FACTORS AFFECTING EASE OF RING FORMATION. THE EFFECT OF ANCHORING SUBSTITUTION ON THE RATE OF
AN INTRAMOLECULAR DIELS-ALDER REACTION WITH FURAN-DIENE

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Summary – Kinetic parameters for the IMDAF reaction of 2 and 3 were determined. For the
equilibrium between 2b and 4b : $\Delta H° = -29.3$ kJ/mol, $\Delta S° = -75$ J/mol.K; for the conversion of 3
into 6 a significant rate enhancement by the anchoring tert-butyl group is observed :
k(3b)/k(3a) = 240. The structure of 6b was proven via X-ray determination of 8.

The quantitative treatment of structural factors which affect the ease of ring formation
from acyclic precursors is a problem of fundamental interest.[2] E.g., it has been recognized
for many years that alkyl substitution promotes the rate of ring formation and increases the
concentration of cyclic material at equilibrium.[3] Certain aspects of this general phenomenon,
which has been popularized as the "gem-dialkyl effect", have been explained on a purely
thermodynamic basis,[4] other aspects have been related more specifically to the "Thorpe-Ingold
effect"[5] and to the release of steric strain in the ground state upon ring closure,[6] and also
to the decrease in unprofitable rotamer distribution in the ground state upon alkyl
substitution.[7,8] The latter explanation is a qualitative version of the classical Winstein-
Holness equation.[9]
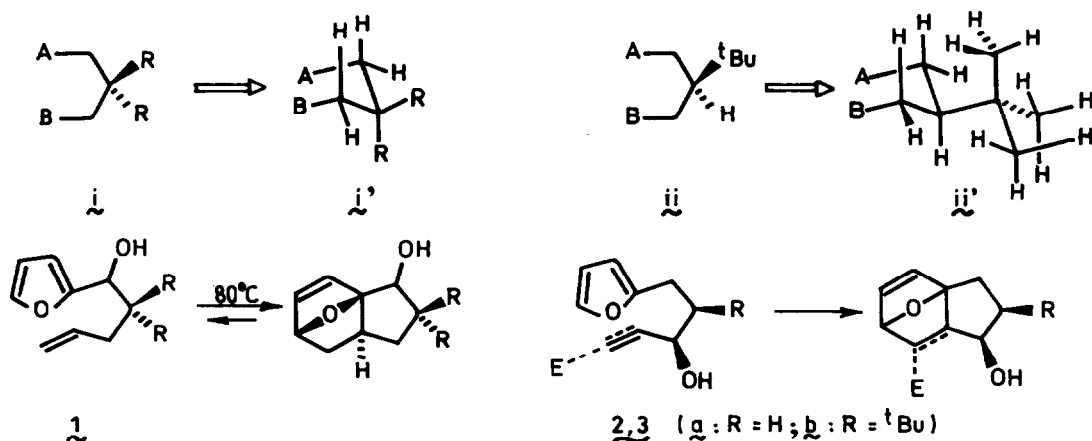
Scheme 1

Recently we have started investigating various aspects which are related to the presence of an anchoring substituent, such as a <u>tert</u>-butyl or trityl group, on an acyclic chain.[10] With respect to 5-membered ring formation (scheme 1) one may intuitively expect the parallel orientation of the reactive termini A and B to be more favored in fragment ii than in the case of the <u>gem</u>-dialkyl substituted i, since in ii' both groups A and B are <u>anti</u> to the large <u>tert</u>-butyl group, whereas in i' both groups are gauche-oriented with one of the <u>gem</u>-alkyl groups R. Over the years numerous quantitative studies related to the <u>gem</u>-dialkyl promoting effect have been reported.[2b,8,11] E.g. the influence of the <u>gem</u>-substitution pattern in the intramolecular Diels-Alder furan reaction (IMDAF) of 1 has recently been reported by Sternbach.[12] Surprisingly, data concerning the above <u>tert</u>-butyl effect are lacking altogether. In this paper we wish to describe the first quantitative results in this area, which were obtained for the IMDAF reaction of the <u>tert</u>-butyl substituted 2b and 3b.

