Pergamon

0040-4020(94)00776-4

The Diels-Alder Reaction of 2,5-Dialkylfurans and Fumaronitrile Revisited

Michael J. Cook* and Steven J. Cracknell

School of Chemical Sciences, University of East Anglia, Norwich, NR4 7TJ, UK

Abstract: The equilibrium reactions of furan and six 2,5-dialkyl derivatives with fumaronitrile were investigated under standard conditions (3.0×10^{-4} M) at four different temperatures in chloroform-d as solvent. Plots of lnK against $1/T$ were linear for each member of the series. The results show that the equilibrium concentration of adduct is sensitive to substituents. At equilibrium, there is a greater proportion of adduct derived from 2,5-dimethylfuran than from furan itself. However, as the length of the substituent chains is increased, the proportion of adduct decreases. Similar trends are also apparent from a more limited study of the equilibria in methanol-d_4 and acetone-d_6 as solvents. The concentrations of adduct in the equilibrium mixtures are highest in chloroform-d and lowest in acetone-d_6. AM1 calculations are reported for model adduct structures.

The importance and versatility of the Diels-Alder reaction for the construction of unsaturated six-membered ring systems is long established and well documented. Reactions of a diene and a simple alkene dienophile give rise to cyclohexene derivatives whereas alkyne dienophiles give rise to rings with a higher degree of unsaturation. An alternative strategy for obtaining the latter via a Diels-Alder approach utilises cyclic dienoid precursors such as cyclopentadienone derivatives, thiophenes, in particular their 1-oxides and 1,1-dioxides,[1] and furans.[2] These give rise to bicyclic adducts, the bridging group of which can be either thermally extruded or eliminated to introduce further double bond unsaturation into the ring. Recently we explored this strategy for the synthesis of some 3,6-dialkylphthalonitriles which we required as precursors to a series of discotic liquid crystalline 1,4,8,11,15,18,22,25-octa-substituted phthalocyanine derivatives.[3,4] One route we investigated is depicted in Scheme 1 and utilises the equilibrium reaction of furans and fumaronitrile which is the subject of this paper.

a	R = H	
b	R = methyl	
c	R = ethyl	
d	R = butyl	
e	R = pentyl	
f	R = iso-pentyl (3-methylbutyl)	
g	R = hexyl	
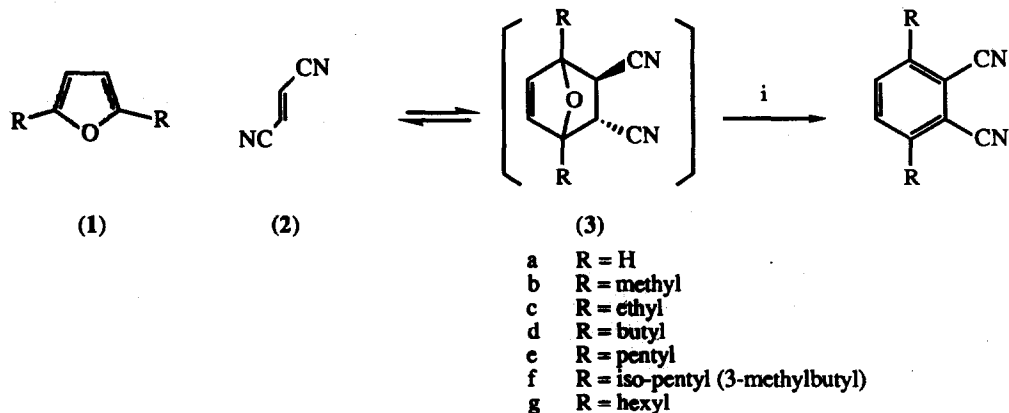
Scheme 1. i $LiN(SiMe_3)_2$ / THF, -78°; H_2O

