Anisotropic Effects in α-Substituted Methoxystilbenes

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The relative upfield chemical shift of a *meta*-substituted methoxy-group upon one of the rings of a *cis*-stilbene gives an indication of the conformational preferences of the molecule. In *E*-α-nitrostilbenes the β ring spends more time than the α ring in planarity with the olefin bridge. In *E*-3-benzylideneindole-2(3*H*)-ones the arylidene ring does not achieve planarity with the indolone. Assignments of configuration to the 3′,4′-dimethoxy α-nitrostilbenes and the 3′,4′-methylenedioxy-analogues have been corrected.

1,2-DIARYLETHYLENES are interestingly situated between rigid and completely non-rigid systems for the examination of diamagnetic anisotropy. With the aryl groups *cis* the rings cannot be coplanar and one should affect the n.m.r. absorption of a group suitably positioned on the other. The Johnson and Bovey shielding contour diagram for benzene[1] can be used for a qualitative assessment of the effects which are necessarily population-weighted average values with contributions from a variety of conformations in which the local magnetic field's shape and intensity are affected by different attitudes of the α and β rings and the position of the group within this field. Conformational preferences would be expected to vary with the structure of the compounds. It is assumed that the α and β rings of the *cis*-isomers can be treated separately since there is little conjugation between them. Thus the net local field generated by the rings can be regarded as being composed of the α and β fields. In an unrestricted environment the hydrogen atoms of an aryl methoxy-group can precess periodically around the Ar–O axis and thus be subjected to a periodically varying deshielding effect. Restriction of this motion might significantly alter the time-averaged effect.

A study of some *E*-α-nitrostilbenes wherein the β ring is more likely to be coplanar with the nitroethylene function shows a variation in the chemical shift of a methoxy-group with its position on the β ring due to net shielding by the α ring (Table 1). A 4′-methoxy-group is too distant to be much affected. A 3′-methoxy-group is shielded during the molecule's passage through a

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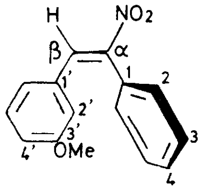
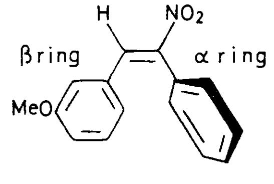
[1] L. M. Jackman and S. Sternhell, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, p. 94.

β-*syn*-conformation (I) which we define as a conformation in which the β ring substituent and the styryl group lie on the same side of a plane perpendicular to the olefin bridge and bisecting the β ring at the point of attachment of the styryl group. The observed net shielding of 0·3 p.p.m. is a population weighted average value dependent upon conformation preferences. The 2′-methoxy-group is probably not brought into the shielding zone of the α ring due to a preference for β-*anti*-conformations which reduce steric interaction between the methoxy-group and the α ring. Photoisomerisation of the *E*-isomers gives the *Z*-α-nitrostilbenes (Table 1) in which the shielding effect of the α ring is eliminated because of the *trans*-relationship of the rings. The relative chemical shifts of the vinyl hydrogen atoms in the two series are explained by a large deshielding effect of the nitro-group [1,2] in the *E*-isomers whereas the *Z*-isomers resemble *trans*-stilbenes in which the vinyl hydrogen atoms absorb at τ *ca.* 2·9.[3] A nitro-group deshields a proton in its plane and shields a proton situated above it.[1] Thus the nitro-group deshields β-H of the *E*-isomer adding its effect to that of the β ring in those conformations in which the nitro-group and the β ring approach or are at coplanarity.



β-*syn*-conformation

(I)



β-*anti*-conformation

(II)

TABLE 1

Chemical shifts [τ (10% w/v $CDCl_3$)] and m.p.s for α-nitrostilbenes

	OR		β-H		M.p. (°C)	
	E	*Z*	*E*	*Z*	*E*	*Z*
α-Nitrostilbene			1·79	3·17	73—73·5[10]	127—128[4]
2′-Methoxy	6·10	6·18	1·35	2·88	117—118[10]	99·5—100
3′-Methoxy	6·50	6·20	1·80	3·20	79·5—80 [a]	80—80·5 [b]
4′-Methoxy	6·23	6·20	1·78	3·25	157—157·5[5,10]	112—113[5]
3′,4′-Dimethoxy	6·14, 6·60	6·11, 6·14	1·75	3·23	107—108[6]	101—101·5[6]
3′,4′-Methylenedioxy	4·06	4·02	1·83	3·28	127·5—128·5[6]	123—123·5[6]
3,4-Dimethoxy	6·05, 6·19		1·86		108·5—109	

[a] From B. Reichert and W. Hoffman, *Arch. Pharm.*, 1936, **274**, 162. [b] Mixed *E*–*Z* m.p. 55—60°.

