*Tetrahedron* Vol 46, No. 12, pp. 4241–4246, 1990
Printed in Great Britain

0040–4020/90 $3.00+.00
Pergamon Press plc

# THE EFFECT OF PARA-SUBSTITUENTS ON THE CONFORMATIONAL BEHAVIOUR OF 2-ARYL-1,3-DITHIANES

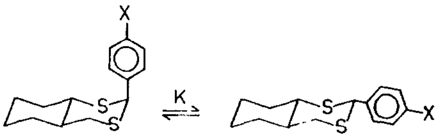
H. KÖHLER, C. TSCHIERSKE, H. ZASCHKE AND E. KLEINPETER*

Sektion Chemie, Martin-Luther-Universität Halle-Wittenberg
Weinbergweg 16, DDR-4010 Halle (Saale), G. D. R.

(*Received in Germany* 20 *November* 1989)

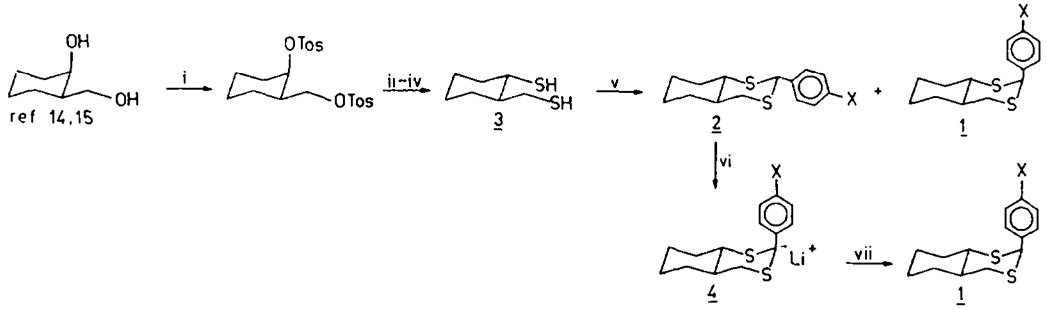
Abstract: The axial-equatorial equilibrium for 2-aryl-1,3-dithianes is remarkly sensitive to the nature of the substituent on the aromatic ring. The effect is solvent dependent and will be discussed in terms of the anomeric effect.

The anomeric effect has been the subject of numerous investigations.[1,2] Despite the fact that electronegative substituents in tetrahydropyran prefer the axial position, it only recently became known that a strong anomeric effect also occurs in 1,3-dithianes.[3-10] However, there is no report on the anomeric effect of the phenylgroup in 1,3-dithianes.[11] As part of a program designed to investigate the influence of conformational effects upon the liquid crystalline behaviour of heterocyclic compounds, we have recently reported on the influence of different substituents on the aromatic ring upon the liquid-crystalline properties of 2-aryl-1,3-dithiane derivatives.[12] In order to estimate the contribution of conformational effects hereby, the conformational analysis of differently para-substituted 2-phenyl-1,3-dithianes is now studied by means of chemical equilibration of anancomeric para-substituted 2-phenyl-1,3-dithiadecalins:



1 2

The compounds have been synthesized according to Scheme 1. Thereby compounds 2 have been obtained by acid catalyzed thio-acetalization of para-substituted benzaldehydes with trans-2-mercaptomethylcyclohexanethiol 3. Inversion of the configuration at C-2 via the carbanion 4 gave the axial substituted compounds 1.[13]



i: TosCl, pyridine, 0-20 °C, 80 hrs.; ii: $Na_2S_2$, DMF, 80 °C, 72 hrs. ref. 16; iii: $LiAlH_4$, $Et_2O$; iv: $H^+$, $H_2O$; v: OHC- -X, $H^+$, toluene, reflux 15 min (X = OMe, Et, H, Cl, CN, $NO_2$); vi: BuLi, n-hexane, THF, 30 min; vii: HCl, $H_2O$, 0 °C (X = OMe, H, Cl).

Scheme 1

The equilibrations were carried out in the following way: the compounds were dissolved in a solvent and three drops $BF_3Et_2O$ were added as catalyst. The sealed tubes were temperated at 57 °C for 10 days. All equilibrations were repeated at least three times and, if possible, were started with both isomers 1 and 2.