The literature on the Diels-Alder reaction using furans is extensive,[2] ranging from mechanistic studies[5,6] to the development of experimental conditions which catalyse[7] or otherwise favour adduct formation.[8] Many dienophiles have been investigated but it was Mowry[9] in 1947 who first reported the reactions of furan (1a) and 2,5-dimethylfuran (1b) with fumaronitrile (2) which are utilised within Scheme 1. Mowry isolated the adducts (3a) and (3b) and demonstrated that the retro Diels-Alder reaction occurred on heating them above their melting points or during recrystallisation in hot ethanol. In devising the route to phthalonitriles via Scheme 1 we were attracted by the ready availability of 2,5-dialkylfurans[3] and the prospect of converting the adduct into the phthalonitrile in the same reaction vessel. However, we became aware that the literature contains some apparently contradictory data concerning the role of substituents on the position of the equilibrium for Diels-Alder reactions of furans with other alkene dienophiles. Dewar and Pierini[6] examined the reaction with maleic anhydride and showed that the rate of the forward reaction is enhanced by the presence of a 2-methyl group and raised further by a second methyl group at the five position. This is in accord with expectations that the methyl groups should lower the energy of the LUMO and facilitate reaction. They also showed that the substituents had an even larger effect on the rates of the retro reaction such that the equilibrium constants imply that the concentration of adduct is lower for the substituted compounds than for furan itself. On the other hand Schuda and Bennett[10] examined the reactions of furan, 2-methylfuran and 2,5-dimethylfuran with α-chloroacrylonitrile and showed that the concentration of adduct at equilibrium increased with methyl substitution. There is also some uncertainty about the effect of temperature on the position of the equilibrium. Kienzle[11] showed that the adduct from furan and acrylonitrile is formed in higher yield at room temperature than at elevated temperature, in line with the expected effect of the entropy of the reaction. However, Schuda and Bennett[10] report that furan and α-chloroacrylonitrile form more adduct at equilibrium at -12° than at 4°. On the other hand, 2-methyl and 2,5-dimethylfuran behaved in accord with expectations. In view of these reports and our own findings[3] that the yields of final products in Scheme 1 appeared to be dependent upon chain length, we have undertaken a systematic analysis of the effect of substituents and temperature on the Diels-Alder equilibrium in Scheme 1. We also report more limited data concerning the effect of solvent on the position of the equilibrium.

EXPERIMENTAL

Materials

Furan (1a), 2,5-dimethylfuran (1b), and fumaronitrile (2) were obtained as commercial samples. The remaining disubstituted furans were available through the synthetic study described elsewhere and involved alkylation of the furan anion, followed by alkylation of the anion of the monoalkylated furan.[3]

Equilibrium studies.

Solutions were prepared containing both the furan derivative and fumaronitrile, each at a concentration of 3.0 $\times 10^{-4}$ M, in chloroform-d, acetone-d_6 and methanol-d_4, and these were transferred into NMR tubes. The latter were sealed under aerobic conditions and maintained in a thermostatted bath at elevated temperature. The progress of the reactions was monitored by ^{1}H-NMR spectroscopy using a JEOL-FX 90 (operating at 90 MHz). Spectra were run periodically until there were no indications of any change from the previous run, typically over a two week period for reactions performed at 45.0° and over a four week period for those at 23.0°. Samples were transferred to a refrigerator for investigations at 1.0° and to a freezing unit thermostatted at -21.4°. Typical times for the reactions to achieve equilibrium at the lower temperature were of the order of three months. All spectra were recorded with the spectrometer probe temperature set at the reaction temperature, the sample tubes being transferred directly from the thermostatted environment with minimal delay.

Semi-empirical MO calculations

Calculations were carried out using the Hyperchem version of AM1 implemented on a SiliconGraphics WorkStation (IRIS) XS24 4000. Heats of formation of model adducts were calculated following geometry optimisation using the Polak-Ribiere algorithm (conjugate gradient). Termination conditions were set at 0.1 Kcal (Å mol) or a maximum of 330 cycles.

