Acid-catalysed Addition of *N*-Aryl Imines to Dihydrofuran. Postulated Dependence of the Reaction Mechanism on the Relative Face of Approach of Reactants[1]

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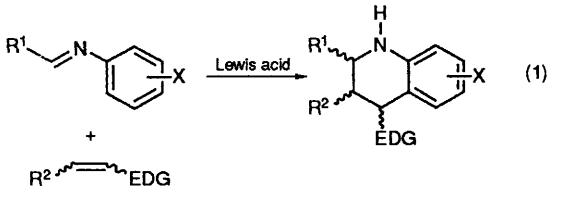
Imines **1a** and **1b** react with dihydrofuran (DHF) under Lewis acid catalysis *via* Diels–Alder-type addition to form the tetrahydroquinoline derivatives **3a, b** and **4a, b**. Besides these compounds, the methanol adduct **2** of **1a**, or **1a** in the presence of methanol, gives the methanol-containing tetrahydrofuran derivative **7a** and the hexahydrofuro[3,2-*b*]furan derivatives **5** and **6**. In the presence of methanol, **1b** gives **3b** and **4b**, and also **7b** and **8**. The products **3a, b, 5, 6** and **7a, b** originate from approach of the *Si* (or *Re*) face of **1a, b** onto the *Si* (or *Re*) face of DHF; **4a, b** and **8** derive from interaction of the *Si* (or *Re*) face of **1a, b** with the *Re* (or *Si*) face of DHF. The dependence of the product distribution on the polarity of the solvent suggests that a concerted mechanism predominates in the former mode and a zwitterionic one in the latter. In the addition of **1a** or **2** the mechanistic preference may be exclusive.

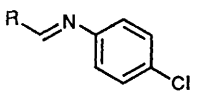
In the mid Sixties, Povarov and co-workers published a series of papers on the cycloaddition reactions of Schiff bases derived from aliphatic and aromatic aldehydes with anilines.[2] These compounds react with a range of electron-rich alkenes under Lewis or protic acid catalysis in an inverse electron demand Diels–Alder process [eqn. (1)]. Since then, the reaction between imines and strongly nucleophilic alkenes has been actively studied, mostly for synthetic purposes, and in some cases also from a mechanistic point of view.[3]



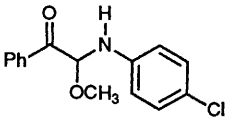
The course of the addition is strongly dependent on the reaction conditions and on the reaction partners. Thus, under acid catalysis, tetrahydroquinoline derivatives[2,4–6] and β-lactams,[7] were obtained in the reaction with enol ethers, whereas substituted enamines,[8] as well as tetrahydroquinolines[9] have been prepared with enamines. In alkaline solutions β-aminothioamides[10] were isolated. In neutral conditions with ketenes, benzylidene anilines were reported to afford azetidinones.[11] On the other hand, application of high pressure conditions has provided a simple route to azetidines and β-amino carbonyl compounds.[12,†]

A few mechanistic investigations of the cycloaddition have been described in the literature,[16] most of them proposing a two-step ionic mechanism; however, they have not assessed some fundamental details of the reaction. The formation of azetidines or azetidinones has been interpreted as either a two-step ionic[11,17] or a concerted process,[17] whereas in reactions with enamines leading to quinolines a zwitterionic intermediate has been proposed.[9] On the other hand, a thorough study of the Lewis-acid-catalysed addition of the neutral 2-azadiene 1,3-diphenyl-2-azapenta-1,3-diene to enamines or enol ethers led to the proposal of a concerted mechanism.[18] Furthermore, the reported specific formation of a single stereoisomer in the reaction with dihydrofuran and dihydropyran[6,19] cannot be easily rationalized.

With the synthesis of nitrogen heterocycles as a goal,[20] we have been investigating the dienic and dienophilic reactivity of a series of *N*-arylimines, activated by the presence of a ketone[21] or ester[22] functionality at the carbon end. In this paper we report the results of a mechanistic investigation of the Lewis-acid-catalysed addition of the anil **1a** (and its methanol adduct **2**), and benzylidene aniline **1b** to 2,3-dihydrofuran (DHF).[1]



1a; R = PhCO
1b; R = Ph

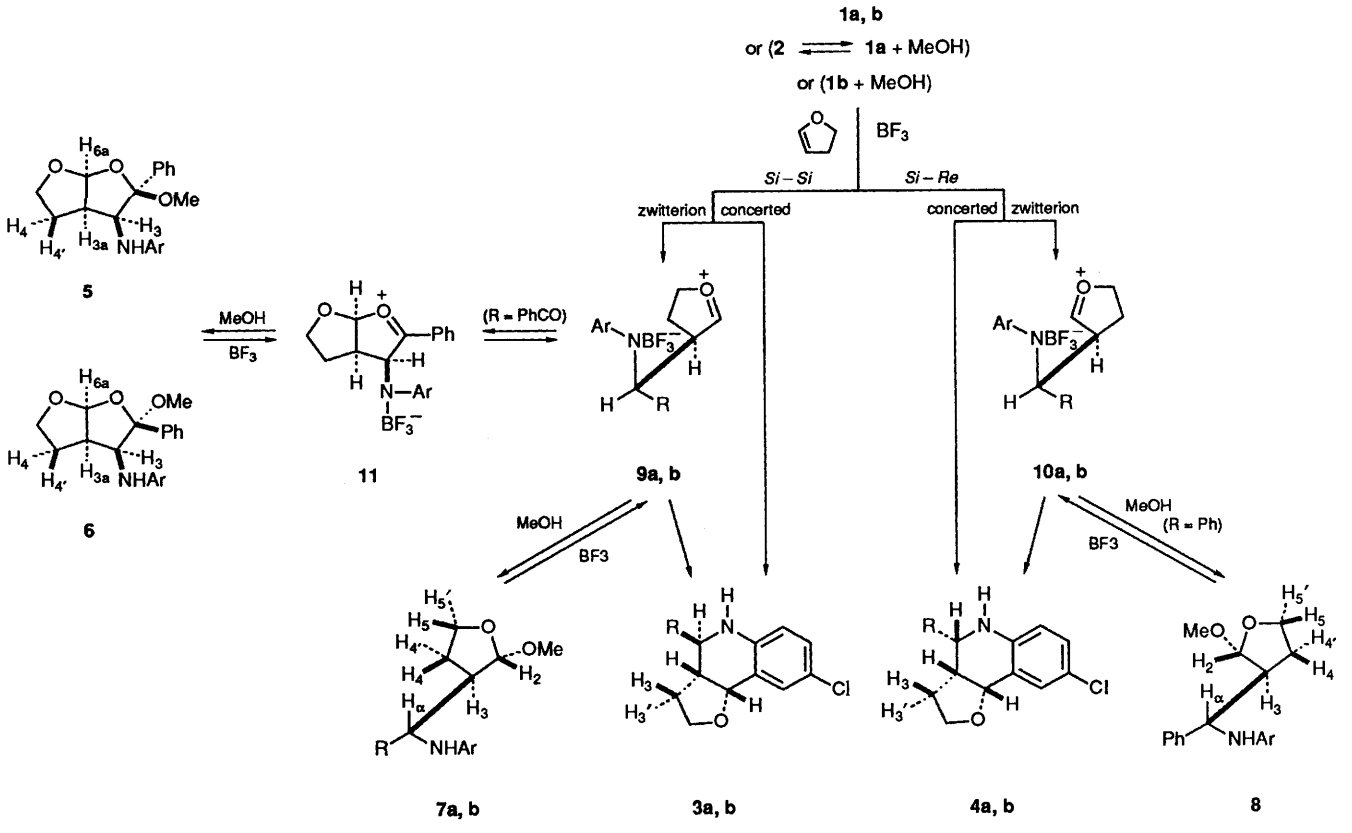


2

Results

The anils **1a, b** can be prepared and purified according to reported procedures.[21,23] Methanol adds readily and quantitatively to the anil **1a**, yielding the adduct **2**.[21] In all solvents listed in Tables 1–4, this adduct partially reverts to the free anil and methanol.[21] Therefore, **2** or **1a** with equimolar methanol show identical reactivity towards DHF. The methanol adduct of **1b** has never been observed.[24] A summary of the reactions of

† In this list of references we have purposely omitted the work regarding 2-azadienes other than benzylidene anilines,[3] 1-azadienes,[3] imines acting as dienophiles,[3] immonium ions,[3,13] the Bradsher reaction.[3,14] A version of this last case was recently reinvestigated by Franck and Gupta. In an elegant synthesis of tetralins, they were able to trap the ionic intermediates, and to 'recycle' them, thus showing the stepwise character of that cycloaddition.[15]



Scheme

these substrates with DHF is outlined in the Scheme and discussed below.