In the *Z*-isomer the nitro-group cannot affect β-H through space and it is likely that the bond transmitted effect is much reduced because coplanarity of the nitro-group and β ring would cause considerable distortion of this molecule. Thus those conformations in which the nitro-group and olefin bridge are coplanar will have the β ring almost perpendicular and thus its deshielding effect will be much reduced.

A net increased population of near planar β-*anti*-conformations resulting from unfavourable steric interactions in the β-*syn*-conformations between the methoxy-group and whichever group is *cis* to the β ring would explain the relative deshielding of the vinyl hydrogen atom in both 2′-methoxy-isomers. The relationship of the chemical shifts of β-H in the *E*–*Z* series of α-nitrostilbenes may thus be used to deduce the configuration of this type of compound in the absence of a suitably affected group upon the β ring. In the *E*-isomers β-H (τ *ca.* 1·8) is deshielded *ca.* 1·4 p.p.m. relative to the *Z*-isomer (τ *ca.* 3·2). The 2′-substituted isomers suggest that in this type of compound both absorptions will be *ca.* 0·35 p.p.m. downfield.

These observations and rationalisations allow the correct assignment of configuration to the isomers of 3′,4′-dimethoxy-α-nitrostilbene and the 3′,4′-methylenedioxy-analogue which appear to have been wrongly assigned on the false premise * that, of a pair of isomers of this type, the *cis*- (here aryl groups *cis*) isomer is lower melting, more soluble, and deeper coloured than the *trans*-isomer.[5,6] The incorrect assignments conflict with the relative stabilities of the isomers on simple steric grounds but seem to have been accepted.[4,7] The dimethoxy-compounds are distinguished by relative shielding (Table 1; 0·46 p.p.m.) of the 3′-methoxy-group and deshielding of the vinyl hydrogen atom in the *E*-isomer. Assignment of the τ 6·60 absorption to the 3′-methoxy-group is based upon comparison with the 3′- and 4′-methoxy-compounds. Since the methylene group in the *E*-methylenedioxy-isomer is held away from the influence of the α ring no significant difference is

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* The rule has high validity, regarding the first two characteristics, in the case of 1,2-disubstituted olefins (see for example E. L. Eliel, ' Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1969, p. 325), and symmetrical stilbenes (see N. Inamoto, S. Musuda, Y. Nagai, and O. Simamura, *J. Chem. Soc.*, 1963, 1433), but in trisubstituted olefins the relationship between such characteristics and configuration is less straightforward, as is shown in Table 1. Only the unsubstituted isomers, out of six pairs, show a significant *cis*-lower melting–*trans*-higher melting relationship with regard to the aryl groups. Whilst the relative disposition of the nitro and β-aryl groups might be considered to be more critical it follows that this also does not hold in the sample population, even if the m.p. differences in the 3′4′, dimethoxy- and 3′,4′-methylenedioxy-isomer pairs are considered significant. Confusion has arisen where the unsubstituted pair is the only example of its type studied.[4] An inconsistency has been noted with the 4′-methoxy-isomers.[5]

[2] W. L. F. Armarego, *J. Chem. Soc.* (*C*), 1969, 986.

[3] H. Güsten and M. Salswedel, *Tetrahedron*, 1967, **23**, 173, 187.

[4] J. P. Freeman and T. E. Stevens, *J. Org. Chem.*, 1958, **23**, 136.

[5] B. Flurscheim and E. L. Holmes, *J. Chem. Soc.*, 1932, 1458.

[6] B. Reichert and W. Kuhn, *Ber.*, 1941, **74**, 328.