Table 1. Data for the equilibrium reaction between furans (1), fumaronitrile (2) and the Diels-Alder adduct (3)

Furan	solvent*	temp. /°C	% (3)	equilibrium ratio $(K)^{\#}$ / L.mol^{-1}	lnK	$\Delta H°$ kJ.mol^{-1}	$\Delta S° + R\ln 2$ Jmol^{-1}.K^{-1} (for solutions in CDCl$_3$)	(r)[‡]
1a; R = H	a	45	3.5	7.30 x10^{-3}	-4.92			
	a	23	4.2	8.68 x10^{-3}	-4.75			
	a	1	5.6	1.19 x10^{-2}	-4.43			
	a	-21.4	7.1	1.54 x10^{-2}	-4.18	-7.6 ± 0.5	-65 ± 2	(0.996)
	b	23	2.8	5.82 x10^{-3}	-5.15			
	b	1	4.4	9.12 x10^{-3}	-4.70			
	c	23	2.0	3.99 x10^{-3}	-5.52			
	c	1	3.7	7.65 x10^{-3}	-4.87			
1b; R = Me	a	45	23.3	6.08 x10^{-2}	-2.80			
	a	23	31.3	9.26 x10^{-2}	-2.38			
	a	1	45.2	1.65 x10^{-1}	-1.80			
	a	-21.4	61.9	3.22 x10^{-1}	-1.13	-16.9 ± 0.4	-77 ± 1	(0.999)
	b	23	22.7	5.87 x10^{-2}	-2.84			
	b	1	30.4	8.75 x10^{-2}	-2.44			
	c	23	10.2	2.27 x10^{-2}	-3.79			
	c	1	16.4	3.91 x10^{-2}	-3.24			
1c; R = Et	a	45	13.8	3.21 x10^{-2}	-3.44			
	a	23	19.9	4.98 x10^{-2}	-3.00			
	a	1	28.4	7.93 x10^{-2}	-2.53			
	a	-21.4	39.6	1.31 x10^{-1}	-2.03	-14.1 ± 0.5	-73 ± 2	(0.999)
	b	23	11.8	2.67 x10^{-2}	-3.62			
	b	1	20.8	5.25 x10^{-2}	-2.95			
1d; R = Bu	a	45	11.7	2.65 x10^{-2}	-3.63			
	a	23	16.1	3.84 x10^{-2}	-3.26			
	a	1	23.3	6.08 x10^{-2}	-2.80			
	a	-21.4	33.2	9.93 x10^{-2}	-2.31	-13.3 ± 0.2	-72 ± 1	(0.999)
1e; R = Pe	a	45	9.8	2.17 x10^{-2}	-3.83			
	a	23	13.1	3.02 x10^{-2}	-3.50			
	a	1	18.5	4.55 x10^{-2}	-3.09			
	a	-21.4	26.3	7.14 x10^{-2}	-2.64	-12.0 ± 0.1	-69 ± 1	(1.000)
1f; R = iso-Pe	a	45	11.6	2.63 x10^{-2}	-3.64			
	a	23	16.2	3.88 x10^{-2}	-3.25			
	a	1	22.4	5.78 x10^{-2}	-2.85			
	a	-21.4	32.5	9.63 x10^{-2}	-2.34	-12.9 ± 0.2	-71 ± 1	(1.000)
1g; R = Hex	a	45	6.1	1.30 x10^{-2}	-4.34			
	a	23	7.5	1.61 x10^{-2}	-4.13			
	a	1	10.4	2.33 x10^{-2}	-3.76			
	a	-21.4	14.4	3.37 x10^{-2}	-3.39	-9.7 ± 0.5	-67 ± 2	(0.998)
	c	23	2.5	5.21 x10^{-3}	-5.23			
	c	1	7.2	1.54 x10^{-2}	-4.17			

* a = CDCl$_3$, b = CD$_3$OD and c = CD$_3$COCD$_3$. # Equilibrium ratio (K) = [3]/[1].[2] where [3] is the concentration of the racemic mixture. ‡ Correlation coefficients.