Addition of the Free Anils **1a**, **b**.—The reaction with DHF at room temperature under Lewis acid (BF_3·Et_2O) catalysis in CH_2Cl_2 yields the adducts **3a**, **b** and **4a**, **b** (see Scheme). The regio- and stereo-chemistry of the adducts was ascertained by NMR spectroscopy. The presence of the ^{13}C carbonyl resonance and of the ^1H pattern of a trisubstituted asymmetric aromatic ring indicates that the aniline ring is involved in the addition, while the carbonyl group is not, implying the quinoline structure **3** or **4**. In the adducts **3a** and **4a** relevant nuclear Overhauser effects[25] (NOE, see Experimental section) interactions are measured between the methylene protons H-3 and the methine proton H-3a, thus indicating the regio-orientation shown in structures **3** and **4**. In the adduct **3a** protons H-3a and H-4 interact through a relevant scalar coupling constant (8.5 Hz), while saturation of H-3a induces a relatively small NOE enhancement (2.1%) of the H-4 multiplet, revealing that the protons are on opposite faces of the tetrahydropyridine ring and *anti* oriented (with the ketone residue in the equatorial orientation). Conversely, irradiation of H-3a in **4a** enhances by 6.6% the intensity of the H-4 multiplet, while the coupling constant is 3.2 Hz, so that the two protons are on the same face of the ring and *gauche* oriented; the spectral proximity has prevented the measurement of a NOE interaction between H-4 and H-9b (observed in other systems with the same stereochemistry[21]). NOE measurements have not been performed on **3b** and **4b**, but the spectral similarity with **3a** and **4a** (the coupling constants $J_{3a,4}$ are 11.0 and 3.1 Hz respectively) makes the stereochemical assignments quite reasonable. These results agree with the reported formation of two [4 + 2] stereoisomers from the addition of benzylidene anilines to vinyl ethers;[4,19] the claimed formation of [2 + 2] adducts[26] has already been challenged.[1,19]

By means of NOE measurements, we have already demonstrated[21] that the anil **1a** is in the preferred *E* configuration. We have also suggested that the catalyst complexes at nitrogen without altering the free base configuration. These considerations can be safely extended to the benzylidene aniline **1b**. Therefore the adducts **3a**, **b** derive from approach (which may be concerted or may require the intermediacy of the zwitterion **9a**, **b**, *c.f.* Scheme) of the *Si* (or *Re*) face of the imine carbon in the anil onto the *Si* (or *Re*) face of C-3 in DHF; they will be designated as *Si–Si* adducts. Conversely, the adducts **4a**, **b**, deriving from the interaction (concerted or through the zwitterionic intermediate **10a**, **b**, *cf.* Scheme) of the *Si* (or *Re*) face of the anil with the *Re* (or *Si*) face of DHF, will be denoted as *Si–Re* adducts.*

Additions of **2** *or* **1a**, **b** *in the Presence of Methanol.—Addition of* **1a** *in the presence of methanol, or of* **2**. Under typical reaction conditions (CH_2Cl_2, catalytic BF_3·Et_2O, less than 1 min at room temperature), either **2** or **1a** with equimolar methanol react similarly, giving, besides **3a** and **4a**, the three isomers **5**, **6** and **7a**. These latter products display very similar mass spectra with M^+ 345, and are therefore addition products which have incorporated a molecule of methanol. In the spectra of **7a**, the presence of the ^{13}C carbonyl resonance and of the ^1H pattern of an unperturbed *para*-substituted aniline ring indicates that neither group participates in the addition, suggesting that the adduct possesses the tetrahydrofuran structure **7**. The NOE technique was not helpful for the configurational determination of the exocyclic carbon: due to the presence of several rotamers, relevant and comparable interactions were detected between H-2, H-3 and H-4 on one side and H-α and N–H on the other. An X-ray diffractometric investigation was necessary, which revealed that the adduct possesses the configuration shown in structure **7a** (Fig. 1), originating from the *Si–Si* zwitterionic

* In the Seebach–Prelog notation, *Si–Si* and *Si–Re* approaches are referred to as *like* and *unlike* relative topicities, respectively.[27]

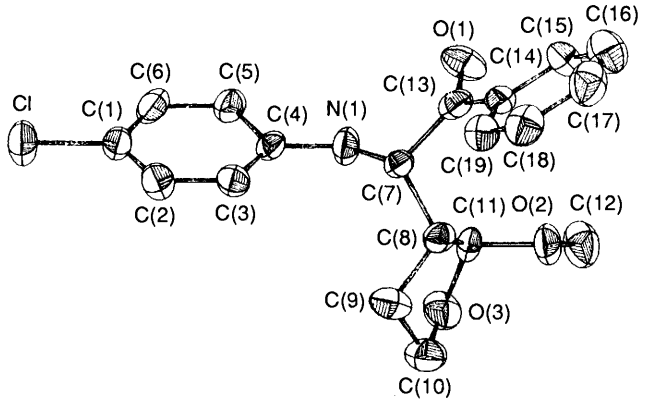


Fig. 1 ORTEP drawing of compound **7a**

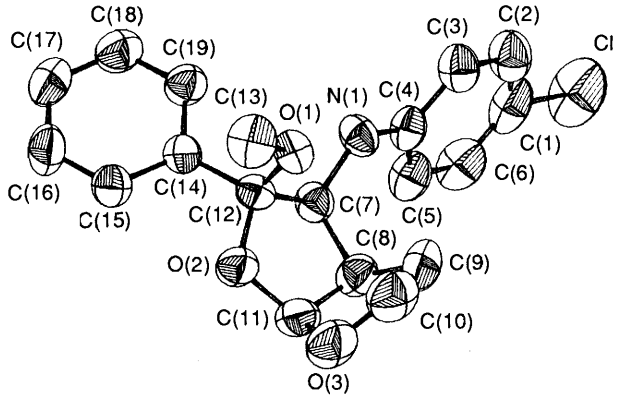


Fig. 2 ORTEP drawing of compound **5**

Table 1 Solvent dependence of product distribution in the reaction of **1a** with DHF

	Si–Si					*Si–Re*
Solvent	**3a**	**7a**	**5**	**6**	Total	**4a**
PhH	45.7				45.7	54.3
Et_2O	47.4				47.4	52.6
$CHCl_3$	48.9				48.9	51.1
CH_2Cl_2	51.6				51.6	48.4
$MeNO_2$	56.1				56.1	43.9
MeOH		65.6	8.4	2.2	76.2	23.8

Table 2 Solvent dependence of product distribution in the reaction of **2** with DHF

	Si–Si					*Si–Re*
Solvent	**3a**	**7a**	**5**	**6**	Total	**4a**
PhH	17.9	10.9	23.9		52.7	47.3
Et_2O	5.4	39.6	9.1		54.1	45.9
$CHCl_3$	15.8	12.9	26.1	1.2	56.0	44.0
CH_2Cl_2	23.2	11.3	21.4	1.1	57.0	43.0
$MeNO_2$	47.4	4.9	8.1		60.4	39.6
MeOH		64.4	11.9		76.3	23.7

intermediate **9a**, quenched by methanol at the less hindered side of the charged carbon atom (Scheme).

