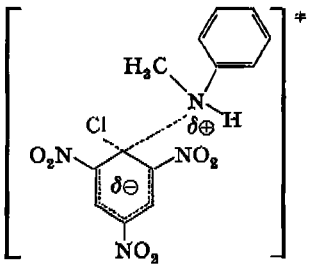
V

[9]) For a recent discussion of the size of electron pairs see [16].

[10]) See [15], p. 366.

[11]) Compounds of this type have recently been directly observed by *Buncel et al.* [17].

It seems reasonable to assume that the transition state for the N-methylaniline reaction will have less σ-complex character as the N-methyl group makes it harder for the nucleophile to approach the reaction center. The transition state structure might be depicted as follows:



VI

This amounts to saying that the transition state of the N-methylaniline reaction is 'early', *i.e.* that it has relatively little σ-complex character or, in other words, is somewhat reactant-like. The transition state for the aniline reaction, on the other hand, is 'late', *i.e.* it is energetically and structurally similar to the *Meisenheimer* complex. This situation is illustrated in the energy diagrams in Fig. 1.

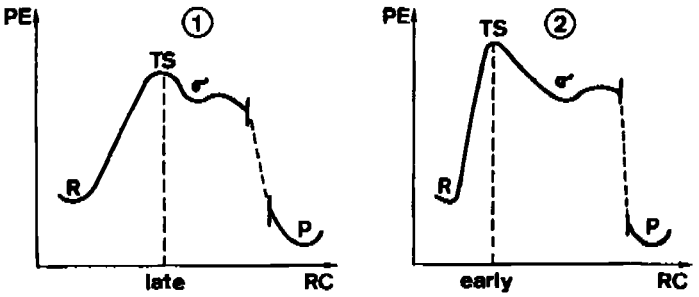
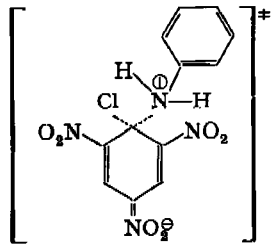


Fig. 1. *Energy diagrams for the reaction of picryl chloride with aniline (1) and N-methylaniline (2) resp.*

PE: Potential energy
TS: Transition state
R: Reactants
P: Products
σ: tetrahedral σ-(*Meisenheimer*) complex

The influence of *para*-substituents is expected to be much greater for late transition states with considerable σ-complex character than for early, reactant-like ones. Molecular orbital calculations [18] [19] and crystal structure determinations [20] [21]



VII

suggest that in *Meisenheimer* complex-type compounds the negative charge is essentially located in the nitro groups and, indeed, a large proportion of it is concentrated in the *para*-position. This would imply a structure for the transition state of the aniline reaction in which contributions from quinoid resonance structures such as (VII) are more important than contributions from structures containing a single C_4–N bond.

In the early transition state which we propose for the N-methylaniline reaction, only a relatively small amount of negative charge will have developed in the nitroaromatic entity by the time the transition state is reached. Consequently, the importance of resonance structures such as (VII) will be much smaller than in a late transition state.

It is interesting to note that we are suggesting an early transition state for the slow reactions with N-methylaniline and, *vice versa*, a late transition state for the fast reactions with aniline as nucleophile. This is in contradiction to the *Hammond* postulate [22], but allows the most reasonable explanation of our results that we can find at present. Apparently, the steric effect of the N-methyl group forces the transition state in the N-methylaniline reaction to occur much earlier on the reaction coordinate than would be the case for a reaction which has the same free energy of activation, but is not influenced by steric effects.

The fact that the fastest reacting substrate, 2,4,6-trinitrochlorobenzene shows the highest selectivity k_A/k_M can be rationalized in terms of the *Hammond* postulate. The fast aniline reaction with the late transition state is much more sensitive to *para*-substituent effects than the slow N-methylaniline reaction (see above). Therefore, although an activating substituent shifts the transition states of both reactions in the direction of lower energy and more reactant-like character (*i.e.* makes it earlier), this shift will be relatively more pronounced for the late than for the early transition state. As a necessary mathematical consequence, then, the selectivity k_A/k_M becomes larger for the more reactive substrates. Fig. 2 shows a pictorial representation of this argument:

