of palladium acetate is reported to produce bis-*exo*-cyclopropane.[25c,27b]

Experimental Section

1-Acetoxy-3-(trimethylsilyl)-2-propanone (4) (X = OAc, R = CH_3). [(Trimethylsilyl)methyl]magnesium chloride [prepared from 6.1 g (50 mmol) of (trimethylsilyl)methyl chloride, 1.22 g (50 mmol) of magnesium turnings and one crystal of iodine in 60 mL of ether] was added dropwise to 10.9 g (50 mmol) of acetoxyacetic anhydride in 60 mL of ether at −78 °C. The mixture was kept at −78 °C for 2 h, warmed to 0 °C within 10 min, and hydrolyzed immediately with 100 mL of aqueous saturated sodium bicarbonate solution. The two-phase system was stirred until the evolution of carbon dioxide ceased. The aqueous layer was extracted with 100 mL of ether once. The combined organic layers were dried with sodium sulfate. After evaporation of the solvent, the residue was fractionally distilled under reduced pressure to give 5.3 g (56%) of the title compound, bp 75 °C (1 Torr). IR ($CHCl_3$): 1745, 1710, 840 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz): δ 4.57 (s, 2 H), 2.20 (s, 2 H), 2.17 (s, 3 H), 0.16 (s, 9 H). Calcd for $C_8H_{16}O_3Si$: 188.0869. Found: 188.0867.

1-[(Methoxycarbonyl)oxy]-3-(trimethylsilyl)-2-propanone (4) (X = OCO_2CH_3, R = CH_3). An identical procedure to the above but utilizing 50 mmol of the mixed anhydride derived from [(methoxycarbonyl)-oxy]acetic acid and methyl chloroformate gave 1.59 g (16%) of the title compound, bp 89 °C (1 Torr). IR ($CHCl_3$): 1740, 840 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz): δ 4.58 (s, 2 H), 3.83 (s, 3 H), 2.22 (s, 2 H), 0.17 (s, 9 H).

1-Acetoxy-3-(dimethylphenylsilyl)-2-propanone (4) (X = OAc, R = Ph). An identical procedure to the above but utilizing [(dimethylphenylsilyl)methyl]magnesium chloride gave 11.1 g (89%) of the title compound, bp 135 °C (0.5 Torr). IR ($CDCl_3$): 1745, 1710, 1370, 1195 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz): δ 7.56-7.49 (m, 2 H), 7.43-7.35 (m, 3 H), 4.38 (s, 2 H), 2.40 (s, 2 H), 2.10 (s, 3 H), 0.44 (s, 6 H). Calcd for $C_7H_{13}O_3Si$: 173.0634. Found: 173.0635.

General Cyclopropanation. All reactions were run on a 1.0-mmol scale. To a mixture of 188 mg (1.0 mmol) of the silyl acetate **4** (X = OAc, R = CH_3) and 2.0 mmol of the olefin was added 0.5 mL (5 mol %) of a freshly prepared catalyst solution [catalyst solution: 260 mg (0.25 mmol) of $dba_3Pd_2{\cdot}CHCl_3$ and 524 mg (2.0 mmol) of triphenylphosphine in 5 mL of benzene-d_6]. The mixture was heated to 80 °C whereby enol silyl ether forms in less than 1 min. After complete disappearance of enol silyl acetate as determined by NMR spectroscopy, 1 h for norbornadiene, 20 h for norbornene, and 2 h for dicyclopentadiene, the mixture was filtered through a pad of silica gel and washed with ether. Flash chromatography on silica gel with 1:2 (v/v) ether/hexane as eluant gave the pure products.

Cyclopropanation of Norbornadiene. 3-Acetyltricyclo[3.2.1.$0^{2,4}$]-6-octene (8). Yield: 83 mg (56%) of oil that crystallizes at −12 °C. IR ($CDCl_3$): 1685 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz): δ 6.41 (m, 2 H), 2.92 (m, 2 H), 2.86 (t, J = 2.2 Hz, 1 H), 2.19 (s, 3 H), 1.67 (m, 2 H), 1.18 (dm, J = 9.9 Hz, 1 H), 1.03 (dm, J = 9.9 Hz, 1 H). Calcd for $C_{10}H_{12}O$: 148.0888. Found: 148.0882.

3,7-Diacetyltetracyclo[3.3.1.$0^{2,4}$.$0^{6,8}$]nonane (9). Yield: 16.9 mg (17%) of crystalline solid, mp 154-5 °C. IR ($CDCl_3$): 1690 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 2.55 (m, 2 H), 2.31 (m, 2 H) 2.17 (s, 6 H), 1.69 (m, 4 H), 0.57 (m, 2 H). Calcd for $C_{13}H_{16}O_2$: 204.1150. Found: 204.1158.

Cyclopropanation of Norbornene. 3-Acetyltricyclo[3.2.1.$0^{2,4}$]octane (10). Yield: 91 mg (61%) of crystalline solid, mp 39-41 °C (lit. mp 38-40 °C). IR ($CDCl_3$): 1690 cm^{-1}. ^1H NMR: δ 2.27 (m, 2 H), 2.11 (s, 3 H), 1.80 (m, 1 H), 1.29 (m, 2 H), 1.40-1.20 (m, 4 H), 0.86 (dm, J = 10.9 Hz, 1 H), 0.62 (dm, J = 10.9 Hz, 1 H). Calcd for $C_{10}H_{14}O$: 150.1045. Found: 150.1049.

Cyclopropanation of Dicyclopentadiene. 9-Acetyltetracyclo[5.3.1.$0^{2,6}$.$0^{8,10}$]-3-undecane (13). Yield: 128 mg (68%) of oil. IR ($CDCl_3$): 1685 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz): δ 5.73 (dm, J = 5.8 Hz, 1 H), 5.54 (dm, J = 5.8 Hz, 1 H), 2.16 (s, 3 H), 2.35-2.15 (m, 3 H), 3.10 (m, 1 H), 2.57 (m, 1 H), 2.42 (1 H, m), 1.96 (1 H, m), 1.52 (dm, J = 7.0 Hz, 1 H), 1.23 (dm, J = 7.0 Hz, 1 H), 1.08 (dm, J = 10.6 Hz, 1 H), 0.94 (dm, J = 10.6 Hz, 1 H). Calcd for $C_{13}H_{16}O$: 188.1183. Found: 188.1188.

Diimide Reduction of 8. Hydrazine hydrate (1.2 mL) was added to a solution of 15 mg (0.1 mmol) of olefin **8** in 1.2 mL of ethanol containing 5 mg of cupric acetate. After stirring for 24 h at room temperature, at which point TLC indicated complete conversion, the mixture was extracted with hexane. The hexane extracts were washed with water, dried over sodium sulfate, evaporated in vacuo, and chromatographed through a short column of silica gel with 1:2 (v/v) of ether/hexane as eluant to give pure saturated ketone **10**.

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Effect of Through-Bond Interaction on Conformation and Structure of Some *N*-Arylpiperidone and *N*-Aryltropanone Derivatives. 2[1]

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Abstract: Through-bond interaction (TBI) in *N*-aryl-4-piperidone derivatives in which the carbonyl group is modified to enhance its electron deficiency is found to stabilize the sterically disfavored axial arrangement of the aryl group, an arrangement also found in the corresponding tropanone derivatives, where it may, however, be favored sterically. In the *N*-arylpiperidone derivatives the relative stability of conformations with axial and equatorial orientation of the phenyl group is markedly influenced by para substitution in the aryl group thus indicating the possibility of long-range stereoelectronic conformational control mediated by through-bond interaction across three σ-bonds. Theoretical predictions regarding the influence of TBI on bond lengths are confirmed in the crystal structures of the compounds studied, while strong TBI is also found to result in significant pyramidalization at C4.