The adducts **5** and **6** are characterized by the absence of the ^{13}C carbonyl resonance, the presence of the unperturbed ^1H aniline pattern, and by a strong deshielded ^1H methine resonance at δ 6.09 and 5.91 respectively. The bicyclic acetal structures **5** and **6** are in accordance with these spectral data. Strong

Table 3 Solvent dependence of product distribution in the reaction of **1b** with DHF

	Si–Si			*Si–Re*		
Solvent	**3b**	**7b**	Total	**4b**	**8**	Total
PhH	30.6		30.6	69.4		69.4
Et_2O	32.8		32.8	67.2		67.2
$CHCl_3$	35.9		35.9	64.1		64.1
CH_2Cl_2	40.3		40.3	59.7		59.7
$MeNO_2$	58.6		58.6	41.1		41.1
MeOH	5.5	55.5	61.0	14.6	24.4	39.0

Table 4 Solvent dependence of product distribution in the reaction of **1b** with DHF in the presence of equimolar MeOH

	Si–Si			*Si–Re*		
Solvent	**3b**	**7b**	Total	**4b**	**8**	Total
PhH	17.0	14.8	31.8	52.7	15.5	68.2
Et_2O	18.6	15.8	34.4	5.3	10.3	65.6
$CHCl_3$	24.5	11.1	35.6	51.5	12.9	64.4
CH_2Cl_2	27.2	13.2	40.4	47.0	12.5	59.6
$MeNO_2$	53.5	5.3	58.8	38.2	3.0	41.2
MeOH	6.1	55.5	61.2	14.3	24.5	38.8

NOE interactions are observed between H-6a and H-3a and between H-3a and H-3, indicating that these protons are on the same side of the tetrahydrofuran ring. Therefore, both adducts derive from the *Si–Si* zwitterionic intermediate **9a**, which undergoes nucleophilic attack of carbonyl oxygen at the charged carbon atom, with formation of the intermediate **11** (see Scheme), followed by methanol quench on either side of the oxocarbonium ion. The intramolecular electrophilic attack of carbocations to carbonyl oxygens is a known procedure for the synthesis of furan derivatives[28] in reactions which have been classified as [3$^+$ + 2] polar cycloadditions.[29]

NOE interactions between H-6a and H-*ortho* of the 2-phenyl ring can discriminate between **5** and **6** (for **5**: 1.4% enhancement of H-6a from saturation of H-*ortho*, 0.5% enhancement of H-*ortho* in the reverse experiment; for **6**, no enhancements were observed). The structure is confirmed by an X-ray determination of adduct **5** (Fig. 2), whereas no proper crystals of **6** could be obtained (**6** converted to **5** under very mild conditions, presumably *via* the intermediacy of **11** and because of the steric congestion between the two aryl rings).

The methanol-quenched *Si–Si* adducts **5**, **6** and **7a** are not stable. Under the usual reaction conditions they interconvert reversibly, and finally convert irreversibly and specifically to the *Si–Si* adduct **3a**. Under particularly mild conditions (BF_3·Et_2O, 10^{-3}–10^{-4} molar equivalent) the reaction, carried out in $CDCl_3$ in an NMR tube, can be continuously monitored from the start. At the beginning only the methanol quenched *Si–Si* adducts **5**, **6** and **7a** can be observed, while the *Si–Si* adduct **3a** shows up only later, at the expense of the former compounds. The *Si–Re* adduct **4a** is present from the beginning, maintaining with the cumulated *Si–Si* adducts a ratio which does not vary during the whole reaction course.

Addition of **1b** *in the presence of methanol.* With equimolar methanol, the addition of **1b** to DHF gives, besides **3b** and **4b**, two other adducts **7b** and **8**. They are characterized by mass spectra with M$^+$ 317 and by strikingly similar ^1H NMR spectra, which display the unperturbed pattern of the aniline ring. These spectral data are only compatible with a tetrahydrofuran structure. Again, the isolated adducts **7b** and **8** are not stable under the reaction conditions, but convert quantitatively and specifically to the tetrahydroquinolines **3b** and **4b** respectively. We

could not ascertain the configurations of the exocyclic carbons in **7b** and **8** by diffractometric analysis, as we were not able to obtain suitable crystals. However, the rigorous specificity of these conversions is sufficient to assert the proposed configurations. Therefore **7b** and **8** derive from the *Si–Si* **9b** and *Si–Re* **10b** zwitterions respectively, both quenched by methanol at the less hindered side of the charged carbon.

At variance with the addition of **2**, in the reaction of **1b** we have observed (by NMR spectroscopy) the initial formation of all four adducts, even with very low catalyst concentration. We are therefore unable to say whether **3b** and **4b** are primary or exclusively secondary products.

Solvent Dependence of Product Distribution.—In order to gain insight into the reaction mechanism, the product distributions for the reactions of **1a**, **1b** and **2** alone, and **1b** in the presence of one equivalent of methanol were determined in a series of solvents with widely differing polarity indexes. The results are reported in Tables 1–4. The reaction conditions (equal for all substrates and solvents) are: substrate and DHF 10^{-2} mol dm^{-3}, BF_3·Et_2O 10^{-4} mol dm^{-3}, 30 min at room temperature. The product distribution was determined through careful integration of selected resonances in the NMR spectra of the reaction mixture. Errors are estimated at *ca.* 2%. With different reaction times, different product distributions having the same stereochemistry of approach were observed, while the ratios between overall *Si–Si* and *Si–Re* modes remained constant within the experimental error. Fairly linear correlations were observed between log(*Si–Si*/*Si–Re*) values and the normalized E_T solvent polarity function.[30] Because of the reasons pointed out in the Discussion, the values for the additions of **1a** and **2** in methanol are to be omitted. The remaining values give slopes of 0.45 and 0.34 respectively. The slopes of the product ratio *vs.* E_T for **1b** alone and with equimolar methanol are equal within the experimental error (1.27 and 1.18 respectively).

Discussion

The following experimental findings should be accounted for by a comprehensive mechanistic hypothesis.

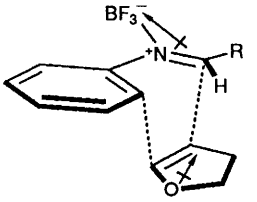
(i) In the addition of **2**, the methanol quenched adducts are only observed for the *Si–Si* approaching mode, where they also appear to be the only primary products. The *Si–Re* approaching mode gives only the Diels–Alder adduct **4a**. At variance, the addition of **1b** in the presence of equimolar methanol gives both the Diels–Alder **3b** and **4b** and the methanol quenched adducts **7b** and **8** for either approaching mode.

(ii) Under stronger conditions (longer reaction times do suffice), the *Si–Si* methanol-quenched adducts **5**, **6** and **7a** convert specifically and quantitatively to the Diels–Alder *Si–Si* adduct **3a**. In the same manner, the *Si–Si* quenched adduct **7b** converts to **3b**, and the *Si–Re* quenched adduct **8** converts to **4b**.

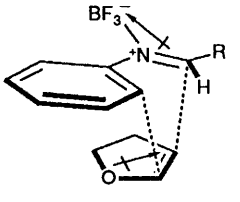
(iii) From inspection of Tables 1–4, it is possible to see that the *Si–Si* addition is always enhanced in more polar solvents. The variation of the *Si–Si*/*Si–Re* ratio as a function of solvent polarity is more pronounced for the addition of **1b** (with or without methanol) than for that of **1a** or **2**.

Although the formation of methanol-quenched adducts indicates that a zwitterionic mechanism is operative,[31] the participation of a concerted mechanism cannot be fully ruled out. We will therefore discuss both mechanistic hypotheses.[32] Furthermore, we will assume that the electrophilic reagent is the free anil **1a**, **b**, alone or in equilibrium with methanolated anil. In the solvent methanol, the equilibrium is completely shifted toward this latter complex, which may react as such. As a matter of fact, the *Si–Si*/*Si–Re* ratios in methanol appear to be anomalous, and are omitted in the correlation with the E_T function.