The equilibrium constants K were obtained from peak area integration of the well separated 2-H signals (1a: 5.18 ppm; 2a: 4.88 ppm).

The free conformational energies $\Delta G^0$ were calculated according to $\Delta G^0 = -RTlnK$. In all the diastereomeric equilibria studied, the phenyl substituent favours the equatorial position. However, the equilibrium $1 \rightleftharpoons 2$ is sensitive to the para substitution: the contribution of the axial substituted isomer increases with growing electron withdrawing properties of the para substituent X (Table 1).

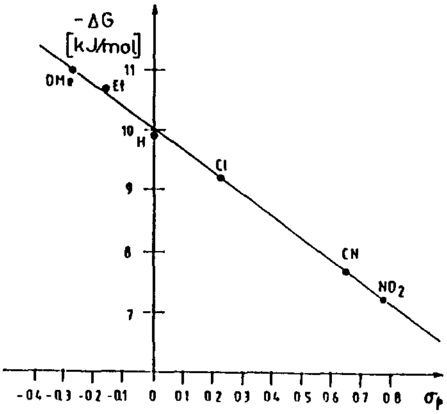
Table 1: Free conformational energy $\Delta G^0$ in $kJmol^{-1}$ of 2-para-substituted aryl-1,3-dithiadecalins at 57 °C in $CCl_4$.[a]

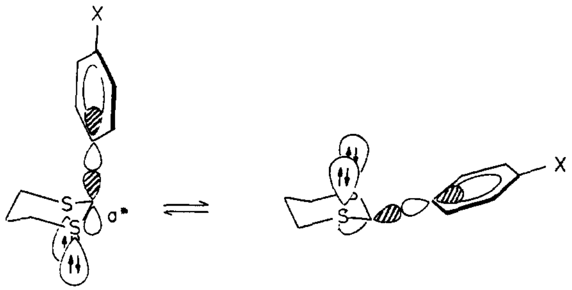
| Comp. | X | 1 mp.(°C) | 2 mp.(°C) | K | $-\Delta G^0$ | $\sigma_p$ |
|---|---|---|---|---|---|---|
| a | OMe | 92 | 103 | 52.63 | 11.0 | -0.268 |
| b | Et | -[b)] | 87 | 50.0 | 10.7 | -0.151 |
| c | H | 95 | 87 | 37.71 | 9.8 | 0 |
| d | Cl | 128 | 116 | 28.57 | 9.2 | 0.226 |
| e | CN | -[b)] | 155 | 16.67 | 7.7 | 0.660 |
| f | $NO_2$ | -[b)] | 107 | 14.28 | 7.3 | 0.778 |

a: recorded on a Bruker WP 200 spectrometer, b: not isolated

As shown in Fig. 1, there is a strictly linear dependence of $\Delta G^0$ on the $\sigma_p$ HAMMETT substituent constants[17] of the para substituents X (corr. coeff. r=0.996). The increase of the free conformational energy with increasing electron withdrawing power of the substituent can be discussed in terms of the anomeric effect between the endocyclic sulphur atoms and the aryl group at C(2). It seems that there is a stabilizing hyperconjugative interaction between the lone pairs on sulphur and the antibonding $\sigma^*$-orbital of the aryl-C(2) bond which is sensitive to variations in electron density at the aryl carbon bond to C(2) in such a way that the axial arrangement is stabilized with decreasing electron density.

Figure 1: Dependence of the free conformational energy $\Delta G^0$ on the HAMMETT constants $\sigma_p$ of the substituent X





a

e

Since the interacting orbitals effectively overlap only in the axially substituted isomers 1 or conformers, only these species can be stabilized by this interaction[18]; the observed dependence of equilibrium $1 \rightleftharpoons 2$ on the para substituents can be readily explained.
This argument is supported by the high field shift of the aromatic para-carbon atom in the axially substituted isomer 1 which can be interpreted in terms of the enhanced electron density in this position.

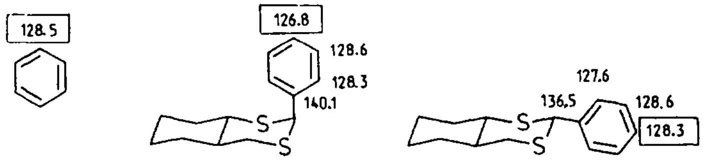


Figure 2: $^{13}C$ NMR chemical shifts of the aromatic carbon atoms in compounds 1c and 2c (50.3 MHz $CDCl_3$, 25 °C, TMS as internal standard)

The $\Delta G^0$ values are also solvent dependent in a way that $-\Delta G^0$ increases with growing polarity of the solvent and display hereby the more polar isomer 2 to be stabilized in more polar solvents.