The term through-bond interaction (TBI) was introduced in 1968 by Hoffmann et al.[2,3] to designate the intramolecular interaction between functional groups via the intervening σ-bonds. Theoretical studies[2-5] show that, e.g., the TBI between two nitrogen lone pairs separated by three σ-bonds will be optimized for the

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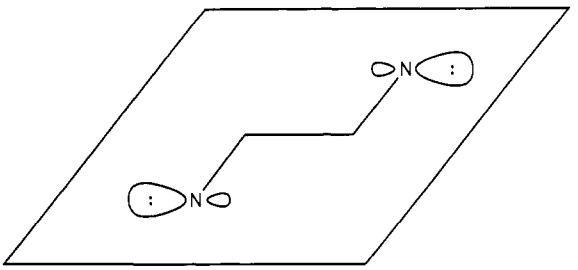
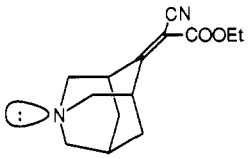


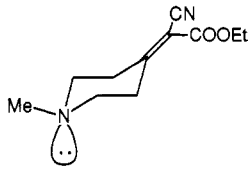
Figure 1. Required orientation for optimal TBI between two nitrogen lone pairs separated by three σ-bonds.

Chart I



1

λ_{CT} = 316 nm
ϵ = 4900 $M^{-1}cm^{-1}$
(n-hexane, 20 ° C



2

no CT-absorption

conformation depicted in Figure 1. The interacting orbitals (i.e., the lone pairs) should be antiparallel to the central C–C bond for an optimal interaction, this by the way is directly related to the prefered "antiperiplanar" arrangement of functional group orbitals in reactions like Grob fragmentation[6] and fragmentation of 1,4-diradicals.[7]

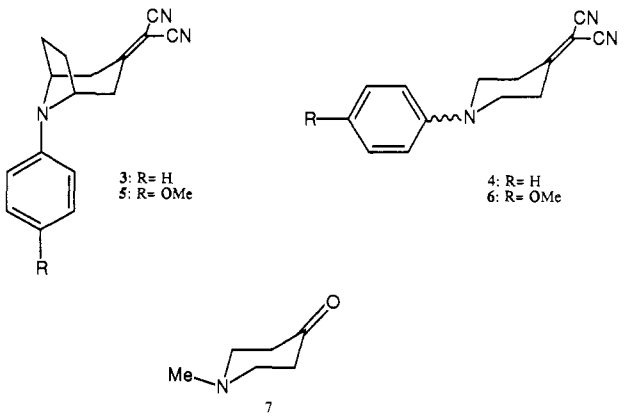
Many spectroscopic studies have shown that TBI between a pronounced one electron donor (D) and acceptor (A) over three or more σ-bonds, may manifest itself by the appearance of a new additional absorption in the UV–vis absorption spectra.[8-10] This absorption is assigned as an intramolecular charge-transfer (CT) absorption, i.e., an optical transition accompanied by electron transport from donor to acceptor. Since this CT absorption is a manifestation of TBI, it should therefore have the same conformational dependence. The β-aminoketones studied by Hudec and Cookson[11-13] are among the earliest examples of systems with an intramolecular CT absorption which was shown to depend strongly on the conformation according to the TBI model put forward by Hoffmann et al.[2,3]

Another example of the conformational requirements for CT absorption mediated by TBI is revealed by comparison of compounds **1** and **2**[9,10] (see Chart I). Both compounds contain a trialkyl amine as a potential donor and a 1-cyano-1-carbethoxyethylene as acceptor separated by three σ-bonds.

The nitrogen lone pair in **1** is forced into an equatorial orientation with respect to the connecting piperidine ring, thus allowing for the required antiparallel orientation to the central C–C bond coupling donor and acceptor and observation of a strong CT absorption was reported.[9,10]

Although **2** contains the same donor and acceptor, it was reported to display no CT absorption.[9,10] From sterical considerations **2** is expected to adopt a conformation with the methyl group

Chart II



3: R= H
5: R= OMe

4: R= H
6: R= OMe

7

Table I. CT Absorption Data for **3–6** in CH_2Cl_2 (293 K)

compd	λ_{CT} (nm)	ϵ ($M^{-1}\cdot cm^{-1}$)
3	360	6100
4	352	3065
5	378	5100
6	368	2130

equatorial and this was assumed[9,10] to suppress TBI sufficiently to make any CT absorption undetectable. In a PES study by Rademacher et al. on cyclic amino ketones, the absence of TBI in *N*-methylpiperidin-4-one (**7**) (see Chart II) was confirmed.[14] These and other experiments[15,16] support the theoretical prediction that TBI should strongly depend on the conformation of the system.

While much experimental verification of the conformational dependence of TBI has thus been put forward, the occurrence of the reverse effect, i.e., changes in the relative population and barriers to interconversion of conformations, has mainly been hinted at,[7] although structural effects of TBI pertaining to the elongation of "prestrained" bonds have been amply discussed.[17-21]

The present paper describes a study on the effect of TBI on the conformation and structure of four unstrained compounds which all consist of a one-electron donor and acceptor separated by three σ-bonds in a well-defined arrangement.

Results and Discussion

Mutual Dependence of TBI and Conformational Preference. Compounds **3–6** (see Chart II) have been synthesized (see Experimental Section), all containing a 1,1-dicyanoethylene chromophore as a strong one-electron acceptor (A) and an aryl nitrogen as donor (D). As reported earlier,[1] compound **3** shows an extremely strong CT absorption (see Table I) in solution as the result of the TBI between D and A. Furthermore it was found[1] that the intensity of this CT absorption remains virtually unchanged upon cooling. These observations indicate that **3** adopts—in solution—a conformation which allows for strong TBI implying (vide supra) that the phenyl group occupies an axial position with respect to the piperidine ring. This leads to the required antiparallel orientation of the nitrogen lone pair to the central C–C bond, thus allowing optimal TBI.

The fact that the N-substituent in **3** adopts an axial position is not surprising since steric hindrance between this group and the exo protons of the ethylene bridge disfavors the equatorial

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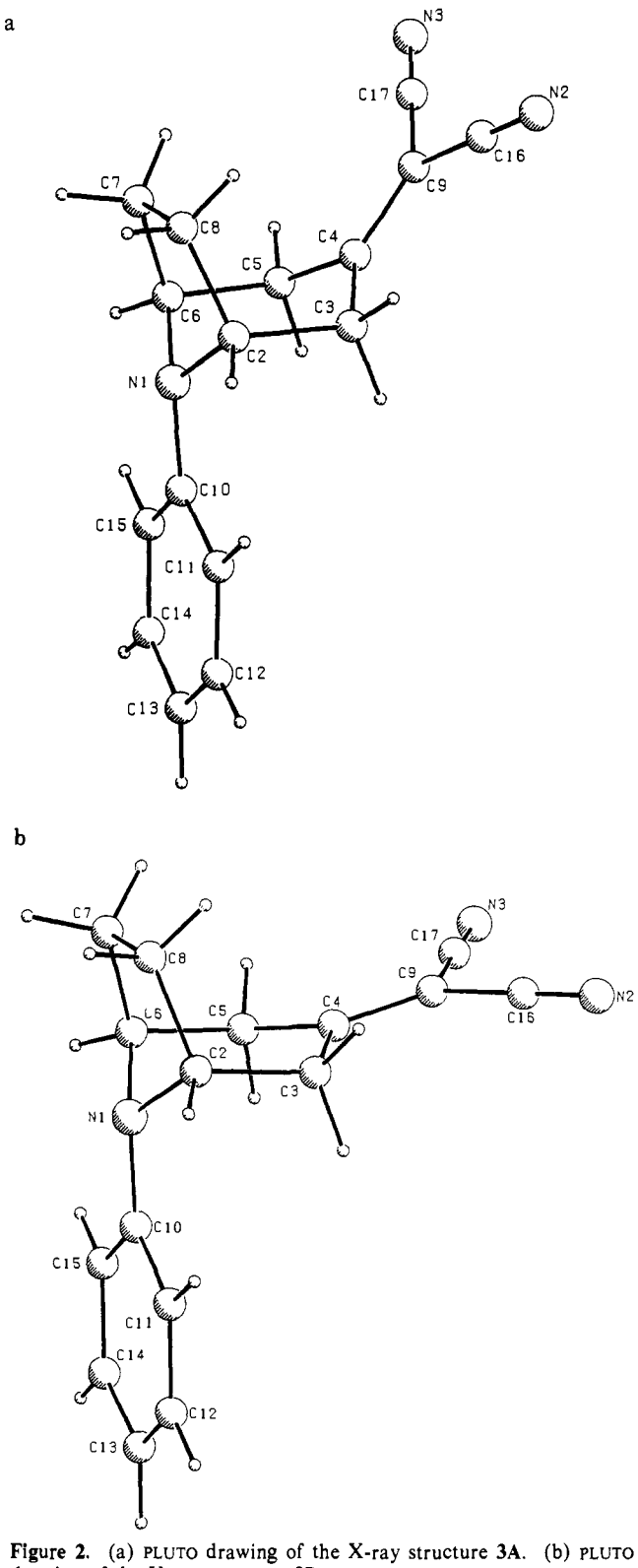