The *exo* and *endo* complexes **12** and **13** originate from concerted *Si–Si* and *Si–Re* approaches respectively, and may lead to the corresponding cycloadducts **3** and **4**. The dependence of the *exo*/*endo* ratio on solvent polarity in some other cycloaddition reactions was rationalized on the basis of the relative orientations of the reagent dipole moments:[33] that approach is favoured which maximizes the cancellation of the dipole moments.

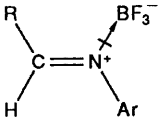


12 (*exo Si – Si*)

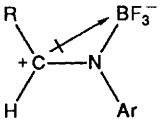


13 (*endo Si – Re*)

The observed dipole moment of the nucleophile DHF is along the line connecting oxygen and the β-vinylic carbon.[34] Consideration of the mesomeric structures of DHF suggests that it is directed from oxygen to the β-vinyl carbon. As for the dipole moment orientation in the electrophilic reagent, it can reasonably be affirmed that the dipole moment of the complex between **1a**, **b** and the Lewis acid is directed from nitrogen to boron, as in mesomeric structure **14**, or from imine carbon to boron, as in structure **14′**, or, more probably, in between. The possibility, which has been sometimes proposed,[35] that BF_3 might complex two basic centres (like nitrogen and the carbonyl oxygen in **1a**) does not significantly alter the dipole moment direction.



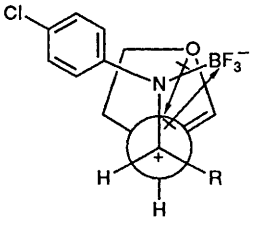
14



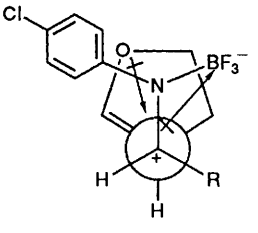
14′

The *exo Si–Si* complex **12** presents the dipole moments pointing in almost the same direction, while in the *endo Si–Re* complex **13** some cancellation occurs. Therefore, more polar solvents would favour the *Si–Si* mode of addition as compared to the *Si–Re*. Although the sole concerted mechanism may explain the increasing *Si–Si*/*Si–Re* ratio with solvent polarity, it cannot account for the formation of quenched adducts.

We will therefore apply the dipole cancellation criterion to the transition states **15** and **16** leading to the zwitterionic intermediates **9** and **10**, where we further assume that electrophile and nucleophile approach with staggered reciprocal orientation.



15 (*Si – Si*)



16 (*Si – Re*)

The two oriented complexes **15** and **16** are those with the greater dipole moment cancellation for the *Si–Si* and *Si–Re* approaches respectively, with the greatest cancellation associated with the *Si–Si* complex **15**. The *Si–Re* zwitterionic complex **16**, which is almost superimposable with the *endo Si–Re* concerted complex **13**, will give rise to zwitterion **10**, which can directly cyclize to **4**, while the corresponding cyclization of

Si–Si **9** (formed *via* **15**) to give **3** requires a rotation around the newly formed bond. On the other hand, the non-rotated conformation of **9a** may be quenched by methanol or directly give **11** *via* nucleophilic attack of the carbonyl oxygen. This can explain why, in the addition of **2**, the formation of the *Si–Re* adduct **4a** appears to be a primary process, with no evidence of methanol quenching, while the *Si–Si* adduct **3a** is secondarily formed from the methanol-quenched adducts **5, 6** and **7a**. This clear-cut differentiation does not occur in the addition of **1b** in the presence of equimolar methanol; this point will be dealt with later. However, in the hypothesis of exclusive zwitterionic mechanism, the *Si–Re* mode should be more stabilized in more polar solvents, leading to a solvent polarity dependence of the *Si–Si*/*Si–Re* ratio opposite to that experimentally observed. Thus we believe that a comprehensive rationalization requires the consideration of both mechanisms.

It is generally accepted that a zwitterionic intermediate is stabilized as such in more polar solvents, while a concerted complex is relatively less affected by solvent polarity. We would propose that in the addition of **1a** or **2** the *Si–Re* approach occurs (perhaps specifically) with the concerted mechanism *via* the *endo* transition state **13**, while the *Si–Si* approach is governed by the zwitterionic mechanism through the intermediate **15**, where the criterion of maximum dipole cancellation is met. Therefore, as observed, in more polar solvents the *Si–Si* approach predominates, while the *Si–Re* approach is relatively more favoured in less polar solvents.

This hypothesis may also offer an acceptable explanation for the different behaviour in the addition of **2** and of **1b** with equimolar methanol. *Ab initio* MO calculations on the model molecules *N*-protonated *N*-phenylimine and *N*-protonated *N*-phenylimino aldehyde[21] have shown that the presence of a carbonyl group lowers the energy of the LUMO, but also decreases the electrophilicity of the iminium carbon (as measured by the contribution to the LUMO of the p orbital associated with this atom). Thus, for the *Si–Re* approach, the concerted mechanism (occurring with inverse electron demand) is relatively more favoured in the addition of anil **1a**, or its methanol adduct **2**, than the zwitterionic reaction, whereas, for both *Si–Si* and *Si–Re* approaches with **1b**, the zwitterionic mechanism is dominant. The greater contribution of the zwitterionic mechanism for both addition modes of **1b** may explain why the corresponding *Si–Si*/*Si–Re* ratio variation is more sensitive to solvent polarity than in the case of the additions of **1a** or **2**.

Experimental

General.—Melting points are uncorrected. ^{1}H NMR spectra and NOE experiments were run on a Bruker WP200SY spectrometer at 200 MHz, ^{13}C spectra were obtained with a Bruker AC400 spectrometer at 400 MHz in $CDCl_3$ as solvent with tetramethylsilane (TMS) as an internal standard. *J* Values are given in Hz. Mass spectra were recorded on a 5970 HP instrument equipped with 5890 HP gas-chromatograph.

Nuclear Overhauser Effect Determination.—The samples (in $CDCl_3$) were freed from oxygen by sonication under nitrogen gas purging. The usual procedure for gated irradiation experiments was modified,[36] and the selected resonance was saturated by an 8 s cyclic perturbation of all lines with a 40–45 dB attenuation of a nominal 0.2 W decoupling power. A reference spectrum was acquired by setting the decoupling frequency off resonance. The enhancements were obtained from the multiplier of the reference spectrum which brings the observed multiplet to exact matching with the corresponding multiplet in the perturbed spectrum. Errors are estimated at *ca.* 0.3%. Only those results relevant for the structural determination are reported with the following convention. Observed nucleus **H-a**: {Saturated nucleus H-b}, % enhancement and/or comments; repeat for other saturated nuclei.

Reaction of **1a**, **b** *or* **2** *with* 2,3-*Dihydrofuran.*—*General procedure.* To a stirred solution of anil **1a**, **b** (or **2**) (10 mmol) in methylene chloride (50 cm^3), BF_3·Et_2O (0.062 cm^3, 0.5 mmol) was added at room temperature, followed by DHF (1.0 cm^3, 13 mmol). After 15 min the reaction was quenched by addition of 5% aqueous sodium bicarbonate (20 cm^3). The organic phase was extracted, washed, and dried over sodium sulfate. The crude product was chromatographed on a silica gel column (toluene). The reaction of **1b** in the presence of 1 mol. equiv. of MeOH was carried out in a similar way, adding 0.4 cm^3 of methanol before the Lewis acid.