RESULTS AND DISCUSSION

The reactions between the furans of series **1** and fumaronitrile were each studied using chloroform-d as solvent at four temperatures over the range -21.4° to 45°. Four examples were also investigated using either or both acetone-d_6 and methanol-d_4 as solvent at two temperatures. Experiments were limited to a study of the 1:1 reaction between addends, as solutions at 3×10^{-4} M. The solutions were contained in NMR tubes sealed under aerobic conditions. The ^{1}H-NMR spectrum of the mixture initially exhibits resonances attributable to the protons of fumaronitrile (δ 6.25) and of the 2,5-dialkylfuran (ca δ 5.5, 2.55, 1.8-0.8) but after a period of time there appear peaks that can be assigned to the adduct formed from the diene and the dienophile (δ 6.45, 2.9). The use of a symmetrical *trans* substituted dienophile ensures that there is just one adduct formed, albeit as a racemic mixture. The solutions were monitored at intervals until equilibrium was reached, as judged by consistent measurements over three consecutive readings. The same solutions were used throughout the study of the temperature dependence of the reactions and no extraneous peaks appeared during this time. Integration of the signals due to the olefinic protons of the adduct (**3**) and of signals for the starting materials (**1**) and (**2**) enabled calculation of the equilibrium ratio (K), defined as $\{[R,R\text{-}3] + [S,S\text{-}3]\}/[1][2]$. This refers to the equilibrium scheme:

$$R,R\text{-}3 \ = \ 1 + 2 \ = S,S\text{-}3$$
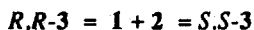
where, clearly, R,R-3 and S,S-3 are not independently variable and where the two formal equilibria have a common $\Delta G°$. Accordingly $K = 2e^{-\Delta G°/RT}$ whence $R\ln K = -\Delta H°/T + \Delta S° + R\ln 2$. The results obtained for K are presented in Table 1. Figure 1 displays the data obtained using chloroform-d as solvent as plots of lnK against 1/T. The plots are linear and from these were obtained values for $\Delta H°$ and $\Delta S°$, Table 1.

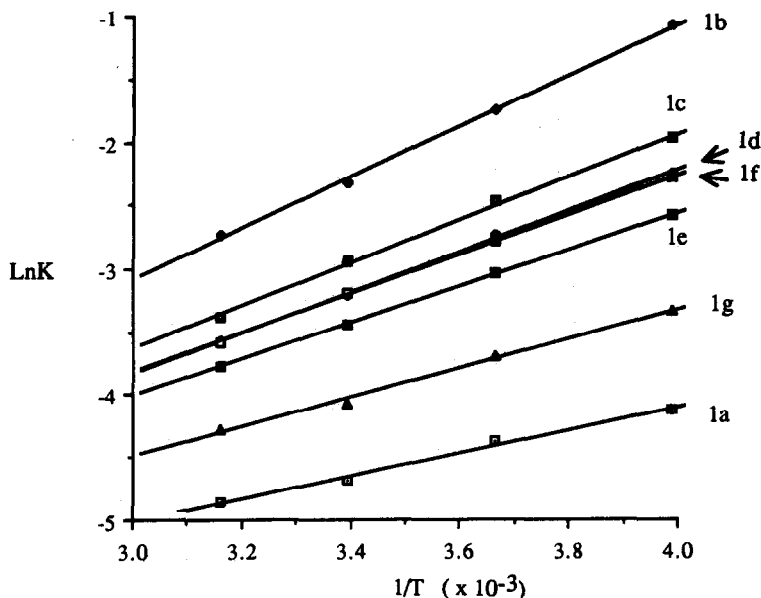Figure 1. Plots of lnK versus 1/T for the Diels-Alder equilibrium reactions between furans (1) and fumaronitrile in chloroform-d as solvent.