Table 2: Solvent dependence of $\Delta G^0$ for the equilibrium $1 \rightleftharpoons 2$ at 57 °C, X = CN.

| Solvent | $\epsilon$ | $-\Delta G^0$ ($kJmol^{-1}$) |
|---|---|---|
| n-hexane | 1.88 | 7.3 |
| $CCl_4$ | 2.25 | 7.7 |
| $C_2H_4Cl_2$ | 10.4 | 8.5 |
| $CH_3CN$ | 37.5 | 9.1 |

Because the dipole moments of the compounds 1 and 2 are affected by the substituent X, the equilibria $1 \rightleftharpoons 2$ could, at least in part, also be influenced by dipole interactions. The contribution of these interactions to the anomeric effect is presently under investigations.

## EXPERIMENTAL

$^1H$ NMR spectra were recorded on a Bruker WP 200 NMR spectrometer at 200 MHz. $^{13}C$ NMR spectra were recorded on a Bruker AC 80 NMR spectrometer at 20.15 MHz and on the Bruker WP 200 at 50.33 MHz; the instruments were operating in pulsed Fourier transform mode and locked on the deuteriu signal of the solvent. Samples were prepared as 5 - 10 % solutions with tetramethylsilane as internal reference.

### Equilibrations

The equilibrations were carried out at 57 °C for 10 days in sealed ampoules containing 3 ml solvent, 50 mg of the substrate in question and 3 drops boron trifluoride diethyletherate as a catalyst. Before the analysis, the equilibrations were quenched by addition of $K_2CO_3$ solution. The resulting mixtures were extracted twice with ether and the latter was evaporated afterwards Then the samples were dissolved in $CDCl_3$ and $^1H$ NMR spectra were recorded. Hereby, the well separated absorptions of the tertiary protons in position 2 (2-H) of the resulting cis/trans isomers have been integrated very carefully. The equilibrations were repeated several times. If both stereoisomers in question were available, the equilibrations were started using samples including initially either the one or the other isomeric form.

## 2β-Phenyl-trans-1,3-dithiadecalines (2)

Solutions of 0.01 mol trans-2-mercaptomethylcyclohexanethiol (3)[19], 0.01 mol of the appropriate 4-substituted benzaldehyde and 100 mg p-toluenesulfonic acid in 150 ml dry benzene were refluxed for 1 h at a water separator. The mixtures were cooled to room temperature, washed successively with 50 ml 5 % aqu. NaHCO$_3$ solution, 50 ml water and 50 ml brine. After drying over Na$_2$SO$_4$, the solutions were filtered and concentrated at reduced pressure. The products were purified by repeated crystallization from methanol. The melting points of the freshly synthesized compounds are collected in Table 1. $^1$H NMR and $^{13}$C NMR spectral data of selected compounds are given below.

## 2α-Phenyl-trans-1,3-dithiadecalines (1a), (1c) and (1d)

To 0.01 mol (2.26g) of 2 in 20 ml dry tetrahydrofuran, cooled to -30 °C and flushed with dry argon was added 0.012 mol of a solution of n-butyllithium in n-hexane by means of a syringe while the solution was stirred with a magnetic stirrer. Stirring was continued for 2 hr at -20 °C and the lithium derivative 4 was quenched with 5 % hydrochloric acid in water (20 ml). The solution was stirred for 10 min and was then concentrated on a rotary evaporator at reduced pressure. The residue was dissolved in 100 ml ethyl ether, washed twice with 50 ml 5 % NaHCO$_3$ solution, once with water, dried over Na$_2$SO$_4$ and concentrated at reduced pressure. The residue was crystallized from methanol to yield 70 - 85 % of the compounds 1a, 1c or 1d, respectively. The melting temperatures are collected in Table 1 and selected NMR data are collected below.

