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## DRAMATIC ACCELERATION OF THE DIELS-ALDER REACTION BY ADSORPTION ON CHROMATOGRAPHY ADSORBENTS

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ABSTRACT. The development of a new method for effecting [4+2] cycloadditions on the surface of chromatographic adsorbents in the absence of solvents that leads to a moderation of the reaction conditions and an increase in selectivity is described.

Adsorption on chromatography adsorbents produces a profound effect on the rate of <u>intra-molecular</u> [2+2+1] cycloadditions<sup>1</sup> (Khand-Pauson) and [3,3] sigmatropic Carrol rearrangements<sup>2</sup>. These results, taken together with related data<sup>3</sup>, prompted us to expand the studies of adsorption effects on the course of various organic reactions. Here we present the results showing that an <u>intermolecular</u> process, namely [4+2] cycloaddition, can be effectively promoted by using adsorbents as a reaction medium.

One might have expected <u>a priori</u> that the use of dry state adsorption conditions (DSAC) instead of the conventional liquid phase conditions (LPC) would produce a negative (if any) effect on the rate of the bimolecular Diels-Alder reaction. To our surprise this turned out not to be the case. Thus, it was found that when an equimolar mixture of myrcene (<u>la</u>) and methylvinyl ketone (<u>2a</u>) was applied to the usual chromatographic grade silica gel, ratio  $SiO_2:(\underline{1a+2a})$  from 10 to 20:1, the [4+2] cycloaddition occurred effectively in the absence of any solvents and produced the anticipated Diels-Alder adduct in 70% yield after heating at 50° for 5h. These conditions are considerably milder than those used under uncatalyzed LPC (140°, 5h)<sup>4</sup>. Additional experiments revealed that under DSAC this reaction can proceed rapidly (within 1h) even at 20° provided the silica gel was additionally activated by drying at 200° for 6h (to remove physically adsorbed water). The rate of the conversion at 20° depended on the ratio (<u>r</u>) SiO<sub>2</sub>:(<u>1a+2a</u>), w/w. Thus, a complete conversion is achieved within 1h for <u>r</u> = 10:1 to 20:1 while with <u>r</u> = 2.1 or 50:1 the conversion for 1h dropped to 20-50%.

Chromatography silica gels of different brands (CSSR, Chemapol, 5/20u, 40/100u, 100/160u; FRG, Woelm, 5/20 u, Mallinckrodt, <150u) are comparable in activity<sup>5</sup>. Magnesium silicate (FRG, florisil, Merck 75/150u) is somewhat less active (even after activation) and requires the use of higher temperatures (by 20-30°) to obtain results comparable with those on dry SiO<sub>2</sub>. The use of chromatography alumina (Hungary, Reanal acidic or neutral; FRG, Woelm) led to poorer results mainly due to the formation of side products. Not unexpectedly the addition of solvents (especially polar) lowers the rate of the conversion on SiO<sub>2</sub>.

The use of DSAC, in addition to the observed rate enhancement, also results in a remarkable improvement in the regioselectivity of the cycloaddition. In fact, under DSAC on activated SiO<sub>2</sub> the adduct formed consisted mainly (>95-97%) of "para" isomer <u>3a</u> (see Table)

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while under ordinary LPC the mixture of "para" and "meta" isomeric adducts are observed in a ratio <u>ca</u> 5:1<sup>4</sup>. Quite similar results were obtained for [4+2] cycloadditions of isoprene (<u>1b</u>), butadiene (<u>1c</u>), 2,3-dimethylbutadiene (<u>1d</u>) and 1,3-cyclohexadiene (<u>1e</u>) with <u>2a</u>, acrolein (<u>2b</u>), methacrolein (<u>2c</u>) or crotonaldehyde (<u>2d</u>).

Table. Adducts formed by the [4+2] cycloaddition between <u>la-e</u> and <u>2a-d</u> under DSAC on SiO<sub>2</sub> (CSSR, 5/20u or 40/100u) at 20°



<u>Typical procedure</u>: To an equimolar mixture of <u>1b</u> and <u>2a</u> cooled to  $0^{\circ}$  was added SiU<sub>2</sub> (Chemapol, CSSR, 40/100u, dried at 200° for 6h; ratio <u>r</u> = 10:1). The mixture was shaken vigorously and allowed to stand at 20° for 30 min in a stoppered flask<sup>6</sup>. Extraction with ether, solvent removal and distillation of the residue gave 70% yield<sup>8</sup> <u>3c</u>, containing as a minor byproduct (3-5%, GLC of 5-acetyl-1-methylcyclohexene). For methyl acrylate (<u>2e</u>) as a dienophile the rate enhancement under DSAC is less pronounced. Thus <u>2e</u> gave cycloadducts with <u>1a</u> and <u>1d</u> in 55-60% yields upon heating on SiO<sub>2</sub> at 100° for 4h. In solution these reactions require a prolonged (8-15h) heating at 140-160°<sup>4</sup>. Quite a noticeable effect has also been observed for [4+2] cycloaddition of cyclopentadiene (<u>1f</u>) with <u>2a-c</u>. Under classical LPC these reactions proceed at 20° over 12h<sup>4</sup> while on silica gel the complete conversion 10 is achieved within 1h at -20° and almost pure endo isomers 4a,b are formed<sup>11</sup>.

