Kinetic Studies on the Catalytic Hydrogenation of Isoergosterone

By EDWARD R. GARRETT, ROBERT A. DONIA, BYRON A. JOHNSON AND LAMBERTUS SCHOLTEN

RECEIVED FEBRUARY 2, 1956

The spectrophotometric study of the kinetics of catalytic hydrogenation of 4,6,22-ergostatrien-3-one (I) (isoergosterone) in methanol was undertaken to determine the conditions of optimum yield of the dihydro product, 4,22-ergostadien-3-one (II) with minimum yield of I and the tetrahydro product, 22-ergosten-3-one (III). Competition of I and II for catalyst was clearly indicated. Addition of alkali and prereduction of the catalyst favored maximum yield of II. The hydrogenation demonstrated zero-order kinetics at constant hydrogen pressure and appeared to be diffusion controlled.

In the course of studies on the conversion of ergosterol to progesterone,[1] the heterogeneous reaction kinetics of the constant pressure hydrogenation of isoergosterone, 4,22-ergostatrien-3-one (I), were studied in an attempt to determine optimum conditions for the yield of the first reduction product. Spectrophotometric assay of aliquots of the reaction system at timed intervals determined the amounts of isoergosterone (I), 4,22-ergostadien-3-one (II) and 22-ergosten-3-one (III) in the postulated reaction sequence.

The rate of the first hydrogenation step, I to II, was best fitted by zero-order plots, and the rate of loss of the trienone I in g./minute (r_1) by catalytic hydrogenation was constant for approximately 80% of the initial trienone I concentration under the conditions of the studied reactions. Figures 1 and 2 are examples of the rate curves. The initial appearance of the enone III was also of apparent zero order, and this initial linear rate $(r_2$ in g./minute) was concomitant with the linear transformation (r_1) rate of 80% of I to II.

Fig. 2.—Rates of the catalytic hydrogenation sequence of isoergosterone (I) at 35° with prereduced catalyst (run 4).

Subsequently, the rate of enone III appearance increases and, in some cases, may be estimated by a linear approximation $(r_3$ in g./minute). This rate was maintained for a significant interval after the maximum in dienone (II) concentration, II_{max}, had been achieved. When the amount of dienone (II) had further diminished, an apparent first-order rate $(r_4$ in min.$^{-1})$ with dependence on concentration of dienone appeared in the reactions carried to completion with sufficient data, as in run 6.

The data from the various hydrogenations are given in Table I. There is little difference among the respective r_1 and r_2 values of runs 1, 9 and 10 at 19°. Run 2 without alkali differed from run 1 with added alkali. Alkali favored increased r_1 and decreased r_2 rates to result in a higher r_1/r_2 ratio and a greater maximum in II. Runs 2 and 6 have approximately the same total catalyst, but the catalyst dispersion is greater in the latter. This favored increased r_1 and r_2 rates, a greater r_1/r_2
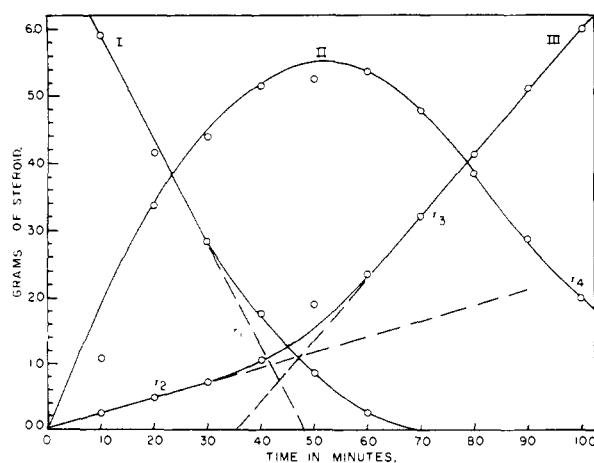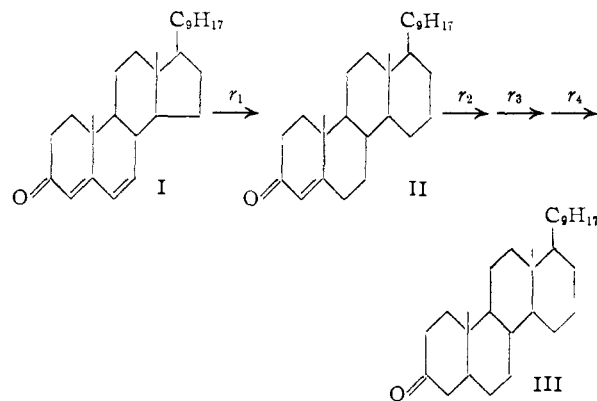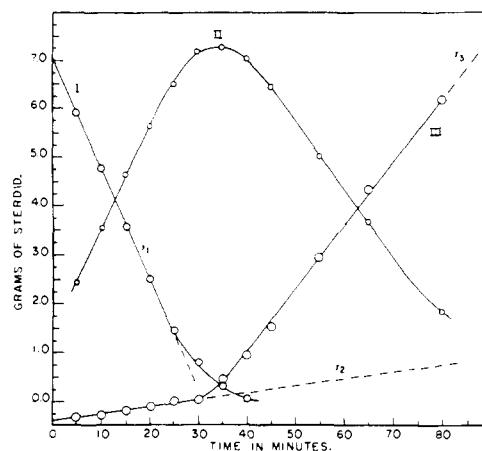