Inspection of the data in table 1 shows that for each reaction, in each of the three solvents, there is a higher conversion of the starting materials into the adduct at the lower or lowest temperature examined, in line with the negative entropy of the process. Several reports intimate that the rate of the Diels-Alder reaction is enhanced with increasing solvent polarity[12] but the effect of solvent polarity on the overall equilibrium position of reactions seems less well documented. The present results provide the basis for some comparisons to be made between the solvents chloroform-d, acetone-d_6 and methanol-d_4. Unfortunately, limited solubility of the materials, especially of the longer chained dialkylfurans in methanol-d_4, precluded a comprehensive study. The results do show, however, that under the standard set of conditions used here the equilibrium ratios exhibit sensitivity to the medium with greatest amounts of adduct formed in chloroform-d and the least in acetone-d_6 as solvent.

The effect of the substituents on the position of the equilibrium is particularly marked. Irrespective of the solvent, methyl substitution of the furan ring as in (1b) increases significantly the equilibrium concentration of the adduct relative to furan itself. The trend is thus consistent with the result reported in ref. 10 and contrary to that of ref. 6. Further extension of the substituent chains of the furan substrate progressively reduces the amount of adduct present at equilibrium, Table 1. Results obtained from the lnK v 1/T plots for the reactions performed in chloroform-d solution indicate that variations in the enthalpy term are probably more significant than entropy effects. The trend within the small variations in -$\Delta S°$ is that the magnitude actually becomes smaller for the equilibria which most favour the addends.

The largest difference in $\Delta H°$ for a change in chain length of just one carbon-carbon linkage is observed for the dimethyl and diethyl derivatives, (1b) and (1c). Since the electronic inductive effects of the two groups are very similar, it can be inferred that there is an enhanced steric effect in the diethyl system. To explore this further we have undertaken a series of semi-empirical calculations using the AM1 method which provides, amongst other output, Heat of Formation, ΔH_f, data. We verified the appropriateness of the AM1 calculations by calculating ΔH_f for the well studied endo and exo isomers of furan and maleic anhydride, Figure 2. AM1 correctly predicts after geometry optimisation that the exo isomer is thermodynamically more stable; furthermore, the difference in the calculated values of ΔH_f, 7.7 kJ.mol^{-1}, is in good accord with the experimental value of 7.9 kJ.mol^{-1} determined for the difference in energies of the isomers (acetonitrile).[13] In order to probe the nature of the strain introduced in the Diels-Alder adducts (3b) and (3c) and to avoid the more complex computation associated with measuring the equilibrium enthalpies of reactions, we performed AM1 calculations on four sets of model structures, Figure 2. The sets were chosen to provide a means of probing the interactions between a bridgehead group and an exo or endo CN substituent; each set contains isomeric structures and are thus in principle available from common precursors. Set A comprises four structures containing a single bridgehead methyl group and a single CN group in various locations. Sets B, C and D comprise similar models but where the methyl has been replaced by an ethyl group. These three sets refer to the three different starting rotamers for the ethyl substituent. The geometries of each of the sixteen input structures were optimised to their local minima. Values for ΔH_f corresponding to the energy minimised structures are shown in Figure 2. The optimised geometries showed rather minor perturbations from the input geometry with the exception of D(iii) for which the minimum energy conformation is one where the torsion angle between the highlighted bonds is reduced from 180° to -145°, locating the CH$_2$-CH$_3$ bond at a torsion angle of 30° to the C-O bond.