[7] K. Yamamura, S. Watarai and T. Kinugasa, *Bull. Chem. Soc. Japan*, 1971, **44**, 2440.

observed between the absorptions of this group in the two isomers but configurations may be assigned on the basis of the chemical shifts of the vinyl hydrogen atoms (Table 2). The small difference between the chemical shifts of the methylene protons in the latter isomers illustrates the point concerning the position of the affected protons in the local field. The methylene protons will experience a greater deshielding effect of the β ring than the methyl protons of the corresponding 3′-methoxy-compounds since they are held in the plane of the β ring. Since the chemical shift differences between the methylenedioxy-isomers and between the 4′-methoxy-isomers are similar it would appear that the α ring can have little effect upon the *E*-methylenedioxy-isomer because the time average position of the 4′-methoxy-protons is even further from the α ring. Thus the observed effect upon the 3′-methoxy-group probably does not include a shielding contribution from a conformation as in the β-*syn*-conformation (I) with the methoxy-methyl occupying much the same position as the methylene group of the methylenedioxy-compound.

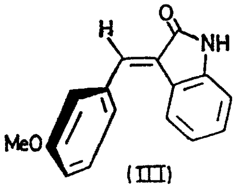
Replacement of the nitro- by a cyano-group reverses the order of thermodynamic stability of the *E*–*Z* pairs on account of steric factors. The *Z*-configuration is shown by the absence of a shielding effect upon a 3′-methoxy-group and the chemical shifts of the vinyl hydrogen atoms (Table 2) compared with the analogous nitro-isomers. The vinyl hydrogen atoms absorb at lower field than in the nitro-compounds and this may be rationalised by an improved degree of planarity (population-weighted average), made possible by the smaller cyano-group, resulting in increased conjugation. Further deshielding in the case of the 2′-methoxy-compound is analogous to the α-nitro-compounds and is explained in the same manner.

TABLE 2

Chemical shifts [τ (10% w/v $CDCl_3$)] for *Z*-α-cyano-stilbenes

	OR	β-H
α-Cyanostilbene		2·50
2′-Methoxy	6·19	2·06
3′-Methoxy	6·16	2·48
4′Methoxy	6·18	2·60
3′,4′-Dimethoxy	6·04, 6·07	2·53
3,4-Dimethoxy	6·07, 6·10	2·60

In an α-substituted stilbene with the aryl groups *trans* the ring attitudes are of no consequence since there can be no shielding of a methoxy-group in this configuration. In the *E*-α-nitrostilbenes with the aryl groups *cis* it is likely that the α ring has, on average, a greater degree of perpendicularity to the nitroethylene function than the β ring. This situation permits favourable linear conjugation of the β ring and the nitro group and is consistent with the anisotropy observed. A reversal of these ring attitudes should be seen in *E*-3-benzylidene-indol-2(3*H*)-ones wherein the α ring in this context is the benzene ring of the indolone and is constrained to be near planar to the olefin bridge. The substituted β ring is here the benzylidene aryl group and is thus likely to be nearly perpendicular, on average, to the rest of the molecule to avoid steric compression [structure (III)].



(III)

This arrangement of the rings should produce little shielding of a 3′-methoxy-group in an *E*-isomer and the data in Table 3 are consistent with this view.

TABLE 3

Chemical shifts {τ [10% w/v $CDCl_3$–CF_3CO_2H(10 : 1)]} for *E*-3-benzylideneindol-2(3*H*)-ones

	OR	β-H
3-Benzylideneindol-2(3*H*)-one		2·13
2′-Methoxy (m.p. 221—223°)	6·12	1·95
3′-Methoxy (m.p. 152—153°)	6·15	2·20
4′-Methoxy	6·12	2·22

A consequence of favoured conformations similar to (IV) for the *E*-isomer of an α-nitrostilbene would be that as far as the shielding effects of the rings are concerned a 3-methoxy-group would not be shielded to the same extent as a 3′-methoxy-group. This follows since molecules in which relative shielding of a 3-methoxy-group occurs are those in which the α ring is near to planarity with the olefin bridge and the β ring is nearly perpendicular in an α-*syn*-conformation (VI).* The population of molecules in or approaching this state is likely to be lower than in other states [(IV) or (V)] thus being reflected in a lower apparent shielding. It is conceivable that anisotropy of the α-nitro-group could play a part in determining the net chemical shift of the protons of a 3-methoxy-group. Since the nitro-group and the α ring can only be coplanar with distortion of the molecule the relative attitudes of the nitro and α ring planes may approach perpendicularity and thus a 3-methoxy-group may at times be in a position to be shielded by the α-nitro-group.