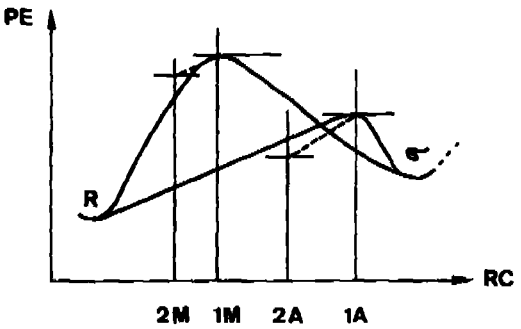


Fig. 2. *Schematic diagram of the shift of a transition state in a potential energy diagram upon going from less to more reactive substrate for early and late transition states*

PE: Potential energy
RC: Reaction coordinate
R: Reactants
σ: Tetrahedral σ-(*Meisenheimer*) complex
1: Transition state for the reaction of aniline (A) and N-methylaniline (M) with 2,6-dinitrochlorobenzene
2: Transition state for the reaction of aniline (A) and N-methylaniline (M) with 2,4,6-trinitrochlorobenzene

A very crude estimate (considering we have data for three substituents only) of how much stronger the *para*-substituent effect is for the aniline reaction than for the N-methylaniline reaction may be obtained from a plot (not shown) of log k_A *vs.* log k_M. Such a plot is approximately linear with a slope of about 1.25. The slope of the straight line is equal to the ratio of the *Hammett* ϱ values for the aniline and N-methylaniline reactions. We may therefore conclude that the aniline reaction is about $10^{0.25}$ times more sensitive to *para*-substituent effects than the N-methylaniline reaction.

Let us now consider in somewhat more detail the nature of the steric effect which causes the reaction of N-methylaniline with 6-substituted 2,4-dinitrochlorobenzenes to be much slower than the corresponding reaction with aniline. The approach of N-methylaniline towards the substrate is accompanied by increasing repulsive interaction between nucleophile and substrate (primary steric effect). We shall not attempt to specify at this point whether the amine specifically interferes with the *ortho*-substituents, the leaving group or the benzene ring carbons and hydrogens. It is obvious that this type of steric hindrance will lead to a transition state geometry resembling the reactants more than the products, in other words to an early transition state. On the other hand, it also brings about a decrease in the reaction rate. The reaction involving steric hindrance therefore has a transition state of higher potential energy and more reactant-like character than a similar reaction which is not subject to steric effects. In an earlier transition state the electron-withdrawing substituents in the substrate cannot exert their activating power as efficiently as in a late transition state. It should be remembered that on the basis of the *Hammond* postulate one would have expected a late, more product-like transition state for the slower reaction.

The very large k_A/k_M ratios for reactions with substrates containing two nitro groups in both positions *ortho* to the leaving group merits some further comment. It is conceivable that the primary steric effect in these cases is enhanced by a secondary effect. The approaching nucleophile may force at least one of the *ortho*-nitro groups out of the plane of the benzene ring, thereby greatly reducing its electron-withdrawing capability and therefore its activating power. An alternative explanation may again involve the position of the transition state on the reaction coordinate. It is known that the *ortho*-nitro groups in many 1-X-2,4,6-trinitrobenzenes are twisted out of the plane of the aromatic ring to a considerable extent. In picryl iodide, for example, both *ortho*-nitro groups are nearly at right angles to the ring plane [23]. In trinitrophenetole dihedral angles of up to 62° between the ring and the *ortho*-nitro groups have been found [24], and in 2,4-dinitrochlorobenzene the *ortho*-nitro group is twisted out of the plane of the aromatic ring by 39° [25]. These data were obtained by X-ray crystallography. NMR. and other spectroscopic measurements have shown that in N-alkyl-2,4,6-trinitroanilines one of the *ortho*-nitro groups is twisted between 60° and 90° out of the ring plane, depending on the size of the alkyl substituent [26]. In the tetrahedral *Meisenheimer* complex, on the other hand, we may expect a relief of the repulsive interaction between the *ortho*-nitro groups and the leaving group. The *ortho*-nitro groups should be able to arrange themselves between the entering and the leaving group, thereby attaining coplanarity (or nearly so). This idea has been put forward by *Hammond & Hawthorne* [27] and later promoted by *Pietra et al.* [28], who also presented experimental data to support this view. It receives still further support from the results of crystal structure determinations of picryl ether adducts with methoxide

which show that the nitro groups in positions *ortho* to the tetrahedral carbon atom are, indeed, nearly coplanar with the ring [20] [21]. It follows that the *ortho*-nitro groups are able to exert their full activating power only in late transition states with considerable σ-complex character. An early transition state, such as we have proposed for the sterically hindered reaction, should therefore have a much higher potential energy, as is found experimentally.