Reaction of **1a**: *Formation of* **3a** (41%) *and* **4a** (38%): *trans* 4-benzoyl-8-chloro-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (**3a**) (27%), m.p. 143 °C (from EtOH) (Found: C, 68.85; H, 5.15; N, 4.5; Cl, 11.25. $C_{18}H_{16}NO_2Cl$ requires: C, 68.90; H, 5.14; N, 4.46; Cl, 11.32); δ_H 1.86 (m, H-3′), 2.23 (m, H-3), 2.73 (tdd, H-3a, $J_{3a,4}$ 8.4, $J_{3,3a}$ 8.1, $J_{3a,9b}$ 5.9, $J_{3',3a}$ 4.4), 3.84 (m, H-2), 3.96 (m, H-2′), 4.20 (br s, N–H), 4.55 (dd, H-4, $J_{4,NH}$ 1.8), 4.65 (br d, H-9b), 6.58 (d, H-6, $J_{6,7}$ 8.6), 7.07 (ddd, H-7, $J_{7,9}$ 2.4, $J_{7,9b}$ 0.5), 7.34 (d, H-9), 7.52 (m, Ph, H-*m*), 7.65 (m, Ph, H-*p*), 7.98 (m, Ph, H-*o*); δ_C 29.19 (t, C-3), 38.70 (d, C-3a), 57.25 (d, C-4), 65.58 (t, C-2), 74.39 (d, C-9b), 198.72 (s, CO); aromatic δ_C 116.43 (d), 121.94 (s), 123.63 (s), 128.67 (d), 128.94 (d), 129.12 (d), 130.30 (d), 133.89 (d), 135.78 (s), 141.86 (s). Selected ^{1}H NMR NOE increments **H-3**: {H-3′}, 30.6; {H-3a}, 5.1; {H-9b}, 1.0. **H-3′**: {H-3}, 30.4. **H-3a**: {H-3}, 8.0; {H-4}, 3.3; {H-9b}, 12.7; {Ph, H-*o*}, 2.5. **H-4**: {H-3′}, 3.3; {H-3a}, 2.9; {H-9b}, nearly isochronous to H-4; {Ph, H-*o*}, 13.0. **H-6**: {H-7}, 10.6; {N-H}, 12.2. **H-7**: {H-6}, 12.8. **H-9**: {H-3a}, −1.3 (H-9, H-9a, and H-3a almost linear); {H-9b}, 18.9. **H-9b**: {H-3}, 1.8; {H-3a}, 13.7; {H-9}, 4.8. **N-H**: {H-6}, 2.8. **Ph, H-*o***: {H-3a}, 1.7; {H-4}, 5.9; *m*/*z* 313 (M$^+$, 100%), 208 (51%), 180 (46%), 105 (28%), 77 (36%).

cis-4-benzoyl-8-chloro-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]-quinoline (**4a**), (38%), m.p. 166–7 °C (from EtOH) (Found: C, 68.65; H, 5.05; N, 4.35; Cl, 11.25. $C_{18}H_{16}NO_2Cl$ requires: C, 68.90; H, 5.14; N, 4.46; Cl, 11.32); δ_H 1.49 (m, H-3), 1.82 (m, H-3′), 2.98 (m, H-3a), 3.71 (m, H-2 and H-2′), 4.60 (br d, N-H), 5.20 (dd, H-4, $J_{3a,4}$ 3.2, $J_{4,NH}$ 1.8), 5.26 (br d, H-9b, $J_{3a,9b}$ 8.0), 6.60 (d, H-6, $J_{6,7}$ 8.6), 7.04 (ddd, H-7, $J_{7,9}$ 2.5, $J_{7,9b}$ 0.5), 7.29 (d, H-9), 7.53 (m, Ph, H-*m*), 7.65 (m, Ph, H-*p*), 7.92 (m, Ph, H-*o*). δ_C 23.84 (t, C-3), 40.98 (d, C-3a), 57.65 (d, C-4), 66.57 (t, C-2), 75.37 (d, C-9b), 197.89 (s, CO); aromatic δ_C 116.19 (d), 123.17 (s), 123.37 (s), 128.04 (d), 128.70 (d), 129.04 (d), 129.13 (d), 133.80 (d), 134.75 (s), 141.75 (s). Selected ^{1}H NMR NOE increments **H-3**: {H-3′}, 36.9; {H-3a}, 4.9; {H-9b}, 0.0. **H-3′**: {H-3}, 36.8. **H-3a**: {H-3}, 6.4; {H-4}, 7.8; {H-9}, −0.4 (H-3a, H-9a, and H-9 almost linear); {H-9b}, 14.1; {Ph, H-*o*}, 5.8. **H-4**: {H-3}, 0.6; {H-3a}, 6.6; {H-9b}, nearly isochronous to H-4; {Ph, H-*o*}, 17.4 H-6: {H-7}, 11.7; {N-H}, 9.6. **H-7**: {H-6}, 13.0. **H-9**: {H-3a}, −1.5 (H-9, H-9a and H-3a almost linear); {H-9b}, 16.8. **H-9b**: {H-3}, −0.6; {H-3a}, 15.9; {H-9}, 4.5. N-H: {H-6}, 1.0. **Ph, H-*o***: {H-3a}, 4.3; {H-4}, 11.8; *m*/*z* 313 (M$^+$, 100%), 208 (53%), 180 (44%), 105 (28%), 77 (37%).

Reaction of **1b**: *Formation of* **3b** *and of* **4b**: *trans*-8-chloro-4-phenyl-1,2,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (**3b**) (30%), m.p. 118–120 °C (from hexane) (Found: C, 71.35; H, 5.55; N, 4.75; Cl, 12.7. $C_{17}H_{17}NOCl$ requires: C, 71.45; H, 5.60; N, 4.90; Cl, 12.43); δ_H 1.72 and 2.02 (m, H-3 and H-3′), 2.45 (m, H-3a), 3.77 (d, H-4, $J_{3a,4}$ 11.0), 3.84 and 4.03 (m, H-2 and H-2′), 4.16 (br s, N-H), 4.55 (d, H-9b, $J_{3a,9b}$ 5.0), 6.56 (d, H-6, $J_{6,7}$ 8.7), 7.07 (dd, H-7, $J_{7,9}$ 2.4), 7.38 (m, 5 H, Ph), 7.39 (d, H-9); *m*/*z* 285 (92%, M$^+$), 240 (100%).

cis-8-chloro-4-phenyl-1,2,3a,4,5,9b-hexahydrofuro[3,2-*c*]-quinoline (**4b**), (45%), m.p. 165 °C (from EtOH) (Found: C,

Table 5 X-Ray crystallographic data for compounds **5** and **7a**. Diffractometer Philips PW 1100, Mo-Kα radiation λ = 0.7107 Å, Multan 80, blocked least squares

Compound	**5** (monoclinic)	**7a** (triclinic)
Formula	$C_{19}H_{20}ClNO_3$	$C_{19}H_{20}ClNO_3$
MW	345.8249	345.8249
Space group	$P2_1/n$	$P\bar{1}$
Z	4	4
a/Å	33.755(3)	17.968(2)
b/Å	6.503(1)	12.360(2)
c/Å	7.987(1)	8.187(1)
α/°	90.0	90.0(1)
β/°	93.3(1)	100.7(1)
γ/°	90.0	99.0(1)
V/Å^3	1750.3	1763.8
D_c/g cm^{-3}	1.31	1.30
Reflections$_{obs}$	1513	3486
R	0.0557	0.0861
Scan mode	ω	θ–2θ
2θ/°	50	50

71.25; H, 5.55; N, 4.9; Cl, 12.45. $C_{17}H_{17}NOCl$ requires: C, 71.45; H, 5.60; N, 4.90; Cl, 12.43); δ_H 1.53 and 2.16 (m, H-3 and H-3′), 2.76 (m, H-3a), 3.73 and 3.83 (m, H-2 and H-2′), 3.89 (br s, N-H), 4.69 (d, H-4, $J_{3a,4}$ 3.1), 5.22 (d, H-9b, $J_{3a,9b}$ 7.9), 6.53 (d, H-6, $J_{6,7}$ 8.5), 7.03 (dd, H-7, $J_{7,9}$ 2.4), 7.39 (d, H-9), 7.40 (m, 5 H, Ph); m/z 285 (87%, M$^+$), 240 (100%).