Figure 2. (a) PLUTO drawing of the X-ray structure **3A**. (b) PLUTO drawing of the X-ray structure **3B**.

orientation. X-ray analysis of **3** indeed shows an axial conformation (cf. Figure 2). Interestingly the unit cell turned out to contain two slightly different conformations (Figure 2 (parts a and b)), but while other structural parameters differ (vide infra) the configuration is axial at N1 in both. That this is also the preferred conformation in solution was inferred from the minor[1] temperature dependence of the CT absorption.

Surprisingly, although from sterical considerations an axial orientation of the phenyl group seems hardly accessible in an *N*-phenylpiperidine derivative, compound **4** shows also a rather strong CT absorption. In this case, however, upon lowering the

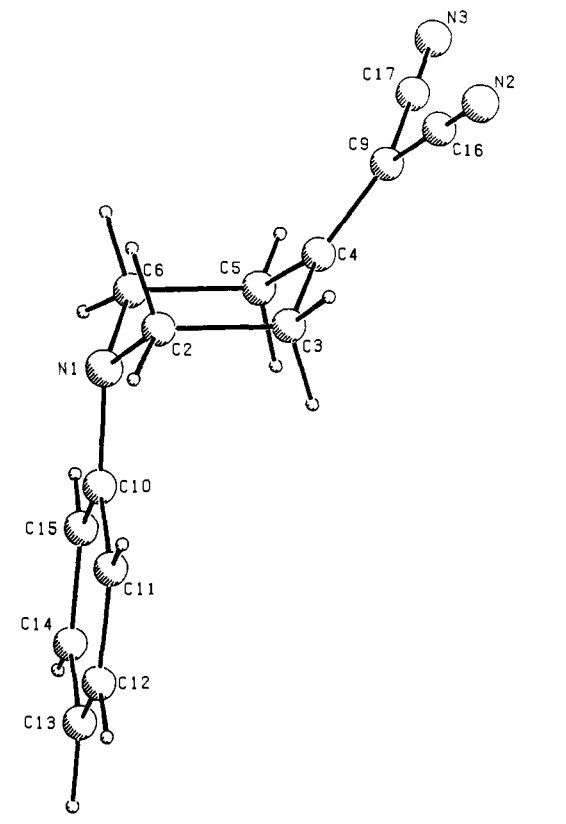
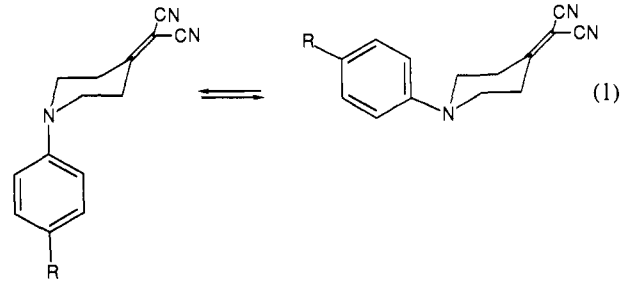


Figure 3. PLUTO drawing of the X-ray structure of **4**.

temperature (range studied 293–183 K in CH_2Cl_2), the CT absorption increases significantly (ca. 36%), while the CT absorption of **3** increases only slightly (ca. 14%) in this solvent.[22] These observations are unexpected, because the equatorial conformation of phenylcyclohexane is about 2.7 kcal/mol more stable than the axial conformation,[23] and this difference tends to be even larger for N-substituted piperidines.[24] In an equatorial conformation, however, little if any TBI is expected to occur.

These facts forced us to conclude[1] that there is a dynamic conformational equilibrium between **4eq** and **4ax** (cf. equilibrium 1). Furthermore, the population of the axial conformer, in which



(1)

TBI and therefore the CT absorption is optimized, must increase at lower temperatures. This requires that in solution the enthalpy of **4ax** lies below that of **4eq**, notwithstanding the severe steric hindrance in such axial orientation. Since this was certainly a fascinating and—for the time being—tentative conclusion, it was extremely gratifying to find now that X-ray analysis of **4** shows the axial conformation to be preferred in the solid state (cf. Figure 3) as well!

Whereas as early as 1972 the possible influence of TBI on the relative energies of conformations was suggested by Hoffmann

(22) The CT absorption of **4** in 2-Me-THF (range studied 293–193 K) was found to increase by 45%, while the CT absorption of **3** increased slightly (ca. 12%).

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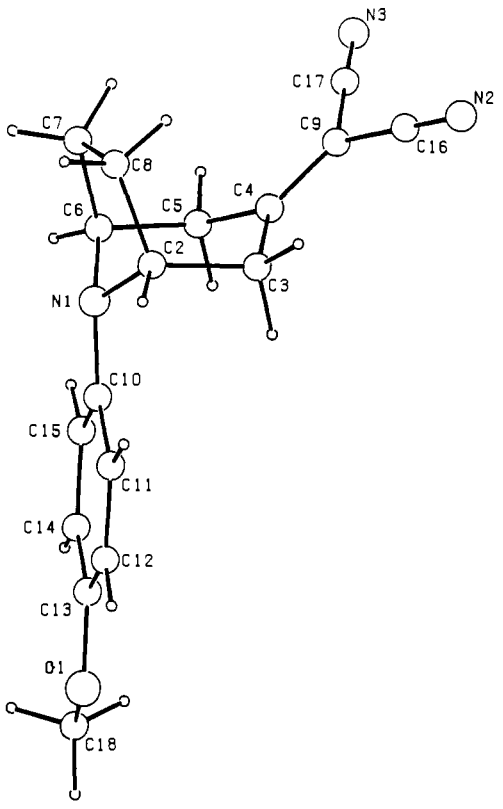

Figure 4. PLUTO drawing of the X-ray structure of **5**.

et al.[7], the behavior of **4** now appears to constitute the first experimental verification of this effect. If so, modifications of the tendency of the functionalities in systems like **4** to enter into TBI, e.g., by changes in the donor, must influence the conformational equilibrium (1).

Comparison of the first vertical ionization potential of trimethylamine (8.5 eV[25]) with *N,N*-dimethylaniline (7.45 eV[26]) indicates that the amino group in **1–2** is a significantly weaker one-electron donor than in **3–4**. Furthermore, the electron acceptor in **1** and **2** is slightly weaker than the one incorporated in **3** and **4**.[10] Apparently these structural modifications significantly diminish the relative stability of conformations that allow for TBI, thereby resulting in the absence of any detectable CT absorption for **2** in solution.