Within each Set, data for structures (i) and (ii) reveal that ΔH_f for the latter, the isomer with the endo CN group vicinal to a bridgehead proton, is marginally lower (ca. 0.3 kJ.mol^{-1}) than for the isomer with the CN group exo. Data for structures A(iii) and A(iv), where the CN groups are vicinal to a bridgehead methyl group, show that ΔH_f values are raised relative to A(i) and A(ii) as follows: $\Delta\Delta H_f$ A(iii) - A(i) = 3.2 kJmol^{-1}, $\Delta\Delta H_f$ A(iv) - A(ii) = 1.2 kJmol^{-1}. This gives an indication of the extent to which strain is introduced into the system. In practice, the numbers are probably an underestimate because there is an extra vicinal Me..H interaction in A(i) which is over and above that in A(iii). However, this factor is unlikely to undermine the conclusion that the Me..exo-CN interaction is more destabilising than the Me..endo-CN interaction. Overall,
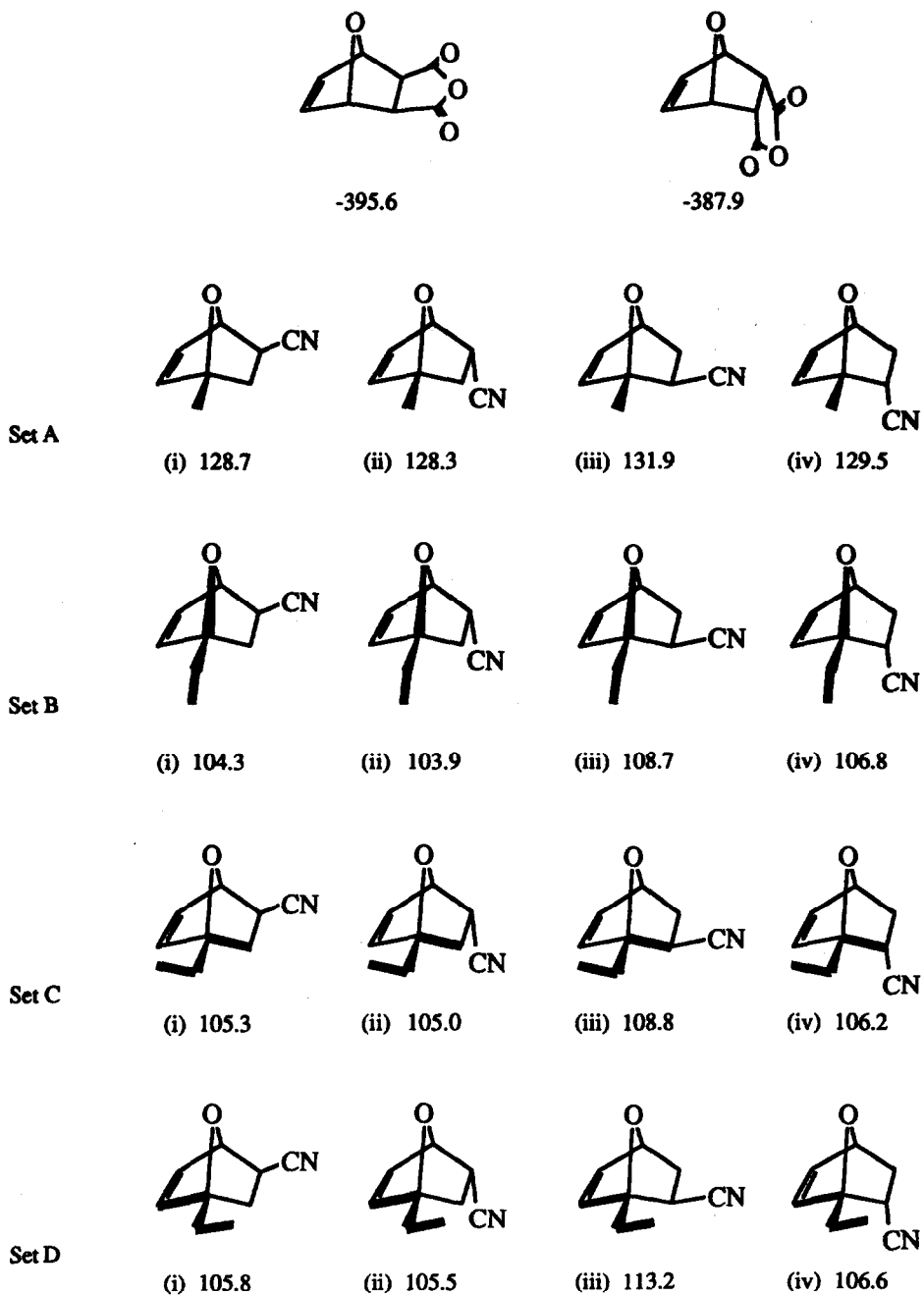
-395.6   -387.9