A heterodienic synthesis also proved to be conducive to the adsorption promotion. The Diels-Alder reaction of 2a (or 2b) with vinyl ethyl ether (5) on florisil (r = 10:1) occurs smoothly at 20° giving the corresponding adducts 6a and 6b in satisfactory yields<sup>12</sup>. The lability of 5 on SiO<sub>2</sub> precluded the use of the latter as an adsorbent. The reaction of 2a with furan (7) or silvane (8) under DSAC revealed a striking dependence on the nature of the adsorbent. Thus exclusive ene reaction leading to the adducts 11 or 12 took place with



extreme ease on  $S_{102}^{13}$ , while the Diels-Alder reaction occurred on Mg0. $S_{102}^{14}$ .

The data shown above clearly demonstrate the wide scope of the applicability of the developed approach based on the use of DSAC to promote various Diels-Alder reactions. Under these conditions [4+2] cycloadditions proceed effectively at much lower temperatures (by  $50-120^{\circ}$ ) than those used under ordinary LPC and produce adducts with enhanced regio- and stereo-selectivity. These results closely parallel those observed for Diels-Alder reactions on zeolites<sup>16</sup> or modified clays (see data in ref. 3). However, in these studies, as in earlier work<sup>17</sup>, the reactions were run in the presence of solvent, a factor that could weaken the adsorption effects (vide supra).

At present it seems hardly possible to provide a concise explanation for the adsorption promoted effect described in this paper and those reported  $earlier^{1-3}$  for a set of other mechanistically different reactions. However, it seems justified to ascribe this phenomenon to the combined action of several effects of adsorbate - adsorbent interaction. The most obvious effect could be associated with the activation of the reacting partners due to the multicentered donar-acceptor interactions with the active sites of the surface. There is a plethora of physical organic data provided by numerous studies in the field of heterogeneous catalysis which attest to the general importance of this effect for various reactions $^{18}$ . The observed acceleration effect of [4+2] cycloaddition under DSAC vs LPC resembles that described ıntermolecular Diels-Alder reactions. for intravs. The thorough analysis of intramolecularity effects has been recently presented by F. Menger<sup>19</sup>. According to his postulate the rigid anchoring of the functionalities within the critical bonding distance is the main factor responsible for the rate enhancement of the reactions proceeding via a preassociation mechanism. It is tempting to speculate that somewhat similar effects due to the proximity imposed by the adsorption of the reacting partner(s) might also be operating for

reactions performed under DSAC. In these cases the adsorbent surface may serve as a matrix facilitating the formation (and probably stabilization) of the pre-reaction complexes between the reacting functionalities strongly held on the adsorption sites. The absence of the solvent shell under DSAC could also be considered as a factor favorable for the formation of these reaction intermediates.

In conclusion we would like to emphasize that the ever increasing body of evidence points to the fruitfulness of the emerging novel approach to enhancement of the rate and selectivity of organic reactions based on the use of adsorbents both as active supports and catalysts<sup>20</sup>.

## Literature and Notes

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- 5. These standard chromatography silica gels possess a rather high specific surface area, S<sub>SD</sub> =  $300-400 \text{ m}^2/\text{g}$ . The activity of silochrome S-120 (USSR) with  $S_{\text{SD}}$  = 120 m<sup>2</sup>/g proved to be substantially lower and it was found necessary to use higher SiO<sub>2</sub>:substrates ratio to achieve a similar conversion rate.
- 6. Alternatively <u>1b</u> and <u>2a</u> can be adsorbed separately on pre-cooled SiO<sub>2</sub> with a subsequent mixing of the two dry powders at 20°.
- 7. Under ordinary (uncatalyzed) LPC the adducts  $3a \longrightarrow 3k$  could be obtained with comparable yields but only after thermolysis for 3-6h at 130-160°4. 8. Yields are for distilled products. Identity was ascertained by comparison (b.p., np<sup>20</sup>,
- GLC, PMR) with authentic samples.
- 9. GLC indicated the presence of less that 3-5% of the minor isomers ("meta" or exo). These are formed in 20-40% under conventional LPC4.
- 10. The completeness of <u>lf</u> conversions at -20° was checked as follows: the reaction mixture <u>lf</u> + 2c on SiO<sub>2</sub> was kept for lh at -20° and then quenched with 1 equiv. of <u>2a</u>. Product analysis after usual treatment revealed the formation 95% of 4c and 5% of 4a. Reaction 1f + 2c on S102 performed at -60° for 2h produced after similar treatment the mixture 4c + 4ain 45:55 ratio (GLC).
- 11. Ratio <u>endo/exo</u> 96:4 (<u>4a</u>); 91:9 (<u>4b</u>); 88:12 (<u>4c</u>); for liquid phase reaction at 20° <u>endo/exo</u> = 80:20 (<u>4a</u>); 75:25 (<u>4b</u>); 80:20 (<u>4c</u>); see Y. Kobuke, T. Fuerio, J. Furukawa, <u>J</u>.
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  <u>12. Uncatalyzed reaction 2a, b with 5 under LPC required thermolysis for 12-19h at 135-155°. R.I. Longley and W.S. Emerson, J. Amer. Chem. Soc.</u>, <u>72</u>, 3079 (1950).
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  <u>14. Diels-Alder reaction of 7 with 2a under LPC requires the use of Lewis acid catalysts or 8 with 2a work of 10 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 2a under LPC requires the use of Lewis acid catalysts or 9 with 9</u></u>
- high pressure<sup>3</sup>. We are unable to find any data dealing with [4+2] cycloaddition between 8 and 2a.
- 15. Low yields of adducts 13 or 14 are partly due to their well-known propensity to undergo retro-Diels-Alder reaction leading eventually to the formation of ene-adducts 11 or 12. This transformation was shown to proceed on SiO2 at 20° within 1h.

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- 20. The authors are grateful to the helpful discussions with Drs. A.A. Lopatkin, A.A. Slinkin, S.S. Yufit, and G.V. Lisichkin and to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

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