Fig. 1.—Rates of the catalytic hydrogenation sequence of isoergosterone at 19° (run 1). Curve I is the time plot of isoergosterone, curve II of the dienone and curve III of the enone in the hydrogenation sequence I $\xrightarrow{r_1}$ II $\xrightarrow{r_2, r_3, r_4}$ III. The original concentration was 8 g. of isoergosterone per 1500 ml. of methanol.

(1) D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, Jr., J. E. Stafford, R. L. Pederson and A. C. Ott, THIS JOURNAL, 77, 1212 (1955).

TABLE I

DATA AND REACTION RATES: HYDROGENATION OF ISOERGOSTERONE (I)ᵃ TO ERGOSTADIENONE (II) TO ERGOSTENONE (III)

Run	t, °C.	Catalyst, g.	Pellets of KOH	II_{max},ᵇ g.	Time of II_{max}, min.ᶜ	Equationsᵈ describing experimental data											
						$I = -r_1t + b_1$ for $a_1 < t < a_1'$				$II = r_2t + b_2$ for $a_2 < t < a_2'$				$III = r_3(t - b_3)$ for $a_3 < t < a_3'$			
						r_1	b_1	a_1	a_1'	r_2	b_2	a_2	a_2'	r_3	b_3	a_3	a_3'
1	19.0	5% Pd/C, 0.30	10	5.4	53	0.144	7.50	8	43	0.026	0.00	0	40	0.088	34	60	100
2	19.0	5% Pd/C, .30	0	4.0	68	.098	6.76	15	56	.048	0.00	0	80	...	..	90	..
3	35.0	5% Pd/C, .30	5	7.2	32	.284	8.36	3	25	.034	−1.16	0	30	0.164	29	29	70
4	35.0	5% Pd/C, .30	5	7.3	35	.232	7.13	3	25	.013	−0.40	0	31	0.128	32	32	82
5	19.0	5% Pd/C, .30	5	5.5	85	.073	6.67	10	75	.028	− .84	0	90	...	..	90	..
6	19.0	0.2% Pd/C, 8	0	5.1	35	.185	6.64	7	32	.054	.56	0	32	0.129	15	32	63
7	34.7	0.2% Pd/C, 8	0	4.4	32	.302	8.00	0	26	.087	.00	0	40	...	..	50	..
8	51.0	0.2% Pd/C, 8	0	4.4	22	.384	8.00	0	18	.136	.00	0	24	...	..	25	..
9	19.0	5% Pd/CaCO₃, 0.75	5	5.5	68	.148	7.88	0	25	.017	− .08	5	40	...	..	40	..
						.102	7.00	20	50								
10	19.0	5% Pd/CaCO₃, 0.75	5	5.4	80	− .138ᵉ	0.00	0	45	.027	−0.32	12	63	...	..	65	..

ᵃ Eight grams of isoergosterone (I) was hydrogenated in 1500 ml. of methanol (except in run 10 which was 4 g./1100 ml. initially and four incremental additions of 1 g. of isoergosterone/100 ml. of methanol were made during hydrogenation). A study similar to run 10 at 4 g. of isoergosterone/1000 ml. at 8° without subsequent addition of isoergosterone showed decided deviation from apparent zero order after 3 g. of isoergosterone had been consumed. In runs 3, 4 and 5 the catalysts were prereduced. ᵇ Probable error of ±0.3 g. of II; in general the amount of I at II_{max} is 0.8 ± 0.3 g., and the subsequent rate of disappearance is of higher order and not constant with time. ᶜ Probable error of ±4 min. ᵈ The curves describing the amounts of I, II and III in grams at any given time during the hydrogenation may be synthesized by means of these equations where t is in minutes, III = 8.00 − (I + II) and where the parameters, r_i and b_i, are valid for the period $a_i < t < a_i'$. In all cases, the rate of III production increased after the limits given for r_2. When sufficient data were available, the zero order rate r_3 could be estimated. Subsequently, the rate of III appearance diminishes and in the case of run 6, the first-order rate constant of II disappearance could be estimated at 0.051 min.⁻¹. The blank spaces for the parameters of the r_3 equation for III were made necessary by insufficient data. However, the rate increased after $t = a_3$ from r_2 before its subsequent decrease. ᵉ The rate expression for run 10 is plotted as the amount (II') of II consumed against time, i.e., II' = $r_1t + b_1$.

ratio and a greater maximum in II in less time of attainment.