Set A

(i) 128.7   (ii) 128.3   (iii) 131.9   (iv) 129.5

Set B

(i) 104.3   (ii) 103.9   (iii) 108.7   (iv) 106.8

Set C

(i) 105.3   (ii) 105.0   (iii) 108.8   (iv) 106.2

Set D

(i) 105.8   (ii) 105.5   (iii) 113.2   (iv) 106.6

Figure 2.   Model structures whose geometries were minimised using the AM1 method (Hyperchem) and the calculated Heats of Formation (ΔH_f) of the energy minimised structures in kJ. mol^{-1}.

the calculations predict that the adduct from 2,5-dimethylfuran is more strained than that obtained from furan itself. That it is formed at greater equilibrium concentrations reflects a marked activation of the furan ring by the methyl groups.

Corresponding comparisons of data from sets B, C and D confirm the greater destabilising interaction involving the bridgehead alkyl group and the exo CN group and, as expected, is more severe for the bulkier ethyl group. Here, values for $\Delta\Delta H_f$ type (iii) - type (i) are raised to 4.4, 3.5, and 7.4 kJmol^{-1}. In contrast values for $\Delta\Delta H_f$ type (iv) - type (ii) are 2.9, 1.2 and 1.1 kJmol^{-1} over the three sets. Among the latter, the value of 2.9 kJmol^{-1} presumably reflects the proximity of the methyl group of the ethyl substituent to the endo CN bond in B(iv); otherwise the values are comparable to that for $\Delta\Delta H_f$ A(iv) - A(ii). In practice, the enhanced strain introduced into the adduct by the ethyl groups replacing the methyl groups is more appropriately assessed by comparing ΔH_f values for the most stable conformations of the pertinent structures, ie $\Delta\Delta H_f$ B(iii) - B(i) = 4.4 kJmol^{-1} and $\Delta\Delta H_f$ C(iv) - B(ii) = 2.3 kJmol^{-1}. These $\Delta\Delta H_f$ values are larger than the corresponding values obtained from the model structures for the methylated adduct and provide a basis for rationalising the difference in the positions of the equilibria for (1b) and (1c).

The empirical data in Table 1 show that lengthening of the alkyl chain beyond ethyl further reduces the proportion of adduct at equilibrium but the incremental changes in ΔH° become smaller. It was not considered appropriate to model the interactions involving the longer chains because of the increasing conformational complexities associated with the longer chains. It seems unlikely that the chain length effect is electronic in origin, rather that increased steric effects ensure less adduct formation by hindering the forward reaction and/or increasing the lability of the adduct. Data for the dibutylfuran (1c) and the di-*iso*-pentylfuran (1e) are very similar and would seem to indicate that the maximum length of the chain is an important factor. That further lengthening of the chains to pentyl and hexyl continues to reduce the amount of adduct formed seems surprising in as much that it implies that the terminal carbons in these long chains continue to increase the steric interactions in the adduct molecules.