As a first step toward a further systematic investigation of such long-range stereoelectronic effects, compounds **5** and **6** have been synthesized that differ from **3** and **4** by introduction of a *p*-methoxy substituent in the phenyl chromophore. Such a *p*-methoxy substituent lowers the ionization potential of the donor moiety as evident upon comparison of the first vertical ionization potentials of *N,N*-dimethylaniline (7.45 eV[26]) and *N,N*-dimethyl-*p*-anisidine (7.18 eV[27]) and should result in a red shift of the CT absorption for **5**.

The *p*-methoxy group, however, not only influences the ionization potential of the donor moiety but also the electron density at N1 in the highest occupied donor MO ($HOMO_D$). According to calculations[28] based on the L.C.B.O. MO method described by Distefano et al.[29] the *p*-methoxy group reduces the orbital coefficient at N1 in $HOMO_D$ from 0.78 in *N,N*-dimethylaniline to 0.65 in *N,N*-dimethyl-*p*-anisidine. The diminished electron density at N1 should result in a decrease of the TBI. Thus **5**, which presumably adopts an axial conformation in solution as well as (vide infra) in solid state, is predicted to display a weaker—but red shifted—CT transition than **3**.

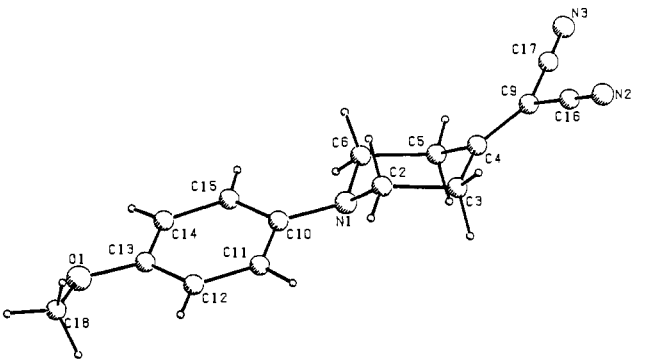

Figure 5. PLUTO drawing of the X-ray structure of **6**.

Table II. Selected Bond Lengths (Å) for **3–6**[a]

bond	3A	3B	4	5	6
C10–N1	1.406 (2)	1.401 (2)	1.412 (2)	1.413 (1)	1.423 (2)
N1–C6	1.458 (2)	1.467 (2)	1.461 (2)	1.460 (1)	1.459 (2)
N1–C2	1.458 (2)	1.467 (2)	1.459 (2)	1.464 (1)	1.461 (2)
C2–C3	1.559 (2)	1.538 (2)	1.546 (2)	1.550 (2)	1.526 (2)
C5–C6	1.559 (2)	1.538 (2)	1.542 (2)	1.546 (2)	1.529 (2)
C3–C4	1.493 (2)	1.505 (2)	1.494 (2)	1.502 (2)	1.489 (2)
C4–C5	1.493 (2)	1.505 (2)	1.495 (2)	1.496 (2)	1.489 (2)
C4–C9	1.355 (3)	1.348 (2)	1.347 (2)	1.344 (2)	1.345 (2)
C9–C16	1.438 (2)	1.438 (2)	1.438 (2)	1.432 (2)	1.434 (2)
C9–C17	1.438 (2)	1.438 (2)	1.436 (2)	1.440 (2)	1.444 (2)
C16–N2	1.134 (2)	1.141 (2)	1.141 (2)	1.143 (2)	1.141 (2)
C17–N3	1.134 (2)	1.141 (2)	1.139 (2)	1.140 (2)	1.139 (2)
C10–C11	1.395 (2)	1.395 (2)	1.395 (2)	1.401 (2)	1.397 (2)
C10–C15	1.395 (2)	1.395 (2)	1.399 (2)	1.392 (1)	1.389 (2)
C11–C12	1.384 (2)	1.382 (2)	1.387 (3)	1.373 (2)	1.388 (2)
C12–C13	1.372 (2)	1.373 (2)	1.373 (3)	1.392 (2)	1.382 (2)
C13–C14	1.372 (2)	1.373 (2)	1.372 (3)	1.378 (2)	1.370 (2)
C14–C15	1.384 (2)	1.382 (2)	1.386 (3)	1.396 (2)	1.386 (2)
C6–C7	1.527 (2)	1.526 (2)		1.534 (2)	
C7–C8	1.530 (2)	1.528 (3)		1.537 (2)	
C2–C8	1.527 (2)	1.526 (2)		1.529 (2)	
C13–O1				1.374 (1)	1.378 (2)
O1–C18				1.426 (2)	1.420 (2)

[a] Standard deviations are in parentheses.

Compound **5** in solution indeed shows a CT absorption at longer wavelength compared to **3** (see Table I). Lowering the temperature has only a minor effect as for **3**. As expected X-ray analysis (cf. Figure 4) reveals an axial conformation.

The significantly lower extinction coefficient of **5** compared to **3** indicates that the donor modification results in an overall decrease of the amount of TBI between D and A. Thus it is of great interest to investigate the result of this modification in **6** where an axial conformation could only prevail by the grace of sufficiently strong TBI as in **4**. In contrast to **4** the CT absorption of **6** is almost temperature independent and less than 50% of that in the tropane analogon, indicating that the axial and equatorial conformations now have almost equal stability with probably a slight preference for the equatorial conformation. Furthermore, X-ray analysis of **6** (cf. Figure 5) shows an equatorial conformation!

Of course, the fact that only the equatorial conformation is detected in the solid state for **6** and the axial conformation for **4** provides no unequivocal proof for a change in the relative stability of these conformers in an isolated state. But in combination with the reduced intensity of the CT absorption in solution it makes plausible a reduction of the relative stability of the axial conformer in **6**.

Thus the behavior of **3–6** not only reconfirms that TBI is conformation dependent but also proves for the first time that the reverse holds as well: the relative stabilities of conformations and therefore the preference for one conformation can be affected by TBI!

X-ray Structure Parameters in Relation to TBI. The availability of the X-ray structures of **3–6** makes it possible to investigate the

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Table III. Selected Bond Angles (deg) for **3–6**[a]

angle	3A	3B	4	5	6
C10–N1–C2	121.9 (1)	121.5 (1)	118.9 (2)	120.7 (1)	115.9 (1)
C10–N1–C6	121.9 (1)	121.5 (1)	118.6 (2)	122.0 (1)	116.4 (1)
C2–N1–C6	104.1 (1)	103.4 (1)	109.9 (2)	103.4 (1)	111.3 (1)
Σ	347.9	346.4	347.4	346.1	343.6
N1–C2–C3	109.6 (2)	109.6 (1)	111.2 (2)	109.6 (1)	111.1 (2)
C2–C3–C4	108.1 (2)	112.8 (1)	109.2 (2)	108.6 (1)	111.3 (2)
C3–C4–C5	115.0 (1)	118.5 (1)	114.0 (2)	115.4 (1)	114.7 (2)
C4–C5–C6	108.1 (2)	112.8 (1)	108.8 (2)	109.8 (1)	112.6 (2)
C5–C6–N1	109.6 (2)	109.6 (1)	110.9 (2)	110.2 (1)	110.9 (1)
C3–C4–C9	122.3 (1)	120.6 (1)	123.0 (2)	122.3 (1)	121.8 (2)
C5–C4–C9	122.3 (1)	120.6 (1)	122.8 (2)	122.2 (1)	123.5 (2)
C4–C9–C16	122.2 (2)	122.7 (1)	122.2 (2)	122.5 (1)	122.2 (2)
C4–C9–C17	122.2 (2)	122.7 (1)	122.6 (2)	122.9 (1)	122.9 (2)
C9–C16–N2	179.0 (1)	178.9 (1)	179.6 (2)	178.6 (2)	179.1 (1)
C9–C17–N3	179.0 (1)	178.9 (1)	179.4 (2)	178.6 (1)	177.3 (2)
N1–C10–C11	120.7 (1)	121.1 (1)	121.8 (2)	119.5 (1)	120.5 (1)
N1–C10–C15	120.7 (1)	121.1 (1)	121.1 (2)	122.9 (1)	122.7 (2)
N1–C2–C8	101.6 (2)	101.7 (2)		102.3 (1)	
N1–C6–C7	101.6 (2)	101.7 (2)		101.6 (1)	
C3–C2–C8	111.1 (2)	113.2 (2)		112.0 (1)	
C5–C6–C7	111.1 (2)	113.2 (2)		111.3 (1)	
C6–C7–C8	104.6 (2)	104.7 (2)		104.4 (1)	
C2–C8–C7	104.6 (2)	104.7 (2)		104.2 (1)	
C13–O1–C18				117.4 (1)	116.9 (2)
C12–C13–O1				115.1 (1)	125.3 (2)
C14–C13–O1				126.0 (1)	116.1 (2)

[a] Standard deviations are in parentheses.