A deshielding effect upon *meta*- and *para*-substituted methoxy-groups could be caused by the other ring in an *E*-isomer. Because of the preferred conformations, *e.g.*

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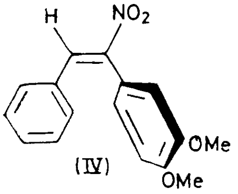
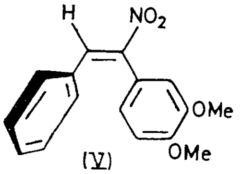
* Ring plane attitudes can be further defined by means of the dihedral angle which each ring makes with the plane of the olefin bridge, where the angles θ_α and θ_β respectively refer to rings α and β. *syn* and *anti* conformations of each ring may be described by a value of θ ranging from (+) 90 through 0 to (−) 90°, the handedness being relative to the coplanar state looking from the olefin bridge. Thus (I) represents a β-*syn*-conformation; $\theta_\alpha > +45° < (+) 90°$, $\theta_\beta \simeq 0°$, and (II) a β-*anti*-conformation; $\theta_\alpha > +45° < (+) 90°$, $\theta_\beta \simeq 0°$. (III) represents a β-*anti*-conformation; $\theta_\alpha \simeq 0°$, $\theta_\beta > -45° < (-) 90°$. (IV) represents an α-*anti*-conformation; $\theta_\alpha > +45° < (+) 90°$, $\theta_\beta \simeq 0°$, (V) an α-*anti*-conformation; $\theta_\alpha \simeq 0°$, $\theta_\beta > -45° < (-) 90°$, and (VI) an α-*syn*-conformation; $\theta_\alpha \simeq 0°$, $\theta_\beta > -45° < (-) 90°$. An appreciation of handedness is not essential with these compounds but the concept has been introduced since atropisomerism[8] may be found in more substituted examples.

[8] E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 156; K. Mislow, 'Introduction to Stereochemistry,' Benjamin, New York, 1965, p. 78.

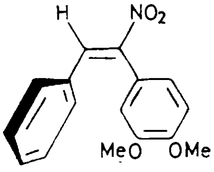
(I), (II), and (IV), it is likely that this would be greater for groups substituted in the α ring than in the β ring. The net result of these factors is likely to be a reduced shielding effect upon a 3-methoxy-group. *E*-3,4-dimethoxy-α-nitrostilbene (Table 1) shows a smaller difference in chemical shift between the protons of the two methoxy-groups than its 3′,4′-isomer. Naturally little difference is seen in *Z*-3,4-dimethoxy-α-cyanostilbene (Table 2). Data concerning some methyl substituted α-stilbenecarboxylic acids[9] agree with our observations in that little difference is seen in the chemical shift of the methyl protons in the *E*- and *Z*-isomers of some 3- and 4-methyl substituted compounds whereas a shielding effect, *ca.* 0·2 p.p.m., is seen in the *E*-isomer relative to the *Z*-isomer of 3′-methyl-α-stilbenecarboxylic acid.



(IV)



(V)



(VI)

EXPERIMENTAL

Materials.—Most were obtained by condensation reactions as published for *E*-α-nitrostilbenes,[10] *Z*-α-cyanostilbenes,[11] and *E*-3-benzylideneindol-2(3*H*)-ones.[12] *Z*-α-Nitrostilbenes were prepared by irradiating the *E*-isomers in methanol in a 100 W medium pressure Hanovia photoreactor. The physical constants of previously reported compounds were in agreement with those published. M.p.s are given in the Tables for the α-nitrostilbenes and elsewhere where the compound appears to be new and pure. Satisfactory elemental analyses were obtained where relevant.

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[10] D. N. Robertson, *J. Org. Chem.*, 1960, **25**, 49.

[11] N. P. Buu-Hoï, G. Saint-Ruf, and B. Lobert, *J. Chem. Soc.* (*C*), 1969, 2069.

[12] G. N. Walker, R. T. Smith, and B. N. Weaver, *J. Medicin Chem.*, 1965, **8**, 626; E. A. Ruveda and H. A. Gonsalez, *Spectrochim. Acta*, 1970, **26A**, 1275.