CONCLUSION

The study was undertaken to explore conditions for performing the Diels-Alder equilibrium reactions between 2,5-dialkylfurans and fumaronitrile with a view to optimising the formation of the adduct and against a background of some apparently conflicting data reported for other Diels-Alder reactions involving furans and alkene dienophiles. Unsubstituted furan and a total of six 2,5-disubstituted derivatives were investigated under standard conditions at four different temperatures in chloroform-d as solvent. In each case the results show that the concentration of the adduct is considerably increased at low temperatures in accord with the negative entropy of the forward process. Plots of lnK against 1/T are linear for each member of the series. Where comparisons are possible, it is clear that the solvent chloroform-d is better than methanol-d$_4$ or acetone-d$_6$ for encouraging conversion to adduct within the equilibrium mixtures. The results also show that the Diels-Alder equilibrium is sensitive to the length of the alkyl chain. At equilibrium, there is a greater proportion of adduct derived from 2,5-dimethylfuran than from furan itself. However, as the length of the substituent chains are increased, the proportion of adduct decreases. AM1 calculations of model structures indicate the presence of an alkyl substituent at the bridgehead destabilises the system through interactions with both the exo and endo CN groups. The former interaction is the larger and appears to be the more sensitive to chain extension as judged by comparisons of ΔH_f values for model structures designed to probe interactions within the bridge methylated and ethylated adducts.

From the point of view of synthetic methodology, the benefit of using a low reaction temperature to favour adduct formation is somewhat offset by the increase in the time required to achieve the higher yields. The use of high pressures for favouring adduct formation is well documented[8] but the necessary facilities were unavailable during our preparative study using scheme 1. In practice we utilised a finding, anticipated from the work of Dewar and Pierini,[6] that the equilibrium ratio in furan Diels-Alder reactions is very sensitive to

concentration. It was shown that adduct (3) could be formed in yields as high as 40 - 55% based on starting furan, even of the longer chained derivatives, at -5° over a week by dissolving the addends into the minimum amount of solvent.[3]

ACKNOWLEDGEMENTS

REFERENCES

1. Katritzky, A.R. *Handbook of Heterocyclic Chemistry*; Pergamon Press: Oxford. **1985**; p 270-271.
2. Sargent, M.V.; Dean, F.M. Furans and their benzo derivatives: (ii) Reactivity. In *Comprehensive Heterocyclic Chemistry. vol. 4*. Eds. Bird, C.W.; Cheeseman, G.W.H. (Series eds. Katritzky, A.R.; Rees, C.W.) 1984, p 599-656.
3. McKeown, N.B.; Chambrier, I.; Cook, M.J. *J. Chem. Soc. Perkin Trans. 1*. **1990**, 1169-1177.
4. Chambrier, I.; Cook, M.J.; Cracknell, S.J.; McMurdo, J. *J. Mater. Chem*. **1993**, *3*, 841-849.
5. eg Lert, P.W.; Trindle, C. *J. Amer. Chem. Soc.* **1971**, *93*, 6392-6395: Seltzer, S. *J. Amer. Chem. Soc.* **1963**, *85*, 1360-1361.
6. Dewar, M.J.S.; Pierini, A.B. *J. Amer. Chem. Soc.* **1984**, *106*, 203-208.
7. Adams, J.M.; Dyer, S.; Martin, K.; Matear, W.A.; McCabe, R.W. *J. Chem. Soc. Perkin Trans. 1* **1994**, 761-765.
8. eg Kotsuki, H.; Nishizawa, H. *Heterocycles* **1981**, *16*, 1287-1290.
9. Mowry, D.T. *J. Amer. Chem. Soc.* **1947**, *69*, 573-575.
10. Schuda, P.F.; Bennett, J.M. *Tetrahedron Lett.* **1982**, *23*, 5525-5528.
11. Kienzle, F. *Helv. Chim. Acta.*.**1975**, *58*, 1180-1183.
12. eg Hunt, I.; Johnson, C.D. *J. Chem. Soc. Perkin Trans. 2* **1991**, 1051-1056, and references therein.
13. Lee, M.W.; Herndon, W.E. *J. Org. Chem* **1978**, *43*, 518.