Table IV. Angles between Calculated Least-Square Planes and Distances of N1 and C4 to the Central Plane a[a]

	3A	3B	4	5	6	7
angle between planes a and b	46.3	23.7	49.0	42.1	42.0	45.8
angle between planes a and c	62.9	64.7	55.1	63.1	53.9	52.5
distance N1 to plane a	0.798	0.823	0.687	0.808	0.666	0.651
distance C4 to plane a	0.580	0.310	0.614	0.538	0.538	0.592

[a] Angles in deg, distances in Å; plane a defined by C2, C3, C5, and C6; plane b defined by C3, C4, and C5; plane c defined by C2, N1, and C6.

influence of TBI on structure parameters in the solid state. Full crystallographic data and the final coordinates and equivalent thermal parameters for the non-hydrogen atoms are listed in the Supplementary Material (Tables S1 and S2), while selected bond lengths and angles are given in Tables II and III.

The asymmetric unit of **3** contains two half molecules (**3A** and **3B**) and a mirror plane through C13, C10, N1, C4, and C9 at $z = 1/4$ generating the other halves, whereas the asymmetric units of **4–6** all contain one molecule.

Configuration of the Piperidine Ring. The occurrence of TBI is thought to be very sensitive to the orientation of the interacting donor and acceptor orbitals with respect to the σ-relay connecting them and for the configuration of that relay. Consequently, the conformation of the central piperidine ring will be examined first.

Least-square planes have been calculated through (C2,C3,C5,C6), (C2,N1,C6), and (C3,C4,C5) to define the ring. The angles between the calculated planes and the distance of N1 and C4 to the central (C2,C3,C5,C6) plane are listed in Table IV, together with the corresponding calculated values for the MM2P optimized structure of *N*-methylpiperidin-4-one (**7**).[30]

As can be seen, **3B** shows a flattening of the C2-6 part of the molecule, leading to a decrease of the angle between the plane (C3,C4,C5) and the central plane and of the distance of C4 to this plane. A possible explanation for this flattening may be found in the orientation of **3B** toward the molecule generated by the symmetry operations $^1/_2 + x, ^1/_2 - y, ^1/_2 - z$ and $^1/_2 + x, ^1/_2 -$

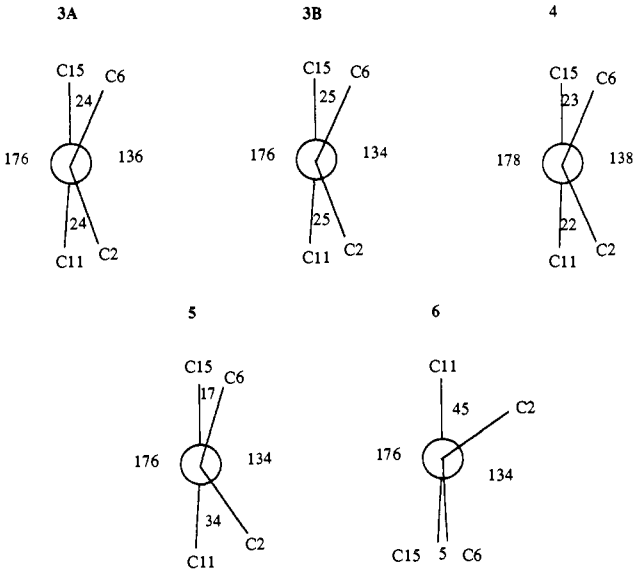

Figure 6. Newman projections along the N1–C10 bond for compounds **3–6**.

y, z. The intermolecular distance between N1 and the generated C17 (and C16) amounts to 3.265 Å. In order to release the intermolecular repulsion between N1 and the nitril groups of the acceptor of the generated molecule, C4 "moves away", leading to flattening of the ring at C4. Because no other intermolecular distances below 3.3 Å could be found, this repulsion offers a plausible explanation for the observed flattening of the piperidine ring of **3B**.

This flattening, leading to a change in orientation of the π-system of the acceptor toward the central C–C bond, should have a profound influence on the TBI between D and A. In the ultimate case of complete flattening of this C2-6 part of the molecule, the σ- and π-systems become orthogonal, resulting in an absence of TBI.

In contrast, the piperidine ring in **3A** adopts a very normal chair conformation. The angles between the planes are rather similar for **3A** and **5**. The same holds for **4** and **6**. Introducing the bridge across C2 and C6 results in a slight increase of the distance of N1 to the central plane. In conclusion, in all systems, except **3B**, the piperidine ring has a normal chair conformation.

Configuration at N1. In all compounds, the piperidine nitrogen N1 adopts a flattened pyramidal configuration, as indicated by the sum of the bond angles of N1 (up to 348° in **3A**; cf. Table III). The angle C2–N1–C6 is significantly smaller for **3** and **5** compared to **4** and **6** as the result of the ethylenic bridge in the tropane derivatives.

The orientation of the phenyl group is indicated in Figure 6 by the Newman projections along the N1–C10 bond. The aromatic π-system and the N1 lone pair in **3** and **4** are parallel, allowing an extensive overlap. This is in contrast with the strongly twisted orientation of the phenyl group in *N*-phenylpiperidine as proposed by Houk et al. from PES data.[31] The introduction of the methoxy group in **5** and **6** is accompanied by a twist of the phenyl group round N1–C10 (cf. Figure 6), thus decreasing the interaction between the two electronic systems. The twisting is accompanied by a slight increase of pyramidalization at N1.

The twist is greatest in the equatorial structure **6** which also shows the strongest pyramidalization at N1 (sum of bond angles 344°; see Table III). It is plausible, therefore, that the observed flattening of N1 is related to conjugative interaction within the anilino chromophore.

Elongation of the "Central" C–C Bond under the Influence of TBI. As mentioned in the introduction, TBI could manifest itself in an elongation of the central C–C bond. In order to establish this effect, one needs to know the "normal" bond lengths in pi-

(30) These calculated values were used in order to compare the experimental X-ray structures with the general accepted standard geometries provided by molecular mechanics.

(31) Rozeboom, M. D.; Houk, K. N.; Searles, S.; Seyedrezai, S. E. *J. Am. Chem. Soc.* **1981**, *104*, 3448.

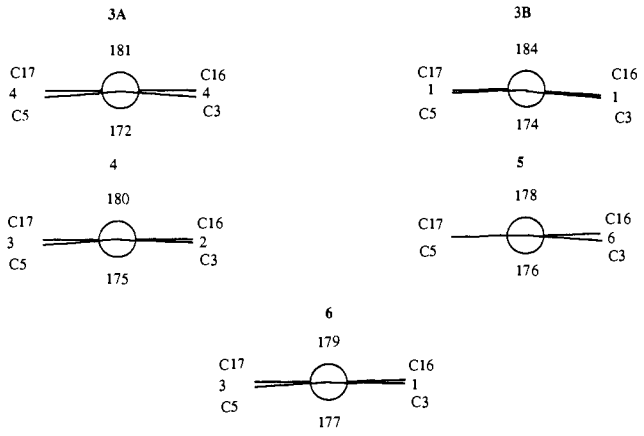

Figure 7. Newman projections along the C4–C9 bond for compounds **3–6**.

peridine and tropane derivatives. A computer search in the Cambridge Structural Data Base resulted in about 15 crystal structures of tropane derivatives. The central C–C bond of the piperidine ring in these compounds has a length of 1.53–1.54 Å, irrespective of an axial or equatorial orientation of the N-substituent. This is slightly longer than the accepted value of 1.52–1.53 Å in the piperidine derivatives. The difference is probably due to the introduction of the bridge across C2 and C6. The observed central C–C bond length of 1.559 Å in **3A** is therefore significantly longer than normal, being one of the first examples of bond elongation caused by TBI over three σ-bonds in relatively simple unstrained organic molecules!