Table 3: Chemical shifts of compounds 1a - f and 2a - f in CDCl$_3$

| Comp. | δ in ppm | | | |
|---|---|---|---|---|
| | H-2 | 4H-Ar | 3H-4$_{ax}$,4$_{eq}$,8a | 9H-4a,5-8 |
| 1a | 4.90 | 7.82-6.84 | 2.72-2.27 | 1.81-0.90 |
| 2a | 5.19 | 7.44-6.79 | 2.78-2.67 | 1.84-1.00 |
| 1b | 4.88 | 7.73-7.48 | 2.82-2.48 | 1.80-0.88 |
| 2b | 5.21 | 7.43-7.09 | 2.78-2.58 | 1.64-0.90 |
| 1c | 4.92 | 7.92-7.26 | 2.73-2.41 | 1.81-0.89 |
| 2c | 5.24 | 7.54-7.29 | 2.79-2.58 | 1.65-0.90 |
| 1d | 4.86 | 7.87-7.27 | 2.50-2.39 | 1.80-0.88 |
| 2d | 5.19 | 7.47-7.21 | 2.77-2.68 | 1.77-0.92 |
| 1e | 4.86 | -$^{a)}$ | -$^{a)}$ | -$^{a)}$ |
| 2e | 5.23 | 7.67-7.52 | 2.79-2.70 | 1.81-1.05 |
| 1f | 4.90 | -$^{a)}$ | -$^{a)}$ | -$^{a)}$ |
| 2f | 5.29 | 8.25-7.54 | 2.81-2.71 | 1.88-0.92 |

a: not isolated

## REFERENCES

1. Szarek, W.A.; Horton, D. "The Anomeric Effect: Origin and Consequences", American Chemical Society: Washington, DC, 1979, ACS Symp. Ser. No. 87.
2. Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen", Springer-Verlag, Berlin, 1983.
3. Juaristi, E.; Tapia, J.; Mendez, R. Tetrahedron, 1986, 42, 1253-1264.
4. Pinto, B. M.; Sandoval-Ramirez, J.; Sharma, R. D. Tetrahedron Lett., 1985, 26, 5235-5238.
5. Pinto, B. M.; Johnston, B. D.; Nagelkerke, R. J. Org. Chem., 1988, 53, 5668-5672.
6. Pinto, B. M.; Johnston, B. D.; Sandoval-Ramirez, J. J. Org. Chem., 1988, 53, 3766-3771.
7. Mikolajczyk, M.; Graczyk, P.; Balczewski, P. Tetrahedron Lett., 1987, 28, 573-576.
8. Mikolajczyk, M.; Graczyk, P.; Kabachnik, M. I.; Baranov, A. P. J. Org. Chem., 1989, 54, 2859-2861 and references therein.
9. Juaristi, E.; Valle, L.; Valenzuela, B. A.; Aguilar, M. A. J. Am. Chem. Soc., 1986, 108, 2000-2005.
10. Arai, K.; Iwamura, H.; Oki, M. Bull. Chem. Soc. Jpn., 1975, 48, 3319-3323.
11. Possible anomeric interactions of 2-phenyl substituents in 1,3-dioxanes are discussed: Eliel, E. L. Angew. Chem., 1972, 84, 779-836.
12. Tschierske, C.; Joachimi, D.; Vorbrodt, H. M.; Zaschke, H.; Wiegeleben, A.; Hauser, A.; Demus, D. Liquid Crystals, 1989, 5, 177-190.
13. Eliel, E. L.; Hartmann, A. A.; Abatjoglou, A. G. J. Am. Chem. Soc., 1974, 96, 1807-1816.
14. Zimmerman, H. E.; English, J. J. Am. Chem. Soc., 1953, 75, 2367-2370.
15. Smissman, E. E.; Mode, R. A. J. Am. Chem. Soc., 1957, 79, 3447-3448.
16. Eliel, E. L.; Rao, U. S.; Smith, S.; Hutchins, R. O. J. Org. Chem., 1975, 40, 524-526.
17. Swain, C. G.; Lupton, E. C. J. Am. Chem. Soc., 1968, 90, 4328-4337.
18. The electron transfer leads to an increased C-C-bond length. Therefore the axial conformer a should additionally be less destabilized by steric interactions.
19. Tschierske, C.; Köhler, H.; Zaschke, H.; Kleinpeter, E. Tetrahedron, 1989, 45, 6987-6998.