Reaction of **2**: *Formation of* **3a** (20%), **4a** (37%), **7a** (9%), **5** (18%) *and* **6** (1%). 2-(4-chlorophenyl)amino-1-phenyl-2-[3′-(2′-methoxy)tetrahydrofuryl]ethanone (**7a**), m.p. 90 °C (from EtOH) (Found: C, 65.9; H, 5.9; N, 4.05, Cl, 10.25. $C_{19}H_{20}NO_3Cl$ requires: C, 65.98; H, 5.83; N, 4.05; Cl, 10.27); δ_H 1.76 (m, H-4), 2.09 (m, H-4′), 2.66 (m, H-3), 3.27 (s, OCH_3), 3.86 (m, H-5′), 3.99 (m, H-5), 4.62 (br d, N-H, $J_{\alpha,NH}$ 9.3), 4.91 (dd, H-α, $J_{\alpha,3}$ 7.1), 4.95 (d, H-2, $J_{2,3}$ 2.1), 6.58 (m, *p*-Cl-C_6H_4, H-*o*), 7.09 (m, *p*-Cl-C_6H_4, H-*m*), 7.50 (m, Ph, H-*m*), 7.62 (m, Ph, H-*p*), 7.97 (m, Ph, H-*o*). δ_C 27.89 (t, C-4), 48.77 (d, C-3), 54.91 (q, OCH_3), 59.12 (d, C-α), 66.61 (t, C-5), 106.19 (d, C-2), 200.20 (s, CO); aromatic δ_C 114.79 (d), 123.19 (s), 128.25 (d), 129.04 (d), 129.25 (d), 133.93 (d), 135.88 (s), 145.72 (s). Selected ^{1}H NMR NOE increments **H-2**: {H-3}, 4.6; {H-α}, nearly isochronous to H-2; {N-H}, 5.4; {MeO}, 11.2. **H-3**: {H-2}, 7.2 (also from {H-α}, nearly isochronous to H-2); {H-4}, 9.6; {H-α}, 9.8 (also from {H-2}); {N-H}, 6.4; {Ph, H-*o*}, 3.6. **H-4**: {H-4′}, 34.4; {H-α}, 4.2. **H-4′**: {H-4}, 33.3; {H-3}, 6.5. **H-α**: {H-3}, 4.6; {H-4}, 3.3; {N-H}, 2.1; {Ph, H-*o*}, 12.1; {*p*-Cl-C_6H_4, H-*o*}, 10.8. **N-H**: {H-3}, 3.7; {*p*-Cl-C_6H_4, H-*o*}, 11.0. **MeO**: {H-2}, 3.6. **Ph H-*o***: {H-3}, 2.1; {H-α}, 13.1; {N-H}, 1.7. ***p*-Cl-C_6H_4, H-*o***: {H-α}, 10.4; {N-H}, 10.4; m/z 345 (M$^+$, 10%), 240 (54%), 208 (37%), 180 (100%), 138 (31%), 105 (21%), 77 (43%).

c-3-(4-chlorophenyl)amino-*r*-2-methoxy-2-phenyl-2,3,3a,4,5,6a-hexahydrofuro[2,3-*b*]furan (**5**), m.p. 88–89 °C (from EtOH) (Found: C, 65.8, H, 5.85, N, 3.95, Cl, 10.15. $C_{19}H_{20}NO_3Cl$ requires: C, 65.98; H, 5.83; N, 4.05; Cl, 10.27); δ_H 1.78 (m, H-4), 2.02 (m, H-4′), 3.15 (s, OCH_3), 3.27 (m, H-3a), 3.81 (t, H-3, $J_{3,3a}$, $J_{3,NH}$ 9.0), 4.01 (m, H-5 and H-5′), 4.85 (br d, N-H), 6.09 (d, H-6a, $J_{3a,6a}$ 5.6), 6.48 (m, *p*-Cl-C_6H_4, H-*o*), 7.07 (m, *p*-Cl-C_6H_4, H-*m*), 7.31 (m, Ph, H-*m* and H-*p*), 7.53 (m, Ph, H-*o*). δ_C 25.59 (t, C-4), 44.44 (d, C-3a), 49.89 (q, OCH_3), 64.05 (d, C-3), 68.08 (t, C-5), 105.02 (s, C-2), 109.17 (d, C-6a); aromatic δ_C 114.03 (d), 121.97 (s), 126.05 (d), 128.26 (d), 128.39 (d), 129.18 (d), 138.98 (s), 145.05 (s). Selected ^{1}H NMR NOE increments **H-3**: {H-3a}, 11.9; {H-6a}, 1.0; {Ph, H-*o*}, 2.9; {*p*-Cl-C_6H_4, H-*o*}, 17.7. **H-3a**: {H-3}, 7.9; {H-4}, 7.5; {H-6a}, 6.4. **H-4**: {H-3a}, 7.1; {H-4′}, 30.2. **H-4′**: {H-4}, 28.6; {N-H}, 5.3. **H-6a**: {H-3}, 1.3; {H-3a}, 19.7; {Ph, H-*o*}, 1.4. **N-H**: {H-4′}, 3.6; {*p*-Cl-C_6H_4, H-*o*}, 8.4. **Ph, H-*o***: {H-3}, 2.9; {H-6a}, 0.5. ***p*-Cl-C_6H_4, H-*o***: {H-3}, 10.3; {N-H}, 7.6; m/z 345 (M$^+$, 12%), 313 (50%), 209 (84%), 208 (93%), 166 (60%), 153 (60%), 138 (90%), 105 (58%), 83 (75%), 77 (93%), 69 (100%). *t*-3-(4-chlorophenyl)amino-*r*-2-methoxy-2-phenyl-2,3,3a,4,5,6a-hexahydrofuro[2,3-*b*]furan (**6**), m.p. 102 °C (from EtOH) (Found: C, 66.2; H, 6.0; N, 4.0; Cl, 10.25. $C_{19}H_{10}NO_3Cl$ requires: C, 65.98; H, 5.83; N, 4.05; Cl, 10.27); δ_H 1.86 (m, H-4 and H-4′), 3.05 (s, OCH_3), 3.05 (br d, N-H, $J_{3,NH}$ 7.3), 3.41 (m, H-3a), 3.86 and 4.04 (m, H-5 and H-5′), 3.99 (t, H-3, $J_{3,3a}$ 7.4), 5.91 (d, H-6a, $J_{3a,6a}$ 5.5), 6.17 (m, *p*-Cl-C_6H_4, H-*o*), 6.98 (m, *p*-Cl-C_6H_4, H-*m*), 7.36 (m, Ph, H-*m* and H-*p*), 7.45 (m, Ph, H-*o*). δ_C 26.98 (t, C-4), 47.11 (d, C-3a), 49.64 (q, OCH_3), 63.85 (d, C-3), 70.32 (t, C-5), 109.17 (d, C-6a), 112.03 (s, C-2); aromatic δ_C 113.80 (d), 122.25 (s), 127.22 (d), 128.55 (d), 128.97

Table 6 Fractional coordinates for compound **5**

Atom	x	y	z
Cl	−0.016 27(4)	1.276 8(3)	0.204 3(2)
O(1)	0.183 18(8)	0.766 3(4)	0.749 0(4)
O(2)	0.189 76(9)	0.464 7(5)	0.592 9(4)
O(3)	0.228 0(1)	0.601 7(7)	0.385 7(5)
N(1)	0.115 3(1)	0.861 4(5)	0.591 6(5)
C(1)	0.021 8(1)	1.148(1)	0.319 6(7)
C(2)	0.041 2(2)	1.248 1(8)	0.453 2(8)
C(3)	0.072 0(1)	1.147 2(8)	0.540 2(6)
C(4)	0.083 7(1)	0.949 0(7)	0.495 8(6)
C(5)	0.063 4(1)	0.853 3(8)	0.362 7(6)
C(6)	0.032 4(1)	0.952 5(9)	0.274 8(6)
C(7)	0.134 6(1)	0.676 4(7)	0.540 1(5)
C(8)	0.160 8(1)	0.691 2(8)	0.385 4(6)
C(9)	0.186 3(2)	0.887(1)	0.373 2(8)
C(10)	0.227 7(2)	0.819(1)	0.414 3(8)
C(11)	0.191 0(1)	0.522 7(8)	0.419 6(6)
C(12)	0.163 5(1)	0.592 0(7)	0.678 4(5)
C(13)	0.215 1(1)	0.725 8(9)	0.872 3(7)
C(14)	0.145 0(1)	0.462 6(7)	0.811 2(5)
C(15)	0.159 0(1)	0.267 5(7)	0.853 6(6)
C(16)	0.141 2(2)	0.153 2(8)	0.973 6(7)
C(17)	0.109 3(2)	0.230 5(9)	1.055 1(7)
C(18)	0.095 6(1)	0.422 3(9)	1.014 6(6)
C(19)	0.113 4(1)	0.542 9(8)	0.896 0(6)