The occurrence of two different structures of **3** in one and the same crystal (and therefore obtained under completely identical conditions!) yields a unique opportunity to establish the effect of TBI on bond lengths. As mentioned above, the flattening of the C2-6 part of the molecule in **3B** should result in a decrease of TBI between donor and acceptor. The central C–C bond in **3B** has a length of 1.538 Å, which is (almost) the normal value for tropane derivatives. This observation offers another very convincing example of the very subtle conformational requirements of TBI.

Recalling the UV data, introduction of the *p*-methoxy group in **5** diminishes the TBI. Consistently this modification also influences the length of the central bond (mean value of 1.548 Å), which is significantly shorter than in **3A**, although the conformation of the central ring is essentially the same. The unbridged compounds **4** and **6** provide further confirmation of the influence of TBI on the length of the central bond. Although at first the equatorial conformation of compound **6** was a bit disappointing (working with these compounds for a long time, one tends to take the abnormal for normal!), it offers a very good reference for the bond length in *N*-phenylpiperidine derivatives with an equatorially orientated phenyl group. The value found (1.526–1.529 Å) testifies the absence of (strong) TBI in such an equatorial conformation. The axially orientated phenyl group in **4**, thus allowing strong TBI, results in a rather long C–C bond of 1.542–1.546 Å. Comparing this value to that of **6** reveals that the TBI causes an elongation of 0.02 Å.

Pyramidalization at C4. Substituted alkenes are known to show often slight deviations from planarity[32] if the two alkene carbons and the four attached atoms cannot define a plane of molecular symmetry. Inspection of the Newman projections along the C4–C9, C3–C4, and C5–C4 bonds (cf. Figures 7–9) reveals a significant nonplanarity in the acceptor moiety.

There are two types of distortion from the ideal planar geometry: twisting around C4–C9 and pyramidalization at C4. Compounds **5** and **6** show a slight twisting of the C4–C9 bond, perhaps the result of crystal field effects.

More interesting is the pyramidalization at C4. A priori, this distortion can direct C9 in two different directions as indicated in Figure 10. The angle Θ, defined in Figure 10, is a measure for the degree and direction of the pyramidalization at C4. A negative value for Θ indicates an equatorial bending of C9 and

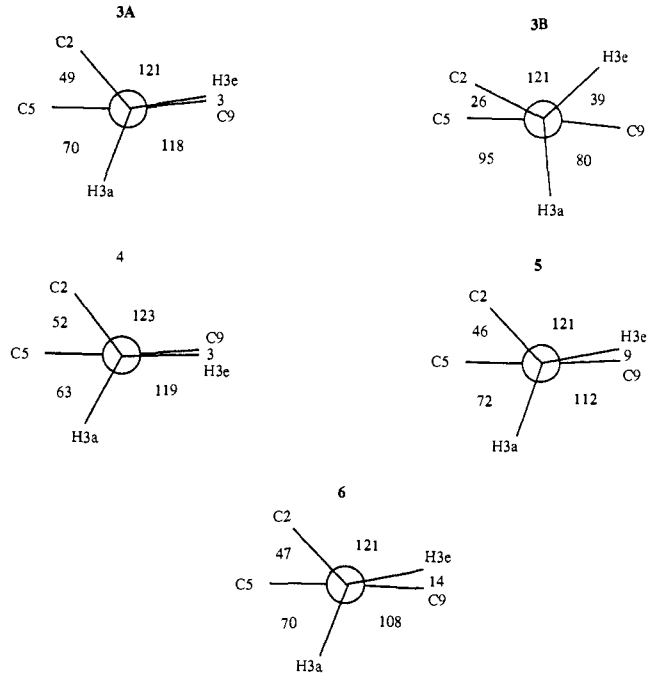

Figure 8. Newman projections along the C3–C4 bond for compounds **3–6**.

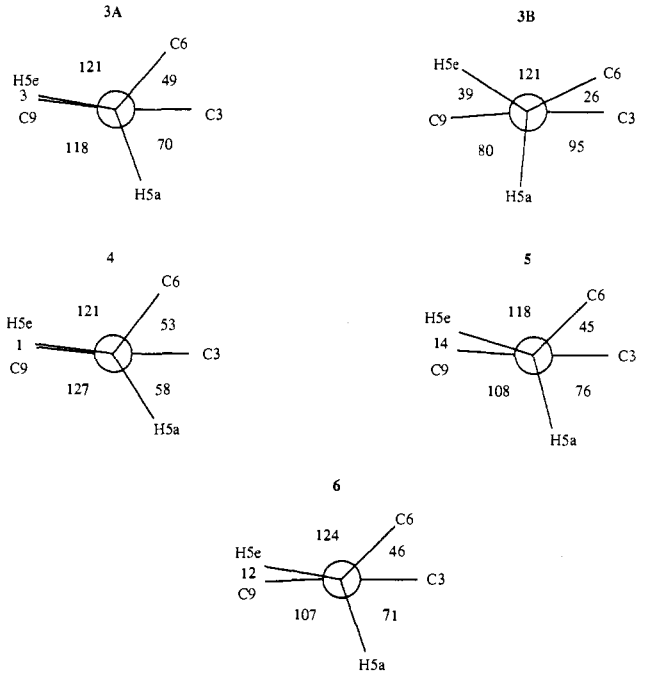

Figure 9. Newman projections along the C5–C4 bond for compounds **3–6**.

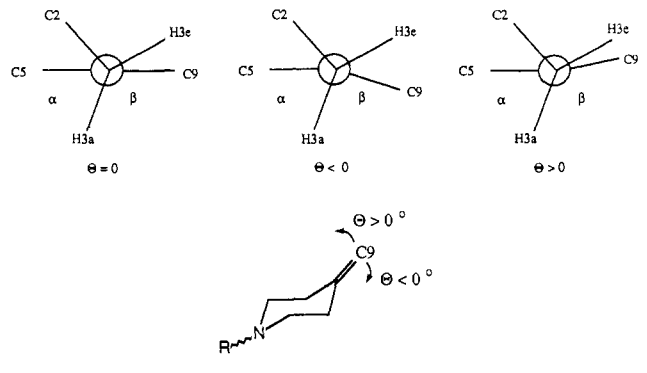

Figure 10. Possible modes of pyramidalization at C4 and the corresponding Newman projection along the C3–C4 bond; $\Theta = (\alpha + \beta) - 180$.

a positive Θ bending into the axial direction.

Theoretical studies on alkenes and carbonyls[32,33] predict that the carbon atom will pyramidalize toward a staggered geometry in order to relieve torsional interactions between the allylic bonds and the two σ bonds and π-orbital attached to the alkene C atom. Such pyramidalization toward the bond most parallel with the π-system is confirmed by a survey of neutron diffraction crystal structures of amino acids and dipeptides.[33] For our systems this would correspond to a bending of C9 into the equatorial direction toward H3a (Θ negative).

This kind of pyramidalization is indeed found in **3B** and **6**, having Θ = −5° and −2°, respectively. In these structures the TBI between donor and acceptor is minimized. The structures **3A**, **4**, and **5**, however, all pyramidalize into the other direction, having Θ = +8°(!),+5°, and +4°, respectively. This is in contrast with the prediction based on the relief of torsional interactions.