The low reactivity of N-methylaniline compared to aniline in many nucleophilic aromatic substitution reactions can thus be rationalized in terms of two factors: (i) A primary steric effect which renders the approach of the nucleophile difficult. (ii) As a result of this primary steric effect the transition state occurs earlier on the reaction coordinate. This shift of the transition state is accompanied by a decrease in activating power of the electron-withdrawing substituents in the substrate.

4. Experimental Part. – *Materials.* Acetonitrile *Merck* Uvasol was found to be equivalent to the solvent purified by the procedure of *Coetzee* [29] and was used throughout this work. Aniline (*Fluka*) and N-methylaniline (*Fluka*) were distilled twice in a dry nitrogen atmosphere under reduced pressure and stored at 0° under nitrogen and in the dark. Commercially available 2,4,6-trinitrochlorobenzene (*Fluka*) (m.p. 82°), 2,4-dinitrochlorobenzene (*Fluka*) (m.p. 51°), 2,6-dinitrochlorobenzene (*EGA*-Chemie) (m.p. 85°), 2,6-dinitro-4-cyanochlorobenzene (*Fluka*) (m.p. 139°) and 1-chloro-2,4-dinitropyridine (*Fluka*) (m.p. 61°) were recrystallized two to four times from ethanol and/or *n*-heptane. *2,4-Dinitro-6-cyanochlorobenzene* was available from an earlier study [30] and was recrystallized twice from *n*-heptane, m.p. 138°. It had been prepared by the method of *Blanksma* [31].

2-Chloro-3,5-dinitrotoluene was prepared by the method of *Morgan & Drew* [32]. 38 g (0.3 mol) of *o*-chlorotoluene (*Fluka*) were added dropwise over a period of 2 h to a stirred mixture of 200 ml conc. sulfuric acid and 80 ml nitric acid. The solution was kept at a temperature of 8–10° during the addition and then heated for 4 hours on a water bath to 50°. The oily organic layer was separated and cooled to –20°. Repeated recrystallization from ethanol and *n*-heptane yielded the pure product, m.p. 60° (lit. [32] 63–64°).

2,4,6-Trinitrodiphenylamine was prepared by the procedure of *Bamberger & Müller* [33]: A solution of 2.5 g (0.01 mol) 2,4,6-trinitrochlorobenzene in 60 ml ethanol was added at room temperature to a stirred solution of 3.7 g (0.04 mol) aniline in 20 ml ethanol. The yellow-orange product crystallized readily. It was filtered off and purified by recrystallization from ethanol (3 ×), m.p. 179° (lit. [34] 179–180°). UV./VIS.: λ_{max} (CH_3CN) 365 nm, log ε 4.152.

The following products were prepared in an analogous manner:

N-Methyl-2,4,6-trinitrodiphenylamine, m.p. 107° (lit. [34] 108°). UV./VIS.: λ_{max} (CH_3CN) 425 nm, log ε 3.778.

2,4-Dinitro-6-cyano-diphenylamine, m.p. 183° (lit. [34] 183°). UV./VIS.: λ_{max} (CH_3CN) 350 nm, log ε 4.167.

N-Methyl-2,4-dinitro-6-cyanodiphenylamine, m.p. 134°. Anal.[18]) calc. for $C_{14}H_{10}N_4O_4$: C 56.38, H 3.38, N 18.79%; found: C 56.10, H 3.51, N 18.73%. – UV./VIS.: λ_{max} (CH_3CN) 400 nm, log ε 3.924.

2,4-Dinitrodiphenylamine, m.p. 156° (lit. [34] 156–157°). UV./VIS.: λ_{max} (CH_3CN) 355 nm, log ε 4.220.

N-Methyl-2,4-dinitrodiphenylamine, m.p. 166° (lit. [34] 166–167°). – UV./VIS.: λ_{max} (CH_3CN) 380 nm, log ε 4.156.

2,6-Dinitro-4-cyanodiphenylamine, m.p. 168°. Anal.[18]) calc. for $C_{13}H_8N_4O_4$: C 54.93, H 2.84, N 19.71%; found: C 54.30, H 2.97, N 19.60%. – UV./VIS.: λ_{max} (CH_3CN) 410 nm, log ε 3.757.