Table 7 Selected bond lengths (Å) for compound **5**

Cl–C(1)	1.751(6)	O(1)–C(12)	1.414(5)
O(1)–C(13)	1.442(6)	O(2)–C(11)	1.437(6)
O(2)–C(12)	1.416(5)	O(3)–C(10)	1.428(8)
O(3)–C(11)	1.391(6)	N(1)–C(4)	1.398(6)
N(1)–C(7)	1.438(6)	C(1)–C(2)	1.380(8)
C(1)–C(6)	1.375(9)	C(2)–C(3)	1.383(7)
C(3)–C(4)	1.400(7)	C(4)–C(5)	1.379(7)
C(5)–C(6)	1.386(7)	C(7)–C(8)	1.565(7)
C(7)–C(12)	1.534(6)	C(8)–C(9)	1.542(8)
C(8)–C(11)	1.511(7)	C(9)–C(10)	1.482(9)
C(12)–C(14)	1.518(6)		

Table 8 Selected bond angles (°) for compound **5**

C(12)–O(1)–C(13)	116.2(3)	C(11)–O(2)–C(12)	111.4(3)
C(10)–O(3)–C(11)	108.5(5)	C(4)–N(1)–C(7)	121.9(4)
Cl–C(1)–C(6)	119.9(4)	Cl–C(1)–C(2)	118.8(5)
C(2)–C(1)–C(6)	121.3(5)	C(1)–C(2)–C(3)	118.3(5)
C(2)–C(3)–C(4)	121.6(5)	N(1)–C(4)–C(3)	117.0(4)
C(3)–C(4)–C(5)	118.4(5)	N(1)–C(4)–C(5)	124.5(4)
C(4)–C(5)–C(6)	120.5(5)	C(1)–C(6)–C(5)	119.9(5)
N(1)–C(7)–C(12)	111.9(4)	N(1)–C(7)–C(8)	117.4(4)
C(8)–C(7)–C(12)	102.9(4)	C(7)–C(8)–C(11)	102.7(4)
C(7)–C(8)–C(9)	116.4(4)	C(9)–C(8)–C(11)	103.7(5)
C(8)–C(9)–C(10)	105.1(5)	O(3)–C(10)–C(9)	106.0(5)
O(3)–C(11)–C(8)	107.5(4)	O(2)–C(11)–C(8)	107.9(4)
O(2)–C(11)–O(3)	111.2(4)	O(2)–C(12)–C(7)	104.6(3)
O(1)–C(12)–C(7)	105.4(3)	O(1)–C(12)–O(2)	111.6(4)
C(7)–C(12)–C(14)	115.4(4)	O(2)–C(12)–C(14)	107.9(4)
O(1)–C(12)–C(14)	111.6(3)		

Table 9 Fractional coordinates for compound **7a**

Atom	*x*	*y*	*z*
Cl	−0.140 18(9)	0.305 9(2)	0.390 5(2)
O(1)	0.322 4(3)	0.509 0(3)	0.563 6(5)
O(2)	0.380 0(2)	0.493 1(3)	0.143 0(5)
O(3)	0.268 1(2)	0.383 7(3)	0.000 5(5)
N(1)	0.189 4(2)	0.432 1(4)	0.366 7(6)
C(1)	−0.043 2(3)	0.346 6(5)	0.385 3(7)
C(2)	−0.020 1(3)	0.438 1(5)	0.301 7(7)
C(3)	0.057 3(3)	0.469 9(4)	0.296 0(6)
C(4)	0.111 4(3)	0.408 6(4)	0.372 8(6)
C(5)	0.087 9(3)	0.319 5(5)	0.465 0(8)
C(6)	0.009 6(3)	0.285 1(5)	0.467 5(8)
C(7)	0.228 6(3)	0.537 6(4)	0.330 8(6)
C(8)	0.258 8(3)	0.537 5(4)	0.164 6(6)
C(9)	0.194 2(3)	0.519 5(5)	0.010 7(7)
C(10)	0.228 6(4)	0.456 6(6)	−0.108 3(8)
C(11)	0.304 6(3)	0.444 0(4)	0.147 9(7)
C(12)	0.430 7(4)	0.414 1(6)	0.151(1)
C(13)	0.297 8(3)	0.575 7(4)	0.469 2(6)
C(14)	0.335 5(3)	0.691 3(4)	0.481 4(6)
C(15)	0.300 0(3)	0.777 4(5)	0.406 0(7)
C(16)	0.336 7(4)	0.883 2(5)	0.429 1(9)
C(17)	0.408 8(5)	0.907 4(6)	0.527(1)
C(18)	0.444 9(4)	0.824 3(8)	0.597(1)
C(19)	0.409 1(4)	0.718 6(6)	0.576 4(8)
ClB	−0.138 71(9)	0.129 9(2)	−0.112 7(2)
O(1)B	0.327 0(3)	1.139 6(3)	0.067 5(5)
O(2)B	0.380 1(2)	0.193 7(3)	−0.349 1(5)
O(3)B	0.266 1(2)	0.240 4(3)	−0.499 5(5)
N(1)B	0.192 0(2)	0.154 8(3)	−0.125 1(5)
C(1)B	−0.041 5(3)	0.133 3(5)	−0.115 7(7)
C(2)B	−0.017 1(3)	0.054 6(5)	−0.199 1(7)
C(3)B	0.059 9(3)	0.057 8(4)	−0.201 9(6)
C(4)B	0.113 8(3)	0.140 9(4)	−0.122 0(6)
C(5)B	0.088 8(3)	0.220 6(5)	−0.028 5(7)
C(6)B	0.011 8(3)	0.217 6(5)	−0.028 8(7)
C(7)B	0.231 7(3)	0.067 7(4)	−0.164 8(6)
C(8)B	0.260 6(3)	0.085 0(4)	−0.331 0(6)
C(9)B	0.196 7(3)	0.067 2(5)	−0.484 2(7)
C(10)B	0.228 1(3)	0.145 7(5)	−0.603 0(7)
C(11)B	0.302 5(3)	0.201 3(4)	−0.347 2(6)
C(12)B	0.425 3(3)	0.297 9(6)	−0.351 2(9)
C(13)B	0.300 8(3)	0.061 1(4)	−0.028 1(6)
C(14)B	0.337 1(3)	0.959 7(4)	−0.017 8(6)
C(15)B	0.410 9(3)	0.964 1(5)	0.077 8(7)
C(16)B	0.444 8(3)	0.872 3(5)	0.091 4(8)
C(17)B	0.408 1(4)	0.773 7(5)	0.018 4(9)
C(18)B	0.335 6(4)	0.768 5(5)	−0.076 4(8)
C(19)B	0.300 8(3)	0.860 9(4)	−0.094 7(6)