Pyramidalization into the axial direction leads to a larger electron density of the π-orbital on C4 into the equatorial direction. As a consequence of this distortion, the π lobe on C4 becomes more antiparallel to the central C–C bond, thus allowing more effective coupling of the acceptor with the N1 lone pair. Hoffmann et al.[2] have pointed at the fact that the (calculated) vicinal trans interaction between orbitals is energetically more favorable than the vicinal cis interaction. The observed pyramidalization increases the orbital density into the equatorial direction, thus increasing the stabilizing vicinal trans interaction of the central C–C bond with the acceptor orbital at C4. This interaction compensates the energetically unfavorable distortion from the ideal planar geometry.

The fact that **3A**, the structure with the strongest TBI, has also the largest pyramidalization only supports the idea that this pyramidalization is correlated with the TBI in these compounds and not with crystal lattice packing effects. The observed pyramidalization of +8° may seem small compared to that found in some *syn*-sesquinorbornene derivatives,[34] but it reflects interactions in the ground state of the molecules which are, according to Houk et al.,[32] related to much larger energetic effects occurring in transition states for addition reactions. The observed pyramidalization could therefore have a profound influence on the stereoselectivity in additions to the acceptor double bond, an effect to be investigated in the near future.

Concluding Remarks

The systems studied are further examples of compounds with strong TBI between a one-electron acceptor and donor, separated by three σ-bonds in a well-defined arrangement. This interaction results in a rather strong intramolecular CT absorption if the conformational requirements for TBI are fulfilled. The systems **4** and **6** are, to our knowledge, the first systems to demonstrate the predicted influence of TBI on the relative stabilities of conformations.

The compounds studied furthermore confirm the influence of TBI on the length of the central C–C bond, and they also show a pyramidalization of the acceptor double bond. The structures **3A** and **3B** prove that the effects of TBI on structural parameters depend very subtly on the conformation of the system.

Semiempirical SCF calculations are in progress in order to gain more insight in the electronic structure of the compounds. We are also searching to quantify experimentally the determination of the conformational equilibrium (1) in solution. New compounds with other substituents in the phenyl group and/or other acceptor chromophores are being synthesized, in order to study systematically the effects of TBI on conformation, structure, photophysical properties, and reactivity of this kind of bichromophoric systems.

Experimental Section

X-ray Crystal Structure Determination. For all compounds the intensity data were collected on a Nonius-CAD 4 diffractometer using graphite monochromated CuK_α radiation (λ = 1.5418 Å). The structures were solved using the direct method program package SIMPEL 83[35] and additional programs from the XRAY 76 package.[36] Block-diagonal least-squares refinement was used, anisotropic for C, N, O and isotropic for H (U_{eq} was kept fixed at 0.045 for **3**). No extinction correction nor absorption correction, except for **5** (range of correction 0.868–1.251 (averaged 1.000)), was made. After completion of the refinements, ΔF-synthesis showed residual densities between ca. −0.2 and 0.2 $eÅ^{-3}$.

Apparatus and Measurements. Electronic absorption spectra were measured on a Hewlett-Packard 8451A diode array spectrophotometer, infrared spectra on a Perkin-Elmer 1310, and the NMR spectra on a Bruker WM250 or a Bruker AC200 apparatus.

The UV spectra recorded at low temperatures were corrected for the change in density of the solvent with temperature, in order to make the spectra comparable.

Synthesis. Compounds **3–6** can be synthesized by Knoevenagel-type condensation of malononitrile with the appropriate ketones **8–11**.

***N*-Phenylpiperidin-4-one (8)** was obtained from R. M. Hermant.[37]

***N*-Phenyl-8-azabicyclo[3.2.1]octan-3-one (9)** was prepared by a double Michael condensation of aniline with 2,6-cycloheptadienone.[38] The latter was synthesized from cycloheptanone as described in literature.[39] The obtained 2,6-cycloheptadienone was only about 80% pure, but it was used without further purification. This compound should be handled with care as it blisters the skin. It should also be used quickly after synthesis because it is not too stable. The yield of **9** (23%) was low (lit. ca. 70%) probably because of the impure 2,6-cycloheptadienone. Recrystallization from methanol/water (1:1) gave a white solid: mp 103–104.5 °C (lit.[38] 107–108 °C); ^1H NMR (250 MHz, CD_2Cl_2) δ 7.30 ppm (m, 2 H), 6.83 ppm (m, 3 H), 4.48 ppm (m, 2 H), 2.68 ppm (dd, $J \approx 15$ Hz, $J \approx 4.6$ Hz, 2 H), 2.30 ppm (dd, $J \approx 15$ Hz, $J \approx 1$ Hz, 2 H), 2.18 ppm (m, 2 H), 1.78 ppm (dd, $J \approx 14.4$ Hz, $J \approx 7$ Hz, 2 H); IR ($CHCl_3$) 3030 (w), 3000 (w), 2960 (w), 1705 (s), 1495 (s) cm^{-1}.

***N*-(*p*-Methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-one (10)** was prepared as **9** by using *p*-anisidine instead of aniline. Product recrystallized from cyclohexane: yield 20%; mp 128–129 °C (lit.[38] 132–133 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 6.87 ppm (m, 4 H), 4.43 ppm (br s, 2 H), 3.78 ppm (s, 3 H), 2.69 ppm (dd, $J \approx 15$ Hz, $J \approx 4$ Hz, 2 H), 2.28 ppm (d, $J \approx 15$ Hz, 2 H), 2.18 ppm (m, 2 H), 1.78 ppm (dd, $J \approx 14$ Hz, $J \approx 7$ Hz, 2 H); IR ($CHCl_3$) 3000 (m), 2960 (m), 2935 (m), 2840 (m), 1705 (s), 1505 (s) cm^{-1}; high-resolution MS found m/z 231.1254, calcd for $C_{14}H_{17}NO_2$ m/z 231.1259.

***N*-(*p*-Methoxyphenyl)-4-piperidone (11)** was prepared as described for **8**[37] by using *p*-anisidine instead of aniline. The crude product was purified by flash column chromatography (Merck kieselgel 60 (0.04–0.0063 mm), *n*-hexane/ether (1:3) as eluens): yield 14%; mp 64–65 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 6.95 ppm (d with fine structure, $J \approx 9.1$ Hz, 2 H), 6.85 ppm (d with fine structure, $J \approx 9.1$ Hz, 2 H), 3.75 ppm (s, 3 H), 3.45 ppm (t, $J \approx 6.1$ Hz, 4 H), 2.55 ppm (t, $J \approx 6.1$ Hz, 4 H); IR ($CHCl_3$) 3010 (w), 2960 (w), 2830 (w), 1705 (s), 1580 (w), 1510 (w) cm^{-1}; high-resolution MS found m/z 205.1104, calcd for $C_{12}H_{15}NO$ m/z 205.1103.

***N*-Phenyl-8-azabicyclo[3.2.1]octylidene-3-malononitrile (3)** was synthesized by stirring and refluxing a mixture of the ketone **9** (0.20 g, 1 mmol), malononitrile (0.08 g, 1.2 mmol), 0.20 g of ammonium acetate, and 0.2 mL of acetic acid in ca. 5 mL of benzene for 2 h in a Dean-Stark apparatus (filled with molsieves 4Å). After cooling, the clear light orange reaction mixture was washed with water and a saturated sodium bicarbonate solution. The organic layer became turbid which disappeared after the addition of some CH_2Cl_2. After extraction with water, the collected water fractions were extracted several times with CH_2Cl_2. The combined organic solutions were dried ($MgSO_4$), filtrated, and evaporated to dryness. The yellow solid was recrystallized from ether/*n*-hexane: yield 64%; mp 150.5 °C (suitable crystals for the X-ray analysis

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were obtained by slow evaporation of an ether/*n*-hexane solution (mp 151-152 °C)); ^{1}H NMR (250 MHz, CD_2Cl_2) δ 7.30 ppm (m, 2 H), 6.85 ppm (m, 3 H), 4.51 ppm (br s, 2 H), 2.86 ppm (dd, $J \approx 15.2$ Hz, $J \approx 1$ Hz, 2 H), 2.73 ppm (dd, $J \approx 15.2$ Hz, $J \approx 3.3$ Hz, 2 H), 2.14 ppm (m, 2 H), 1.69 ppm (dd, $J \approx 14.6$ Hz, $J \approx 6.8$ Hz, 2 H); IR ($CHCl_3$) 3030 (w), 2960 (m), 2880 (w), 2230 (s), 1590 (s), 1495 (s) cm^{-1}.