Scheme 2
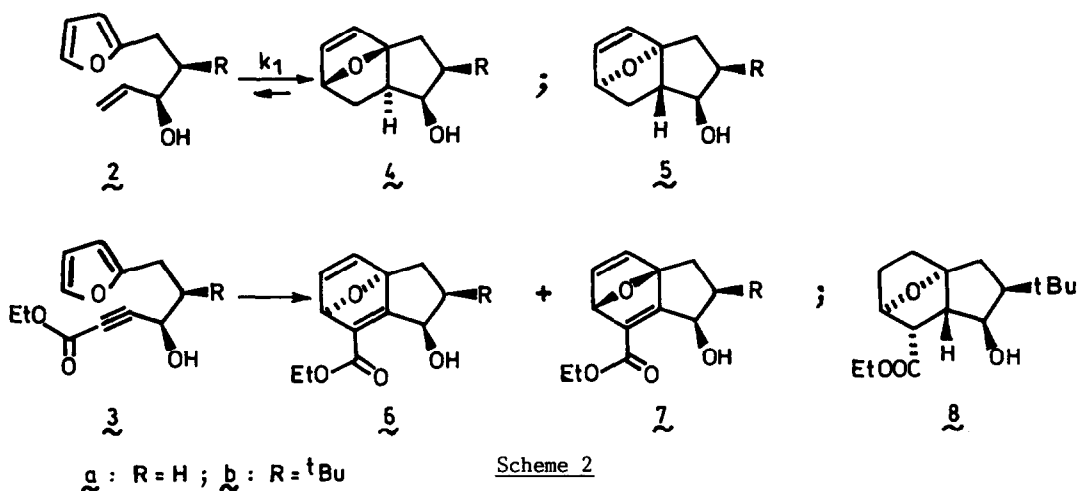
The studied Diels-Alder precursors 2 and 3 in the two series a (R = H) and b (R = <u>tert</u>-butyl) were readily obtained from 3-(2-furyl)propionaldehyde[13] and 2-<u>t</u>-butyl-3-(2-furyl)-propionaldehyde,[14] respectively, via reaction with vinylmagnesium bromide (2a : 90 %, 2b[15] : 90 % yield) and lithium ethyl propiolate[16] (3a : 66 %, 3b[15] : 60 % yield). In accord with the Felkin rule, a single diastereomer is formed in the b-series.[17]

In contrast with olefin 2a (R = H), which was found unreactive in refluxing benzene, the <u>tert</u>-butyl substituted 2b gave rise to an equilibrium mixture after 48 h, consisting of 2b (20 % isolated) and a single adduct 4b (70 % isolated).[15] In toluene at 111°C the equilibrium was shifted towards starting material (40 % and 60 % isolated of 2b and 4b, respectively), while 2a was found to decompose after extended reaction times. At both temperatures the equilibrium constants and the first order rate constants for the forward reaction of 2b were determined (table).[18]

The first order rate constants of the irreversible cycloaddition at 80°C in benzene of acetylenes 3a and 3b were also determined (table). The reaction of 3a is very slow ($t_{1/2}$ = 100 h) and leads to a mixture of 6a and 7a,[15] in which 6a predominates.[18] The analogous reaction of the <u>tert</u>-butyl derivative 3b is much faster ($t_{1/2}$ = 26 min) and leads to a single

adduct **6b**, whose structure follows from the X-ray diffraction analysis of **8**, obtained via catalytic hydrogenation of **6b** (10 % Pd–CaCO$_3$; 75 % yield).

<u>Table</u> : Kinetic parameters for the cycloaddition of **2b**, **3a** and **3b**.[18]

Substrate	conditions	K	$k_1 \cdot 10^5 s^{-1}$	$t_{1/2}$ (h)
2b	benzene, 80°C	3.3	2.8	6.9
2b	toluene, 111°C	1.4	29.0	0.66
3a	benzene, 80°C	–	0.19	100.0
3b	benzene, 80°C	–	45.0	0.43

Figure 1 shows a stereoscopic view for one enantiomer of **8**.[20] The crystallographic data are as follows : $C_{16}H_{26}O_4$, Mr = 282.38, monoclinic, C2/c with <u>a</u> = 28.797(9), <u>b</u> = 6.322(1), <u>c</u> = 18.377(5)Å, β = 109.17(2)°, V = 3160(1)Å^3, Dx = 1.19 gcm^{-3} for Z = 8. The intensities of 2814 independent reflections were collected on a Huber four circle diffractometer using CuKα graphite monochromatized radiation (λ = 1.5418). 2355 reflections with I > 2.5σ(I) were used in the refinement. The structure was solved by direct methods using SHELXS-86[21]. Anisotropic least squares refinement on F with SHELXS-76[22]. All hydrogen atoms were located from a difference Fourier synthesis and included in the refinement with a common isotropic temperature factor. The final R index is 0.059 for 2355 observed reflections. The list of atomic coordinates and molecular dimensions has been deposited with the Cambridge Data Centre.
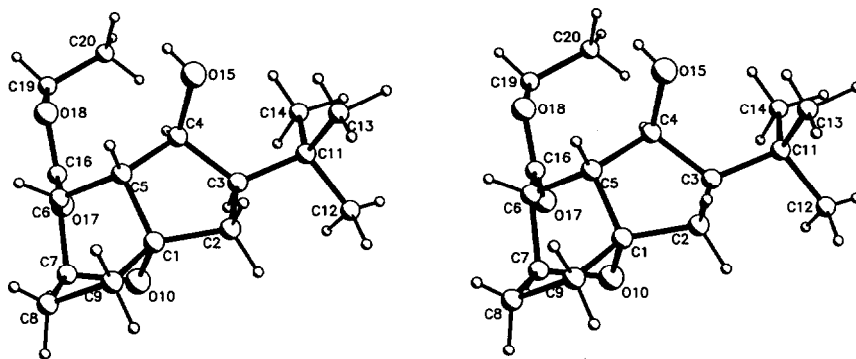