Table 10 Selected bond lengths (Å) for compound **7a**

Cl–C(1)	1.744(6)	O(1)–C(13)	1.209(7)
O(2)–C(11)	1.403(6)	O(2)–C(12)	1.429(9)
O(3)–C(10)	1.437(8)	O(3)–C(11)	1.419(6)
N(1)–C(4)	1.396(7)	N(1)–C(7)	1.439(6)
C(1)–C(2)	1.370(9)	C(1)–C(6)	1.386(9)
C(2)–C(3)	1.396(8)	C(3)–C(4)	1.384(8)
C(4)–C(5)	1.391(8)	C(5)–C(6)	1.409(8)
C(7)–C(8)	1.556(7)	C(7)–C(13)	1.531(6)
C(8)–C(9)	1.536(7)	C(8)–C(11)	1.540(8)
C(9)–C(10)	1.52(1)		

(d), 129.01 (d), 135.71 (s), 146.30 (s). Selected ^{1}H NMR NOE increments **H-3**: {H-3a}, 8.5; {H-6a}, 0.0; {Ph, H-*o*}, 3.4; {*p*-Cl-C_6H_4, H-*o*}, 15.5. **H-3a**: {H-3}, 10.4; {H-4}, 10.2; {H-6a}, 6.4. **H-4**: {H-3a}, 3.6; {H-4′}, nearly isochronous to H-4. **H-4′**: {N-H}, 0.8. **H-6a**: {H-3}, 0.9; {H-3a}, 14.5; {Ph, H-*o*}, 0.0. **N-H**: {H-4′}, 2.5; {*p*-Cl-C_6H_4, H-*o*}, 8.3. **Ph, H-*o***: {H-3}, 2.2; {H-6a}, 0.0. ***p*-Cl-C_6H_4, H-*o***: {H-3}, 8.8; {N-H}, 6.8; *m*/*z* 345 (M^+, 12%), 313 (50%), 209 (84%), 208 (93%), 166 (60%), 153 (60%), 138 (90%), 105 (58%), 83 (75%), 77 (93%), 69 (100%).

Table 11 Selected bond angles (°) for compound **7a**

C(11)–O(2)–C(12)	112.0(6)	C(10)–O(3)–C(11)	107.3(5)
C(4)–N(1)–C(7)	124.8(7)	Cl–C(1)–C(6)	118.8(6)
Cl–C(1)–C(2)	120.3(6)	C(2)–C(1)–C(6)	120.9(8)
C(1)–C(2)–C(3)	120.2(7)	C(2)–C(3)–C(4)	120.4(6)
N(1)–C(4)–C(3)	123.9(6)	C(3)–C(4)–C(5)	118.8(7)
N(1)–C(4)–C(5)	117.2(7)	C(4)–C(5)–C(6)	120.9(7)
C(1)–C(6)–C(5)	118.5(7)	N(1)–C(7)–C(13)	110.5(5)
N(1)–C(7)–C(8)	113.1(5)	C(8)–C(7)–C(13)	107.3(5)
C(7)–C(8)–C(11)	113.4(5)	C(7)–C(8)–C(9)	113.1(6)
C(9)–C(8)–C(11)	103.3(5)	C(8)–C(9)–C(10)	102.3(6)
O(3)–C(10)–C(9)	102.7(5)	O(3)–C(11)–C(8)	106.9(5)
O(2)–C(11)–C(8)	106.9(6)	O(2)–C(11)–O(3)	112.8(6)
O(1)–C(13)–C(7)	118.9(6)	C(7)–C(13)–C(14)	120.2(5)
O(1)–C(13)–C(14)	120.9(5)		

Reaction of **1b** *in the presence of* 1 *mol. eq. of* MeOH: *Formation of* **3b** (23%), **4b** (41%), **7b** (11%) *and* **11b** (11%). *trans*-(4-chlorophenyl)aminophenyl-[3′-(2′-methoxy)tetrahydrofuryl]methane (**7b**), m.p. 78–80 °C (from hexane) (Found: C, 68.15; H, 6.25; N, 4.35; Cl, 11.2. $C_{18}H_{10}NO_2Cl$ requires: C, 68.03; H, 6.30; N, 4.41; Cl, 11.18); δ_H 1.75 (m, H-4 and H-4′), 2.44 (m, H-3), 3.37 (s, OCH_3), 3.85 and 3.99 (multiplets, H-5 and H-5′), 4.15 (br d, H-α, $J_{\alpha,3}$ 8.8), 4.61 (br s, N-H), 4.95 (d, H-2, $J_{2,3}$ 2.7), 6.41 (m, *p*-Cl-C_6H_4, H-*o*), 7.00 (m, *p*-Cl-C_6H_4, H-*m*), 7.31 (m, 5 H, Ph). Selected ^{1}H NMR NOE increments **H-2**: {H-3}, 3.3; {H-α}, 8.7; {N-H}, 1.7; {MeO}, 7.5; {Ph, H-*o*}, 1.7. **H-3**: {H-2}, 2.5; {H-4′}, 10.6; {H-α}, 6.4; {N-H}, 10.0; {Ph, H-*o*}, 5.6. **H-4**: {H-4′}, nearly isochronous to H-4; {H-α}, 3.8; {Ph, H-*o*}, 2.1. **H-4′**: {H-3}, 3.8. **H-α**: {H-2}, 2.5; {H-3}, 5.6; {H-4}, 2.1; {Ph, H-*o*}, 7.4; {*p*-Cl-C_6H, H-*o*} 11.9. **N-H**: {H-3}, 5.8; {Ph, H-*o*}, 2.9; {*p*-Cl-C_6H_4, H-*o*}, 9.7. **MeO**: {H-2}, 2.0. **Ph, H-*o***: {H-3}, 1.5; {H-α}, 2.8. ***p*-Cl-C_6H_4, H-*o***: {H-α}, 11.7; {N-H}, 8.7; *m*/*z* 317 (M^+, 12%), 216 (100%).

cis-(4-chlorophenyl)aminophenyl-[3′(2′-methoxy)tetrahydrofuryl]methane (**8**), m.p. 144–5 °C (from EtOH) (Found: C, 67.9; H, 6.2; N, 4.4; Cl, 11.15. $C_{18}H_{20}NO_2Cl$ requires: C, 68.03; H, 6.30; N, 4.41; Cl, 11.18); δ_H 1.91 (m, H-4 and H-4′), 2.61 (m, H-3), 3.25 (s, OCH_3), 3.88 and 4.04 (m, H-5 and H-5′), 4.30 (br s, N-H), 4.36 (br d, H-α, $J_{\alpha,3}$ 6.3), 4.81 (d, H-2, $J_{2,3}$ 1.7), 6.40 (m, *p*-Cl-C_6H_4, H-*o*), 7.00 (m, *p*-Cl-C_6H_4, H-*m*), 7.32 (m, 5 H, Ph). Selected ^{1}H NMR NOE increments **H-2**: {H-3}, 3.3; {H-α and/or N-H, nearly isochronous}, 12.5; {MeO}, 9.0; {Ph, H-*o*}, 3.7. **H-3**: {H-2}, 2.8; {H-4′}, 13.7; {H-2 and/or N-H}, 15.2; {Ph, H-*o*}, 5.8. **H-4**: {H-4′}, nearly isochronous to H-4; {H-α and/or N-H}, 3.8; {Ph, H-*o*}, 2.0. **H-4′**: {H-3}, 5.0. **H-α**: {H-3}, 6.4; {H-4}, 3.3; {Ph, H-*o*}, 4.8. **N-H**: {H-3}, 4.5; {H-4}, 3.3; {Ph, H-*o*}, 3.9; {*p*-Cl-C_6H_4, H-*o*}, 10.5. **MeO**: {H-2}, 2.7. **Ph, H-*o***: {H-2}, 1.0; {H-3}, 1.3; {H-α}, 3.3; {H-4}, 3.3. ***p*-Cl-C_6H_4, H-*o***: {H-α and/or N-H}, 21.1; *m*/*z* 317 (10%, M^+), 216 (100%).

Crystal Structure Analysis. Data Collection and Processing.—Diffractometer Philips PW 1000, Mo-Kα radiation, λ = 0.7107, Multan 80, blocked least square. Crystal data for compounds **5** and **7a** are reported in Tables 5–11.

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