N-Methyl-2,6-dinitro-4-cyanodiphenylamine, m.p. 181°. Anal.[18]) calc. for $C_{14}H_{10}N_4O_4$: C 56.38, H 3.38, N 18.79%; found: C 56.33, H 3.43, N 18.96%. UV./VIS.: λ_{max} (CH_3CN) 415 nm, log ε 3.545.

[18]) Elemental analyses were carried out in the microanalytical laboratory of our Department.

2,6-Dinitrodiphenylamine, m.p. 104°. Anal.[12]) calc. for $C_{12}H_9N_3O_4$: C 55.60, H 3.50, N 16.21%; found: C 55.54, H 3.70, N 16.33%. – UV./VIS.: λ_{max} (CH_3CN) 420 nm, log ε 3.754.

2,4-Dinitro-6-methyldiphenylamine, m.p. 162°, Anal.[12]) calc. for $C_{13}H_{11}N_3O_4$: C 57.14, H 4.06, N 15.38%; found: C 57.05, H 4.15, N 15.40%. – UV./VIS.: λ_{max} (CH_3CN) 370 nm, log ε 4.126.

N-2',4'-Dinitropyridinylaniline, m. p. 149°. Anal.[12]) calc. for $C_{11}H_8N_4O_4$: C 50.77, H 3.10, N 21.53%; found: C 50.56, H 3.34, N 22.01%. – UV./VIS.: λ_{max} (CH_3CN): 348 nm, log ε 4.246.

N,N-2',4'-Dinitropyridinyl-methylaniline, m.p. 142°. Anal.[12]) calc. for $C_{13}H_{10}N_4O_4$: C 52.55, H 3.68, N 20.43%; found: C 52.54, H 3.71, N 20.49%. – UV./VIS.: λ_{max} (CH_3CN) 360 nm, log ε 4.298.

N-Methyl-2,4-dinitro-6-methyl-diphenylamine. A solution of 0.25 g (0.001 mol) 2-chloro-3,5-dinitrotoluene in 3 ml ethanol was added to 2.1 g (0.02 mol) N-methylaniline and heated to reflux in a nitrogen atmosphere and in the dark for one month. The excess N-methylaniline was removed by distillation. The dark-red, viscous reaction product was separated into 12 fractions by means of thick-layer chromatography (*Merck* silica gel plates, benzene). The third fraction from the solvent front (Rf = 0.55) was extracted with methanol and purified a second time by thick-layer chromatography. Recrystallization from ethanol finally yielded the pure product, m.p. 116°. – IR. (KBr): No band around 3300 cm^{-1} (NH). – MS.: M^+ at *m/e* 287. – Anal.[12]) calc. for $C_{14}H_{13}N_3O_4$: H 4.56%; found: H 4.68%. – UV./VIS.: λ_{max} (CH_3CN) 387 nm, log ε 3.589.

N-Methyl-2,6-dinitrodiphenylamine: 2 g (0.01 mol) 2,6-Dinitrochlorobenzene and 10 g (0.1 mol) N-methylaniline were dissolved in 10 ml ethanol and heated to reflux in a nitrogen atmosphere and in the dark for one month. After removing the excess N-methylaniline by distillation, the viscous red product was purified by thick-layer chromatography (*Merck* silica gel plates, benzene). The most intense yellow fraction (Rf = 0.46) was extracted with methanol. Recrystallization of the solid material from ethanol produced two products, one in the form of orange needles, the other in the form of dark-red plates. The latter material was separated manually (spatula) from the orange needles and recrystallized again from ethanol, yielding the desired product, m.p. 101°. – IR. (KBr.): No band around 3300 cm^{-1} (NH). – MS.: M^+ at *m/e* 273. – UV./VIS.: λ_{max} (CH_3CN) 410 nm, log ε 3.004.

Kinetic measurements. The reaction rates were determined spectrophotometrically by monitoring the increase in the amount of reaction product as a function of time at the wavelength of maximum absorption. The absorption of the reactants was negligible in all cases. The faster reactions were carried out directly in the spectrophotometer cell. This procedure allowed the optical density to be recorded continuously. In the case of slower reactions, samples were taken at appropriate time intervals and transferred to the spectrophotometer cell for measurement. A *Beckman* Acta III UV./VIS. spectrophotometer equipped with thermostatted cell block and iron-constantan thermocouple to monitor the temperature in the cells was used throughout this work.