***N*-Phenyl-4-azacyclohexylidenemalononitrile (4)** was synthesized by stirring and refluxing under nitrogen a mixture of **8** (1.60 g, 9.1 mmol), malononitrile (0.59 g, 8.9 mmol), 0.67 g of ammonium acetate, and 1.5 mL of acetic acid in ca. 50 mL of benzene for 1.5 h in a Dean-Stark apparatus. After cooling, the clear light orange reaction mixture was washed with water, saturated sodium bicarbonate, and water. The combined organic solutions were dried ($MgSO_4$), filtrated, and evaporated to dryness. The yellow solid was recrystallized from ethyl acetate: yield 60%; dec ca. 139 °C (suitable crystals for X-ray analysis were obtained by slow evaporation of an ether/CH_2Cl_2 solution); ^{1}H NMR (250 MHz, CD_2Cl_2) δ 7.28 ppm (m, 2 H), 6.91 ppm (m, 3 H), 3.48 ppm (t, $J \approx 6$ Hz, 4 H), 2.84 ppm (t, $J \approx 6$ Hz, 4 H); IR ($CHCl_3$) 3050 (w), 3020 (w), 2970 (w), 2830 (w), 2230 (s), 1600 (s), 1500 (s) cm^{-1}; high-resolution MS found m/z 223.1092, calcd for $C_{14}H_{13}N_3$ m/z 223.1074.

***N*-(*p*-Methoxyphenyl)-8-azabicyclo[3.2.1]octylidene-3-malononitrile (5)** could be synthesized by stirring and refluxing a mixture of the ketone **10** (216.9 mg, 0.94 mmol), malononitrile (74.5 mg, 1.13 mmol), 222 mg of ammonium acetate, and 0.2 mL of acetic acid in ca. 5 mL of benzene for 2.25 h in a Dean-Stark apparatus (filled with molsieves 4Å). The same workup as described for **3** yielded a yellow solid which was recrystallized from ether/CH_2Cl_2: yield 53%; Mp 200 °C (suitable crystals for X-ray analysis were obtained by slow evaporation of an ether/CH_2Cl_2 (1:1) solution; mp 202 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.86 ppm (m, 4 H), 4.44 ppm (br s, 2 H), 3.78 ppm (s, 3 H), 2.84 ppm (d with fine coupling, $J \approx 14$ Hz, 2 H), 2.75 ppm (d with fine coupling, $J \approx 14$ Hz, 2 H), 2.16 ppm (m, 2 H), 1.68 ppm (m, 2 H); IR ($CHCl_3$) 3030 (w), 2960 (m), 2225 (m), 1580 (m), 1510 (s) cm^{-1}; high-resolution MS found m/z 279.1355, calcd for $C_{17}H_{17}N_3O$ m/z 279.1372.

***N*-(*p*-Methoxyphenyl)-4-azacyclohexylidenemalononitrile (6)** was prepared by stirring and refluxing the ketone **11** (146.9 mg, 0.72 mmol), malononitrile (73.1 mg, 1.11 mmol), 150 mg of ammonium acetate, and 0.11 mL of acetic acid in 3 mL of toluene for 2.5 h in a Dean-Stark apparatus. After the usual workup, a red oil, which became solid in the refrigerator, was isolated. Recrystallization from CH_2Cl_2/ether (1:1) yielded red crystals. Further purification by flash column chromatography (Merck kieselgel 60 (0.04-0.063 mm), PE/ether (1:3) as eluens) yielded a yellow crystalline compound: yield 76%; mp 129-130 °C (suitable crystals for X-ray analysis were obtained by slow evaporation of an ether/CH_2Cl_2 solution); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.87 ppm (m, 4 H), 3.77 ppm (s, 3 H), 3.34 ppm (t, $J \approx 5.6$ Hz, 4 H), 2.86 ppm (t, $J \approx 5.6$ Hz, 4 H); IR ($CHCl_3$) 3000 (m), 2960 (m), 2930 (m), 2905 (m), 2830 (m), 2230 (m), 1595 (m), 1510 (s) cm^{-1}.

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Supplementary Material Available: Tables (S1 and S2) giving the crystallographic data, the final coordinates, and equivalent thermal parameters for compounds **3-6** (4 pages). Ordering information is given on any current masthead page.

Nature of Coenzyme Binding by Glyceraldehyde-3-phosphate Dehydrogenase: ^{13}C NMR Studies with Oxidized [4-^{13}C]Nicotinamide Adenine Dinucleotide†

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Abstract: The tetrameric enzyme glyceraldehyde-3-phosphate dehydrogenase from sturgeon muscle is known to exhibit negative cooperativity of NAD binding, with the first two coenzyme molecules being bound much tighter than the third and fourth molecules. We have examined the binding process directly using 125-MHz ^{13}C NMR spectroscopy by titrating the apoenzyme (ca. 170 μM) at 15 °C with the labeled coenzyme [4-^{13}C]NAD. At a stoichiometry of 2 NAD/tetramer virtually all the coenzyme is bound, but only the hint of a broad signal for the bound β-[4-^{13}C]NAD could be seen. At 4 NAD/tetramer a strong signal for bound NAD (δ_c = 153 ppm, $\Delta\nu$ = 260 Hz) was detected, but it integrated to just 2 equiv/tetramer, while the other two NAD remained "invisible". With 5-6 NAD/tetramer the expected amount of free NAD was detected (δ_c = 146.95 ppm), and the integral of the bound NAD signal also increased to show four equivalent NAD molecules bound. This behavior requires a model in which the first two NAD bind tightly, but in a complex which exhibits an intermediate rate of exchange between two bound forms, E·NAD and E′·NAD, with different NAD chemical shifts, leading to coalescence broadening ($\Delta\nu > 500$ Hz). Binding of the third NAD results in the stabilization of the E′·NAD conformation for one subunit and the appearance of a detectable signal for bound NAD. Binding of the fourth NAD leads to a cooperative transition to give the symmetrical holoenzyme with four E′·NAD subunits. The driving force for this E → E′ conversion is provided at the expense of the binding energy of the third and fourth NAD (negative cooperativity). Analysis of the ^{13}C NMR line-width behavior of free NAD yields the apparent dissociation rate constant for NAD from the holoenzyme, k_{-1}^{app} = 23 s^{-1} at 15 °C. The 6 ppm downfield shift of C-4 for bound vs free NAD rules out mechanistic models involving nucleophilic addition at C-4 of Cys^{149}, for example.

Glyceraldehyde-3-phosphate dehydrogenase from various sources is a tetramer with MW ~ 145 000. The subunits are identical in their amino acid sequence,[1] and no differences between the individual polypeptide chains could be detected with respect to their conformation as determined by X-ray diffraction at 2.4-3.0-Å resolution.[2] Kinetic and equilibrium studies revealed, however, that the enzyme isolated for instance from sturgeon muscle,[3] from *Bacillus stearothermophilus*,[4] from rabbit muscle,[4-6]

† Dedicated to Professor Duilio Arigoni on the occasion of his 60th birthday.
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