<u>Figure</u>. Stereoscopic view of **8**

The structural elucidation of adduct **4b** in the thermodynamically controlled cyclo-addition of **2b** rests primarily on ^{1}H NMR spectral grounds.[23] Although the pure <u>tert</u>-butyl effect cannot be assessed here, it is interesting to note that a similar equilibrium situation was reached for the cycloaddition of **1** (R,R = S-(CH$_2$)-S) in refluxing benzene (K = 3.2)[12a], albeit slower (k = 0.60 $10^{-5}s^{-1}$) than in the present case (k = 2.8 $10^{-5}s^{-1}$). The thermo-dynamic parameters, extracted from the equilibrium constants obtained at 80°C and 111°C, i.e., ΔH° = –29.3 kJ/mol and ΔS° = –75 J/mol.K, reveal a quasi normal entropy contribution but a poorly exothermic cycloaddition.[24] On the other hand, comparison of the rate constants obtained for the cycloaddition of **3a** and **3b** reveal the <u>tert</u>-butyl effect to be worth a rate enhancement factor of 240. This factor is synthetically significant, especially if one compares this value with the 3.9-5.4 rate enhancement observed in a series of <u>gem</u>-dimethyl accelerated IMDA reactions.[8a]

References and notes
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15. Satisfactory data were obtained for all compounds. Relevant ^{1}H NMR data (200 or 360 MHz, ppm downfield from Me$_4$Si, CDCl$_3$);
2b : 7.27 (1H, br s), 6.26 (1H, dd : 3.1, 2.0 Hz), 5.98 (1H, dd : 3.1, 0.6 Hz), 5.67 (1H, ddd : 17.4, 10.5, 4.8 Hz), 5.08 (1H, m), 4.94 (1H, m), 4.54 (1H, br s), 2.83 (1H, ABX : 16.0, 8.1 Hz), 2.71 (1H, ABX : 16.0, 4.7 Hz), 1.76 (1H, ddd : 8.1, 4.7, 1.5 Hz), 1.60 (1H, s), 1.02 (9H, s). 3b : 7.29 (1H, d : 1.9 Hz), 6.26 (1H, dd : 3.2, 1.9 Hz), 6.11 (1H, d : 3.2 Hz), 4.84 (1H, dd : 6.8, 1.7 Hz), 4.18 (2H, q : 7.3 Hz), 2.93 (1H, ABX : 15.5, 10.4 Hz), 2.87 (1H, ABX : 15.5, 4.4 Hz), 2.21 (1H, d : 6.8 Hz), 2.00 (1H, ddd : 10.4, 4.4, 1.7 Hz), 1.28 (3H, t : 7.3 Hz), 1.02 (9H, s). 4b : 6.35 (1H, ABd : 5.8, 1.5 Hz), 6.33 (1H, AB : 5.8 Hz), 4.92 (1H, dd : 4.6, 1.5 Hz), 4.09 (1H, ddd : 11.8, 4.5, 3.1 Hz), 2.32 (1H, d : 11.8 Hz), 2.26 (1H, m), 2.16 (1H, ddd : 11.8, 4.7, 3.2 Hz), 1.88 (1H, ddd : 7.8, 4.4, 3.2 Hz), 1.28 (1H, dd : 11.8, 8.2 Hz), 1.05 (9H, s). 6a : 7.25 (1H, dd : 5.2, 2.0 Hz), 7.00 (1H, d : 5.2 Hz), 5.71 (1H, d : 2.0 Hz), 5.13 (1H, t : 6.2 Hz), 4.24 (2H, q : 7.0 Hz), 1.32 (3H, t : 7.0 Hz). 6b : 7.12 (1H, dd : 5.4, 2.0 Hz), 6.94 (1H, d : 5.4 Hz), 5.66 (1H, d : 2.0 Hz), 5.15 (1H, d : 3.2 Hz), 4.22 (1H, q : 7.2 Hz), 1.31 (3H, t : 7.2 Hz), 1.16 (1H, s), 1.10 (9H, s). 7a : 7.18 (1H, dd : 5.4, 2.0 Hz), 6.82 (1H, d : 5.4 Hz), 5.63 (1H, d : 2.0 Hz), 4.97 (1H, dd : 9.0, 7.2 Hz), 4.26 (2H, m), 1.34 (3H, t : 7.0 Hz). 8 : 4.70 (1H, d : 5.5 Hz), 4.17 (2H, q : 7.1 Hz), 4.07 (1H, dd : 5.9, 2.7 Hz), 3.02 (1H, d : 9.9 Hz), 2.32 (1H, dd : 9.9, 2.6 Hz), 1.28 (3H, t : 7.1 Hz), 1.04 (9H, s).
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