The reaction solutions were prepared in V-tubes. 3 ml of the reactant solutions were pipetted into each arm of the tube and the stoppered tube thermostatted at the appropriate temperature. After the solutions had equilibrated, the reaction was started by inverting the tube and thoroughly mixing the two solutions. The extremely slow reactions of 2,6-dinitrochlorobenzene and 2,4-dinitro-6-methylchlorobenzene with N-methylaniline were carried out in evacuated ampoules in the dark. When this technique was used, no traces of side reactions which occurred in an air, nitrogen or argon atmosphere could be detected.

All the reaction rates were measured under practically second order conditions, *i.e.* the amine was present in a 2 to 10-fold excess over the aromatic substrate. Initial substrate concentrations varied between 10^{-4} and 10^{-1} mol/l, depending on the rate of the particular reaction[13]). *Pseudo* first-order conditions with the amine in large excess proved to be impractical, as minute amounts of aniline present in N-methylaniline are liable to cause complications in the kinetics. No deviations from the second-order rate law were observed in any of the reactions. The optical density of reaction solutions at time infinity was equal to the absorbance of mock infinity solutions prepared by dissolving appropriate amounts of the pure reaction products in acetonitrile.

[13]) For further details see [35].

The rate constants were calculated by standard methods[14]), taking into account the fact that two amine molecules per substrate molecule were consumed in the reaction – one amine molecule acting as a nucleophile, the other as a proton acceptor[15]). The rate constants given in Tables 2 and 3 represent the average of 3 to 6 kinetic runs. The individual measured values agreed to within ± 3%[13]). The activation parameters were determined in the usual manner from the temperature dependence of the reaction rates.

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[14]) See *e.g.* [36], p. 58.
[15]) Cf. *B. Bitter & H. Zollinger* [37].

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32. Synthetische Juvenilhormone

1. Mitteilung

p-Substituierte β-Methyl-Zimtsäurederivate

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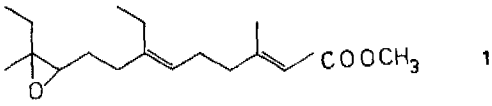
(27. IX. 74)

Summary. In the first communication the synthetic methods are described for preparing aromatic analogues of juvenile hormone like activity. The para-substituted 2-methyl-cinnamic acid derivatives are formed by a *Friedel-Crafts* acylation of a phenol, followed by the *Wadsworth-Emmons* (*Wittig-Horner*)-Reaction with the corresponding phosphonates. More than 120 compounds are listed.

Das Juvenilhormon (*Corpus-allatum*-Hormon) der Insekten reguliert zusammen mit dem Häutungshormon Ecdyson den Ablauf der Insektenmetamorphose.

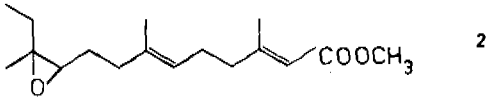
Die Häutungen der Larvenstadien werden durch die Juvenilhormone induziert, während die Umwandlung des letzten Larvenstadiums zur Puppe bzw. zur Imago nach dem Absinken des Juvenilhormonspiegels durch ein relatives Überwiegen des Ecdyson ausgelöst wird. Während des Puppenstadiums sistiert die Sekretion der Juvenilhormon produzierenden Zellen. Sie sezernieren erst wieder bei den Imagines.

Extrakte mit Juvenilhormonaktivität wurden 1956 erstmals von *Williams* [1] aus dem Abdomen der männlichen *Cecropia*-Motte hergestellt. Im Jahre 1965 isolierte *Röller* [2] die aktive Komponente, und zwei Jahre später identifizierte er sie als einen Isoprenoidabkömmling **1**:



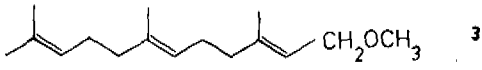
1

Die zweite aktive Komponente wurde 1968 von *Meyer* [3] in ihrer Struktur aufgeklärt **2**:



2

Karlson & Schmialek [4] berichteten 1959 von einer Juvenilhormonaktivität im Kot des Mehlwurms; die aktiven Substanzen wurden von *Schmialek* [5] zwei Jahre später als Farnesol und Farnesal erkannt. *Schmialek* [6] stellte ausserdem fest, dass Farnesylmethyläther **3** eine starke Juvenilhormonwirkung zeigt:



3