In runs 3, 4 and 5 the catalyst was prereduced and the highest maximum in II was achieved, especially in the first two runs at 35°.

Runs 6, 7 and 8 were studied under the same conditions, except for temperature, and the r_1/r_2 ratios were similar. However, both r_1 and r_2 did increase with temperature and the estimated apparent heats of activation for both phases of the hydrogenation are 6 kcal./mole.

In order to verify the apparent initial zero-order conversion of I to II, isoergosterone (I) was incrementally added to the hydrogenating system. The details of the reaction are graphically shown in Fig. 3 where r_1 and r_2 are of apparent zero order and the value of II_{max} does not change significantly from that in non-incremental addition under comparable conditions.

Experimental

The hydrogenating system consisted of a 2-l., three-neck, round-bottom flask submerged in a constant temperature bath and equipped with a mercury sealed, motor driven stirrer in the center neck. One neck was fitted with a gas-tight hydrogen glass inlet tube submerged under the solution, connected to a mercury manometer as well as to the hydrogen tank and equipped with a vacuum sampling device. The other neck was fitted with a glass outlet tube above the solution, connected to a mercury manometer and led under water in a cylinder. The inlet mercury manometer was held at a differential of 2.0 inches and the outlet at 1.0 inch for runs 1, 2, 6 and 7 and at a differential of 1.8 and 0.9 inches for all other runs (see Table I).

The 8 g. of isoergosterone (I), and the potassium hydroxide, when used, was dissolved in 1500 ml. of absolute methanol and the catalyst[1] was suspended in the solution for all runs but 3, 4, 5 and 10. The precise amounts are given in Table I. Only 4 g. of isoergosterone (I) was dissolved in 1100 ml. of methanol for run 10 and four additions of 1 g. in 100 ml. were made at subsequent intervals.

In runs 3, 4 and 5 the catalyst was prereduced at the temperature of the subsequent hydrogenation. The catalyst was suspended and the alkali dissolved in 1000 ml. of methanol. A stream of hydrogen was bubbled through the stirred solution for 15 minutes. Subsequently, the isoergos-
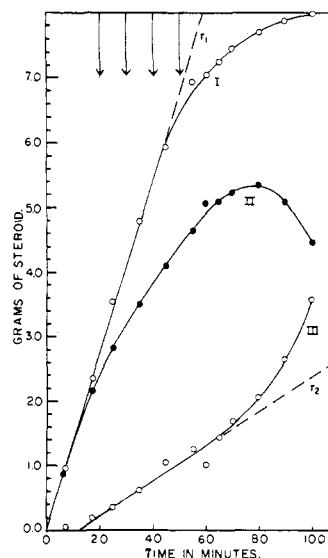

Fig. 3.—Rates of the catalytic hydrogenation sequence with incremental addition of isoergosterone at 19° (run 10). Curve I is the time plot of isoergosterone consumption, curve II is the time plot of the dienone and curve III of the enone in the hydrogenation sequence: I $\xrightarrow{r_1}$ II $\xrightarrow{r_2r_3}$ III. The original concentration was 4 g. of isoergosterone per 1100 ml. of methanol. At the times indicated by the arrows 1 g. of isoergosterone was added in 100 ml. of methanol for a total of 8 g. in 1500 ml.

terone (I) dissolved in 500 ml. of methanol, was added and hydrogenation begun.

The solutions were sampled at intervals, filtered and analyzed spectrophotometrically at appropriate dilutions. The standards absorptivities were a_{288} 29,014 for isoergosterone (I) and a_{242} 16,500 for ergostadienone (II). The 242 mμ reading of the aliquots had to be corrected for the absorptivity of isoergosterone (I) used in each study and was generally a_{242} 2,800. The amount of ergostenone (III) was calculated by difference as the ultraviolet chromophore ultimately disappeared.

The physicochemical constants for these steroids have been given previously.[1]

Discussion

The estimated apparent heat of activation under the conditions of these studies is low (6 kcal./mole for runs 6, 7 and 8 for r_1 and r_2). This is most consistent with a diffusion controlled rate-determining step in the transformation of I to II.

The apparent zero order of the rate r_1, independent of the concentration of I, conforms to the postulated mechanisms of heterogeneous reaction kinetics[2] when the solid phase is saturated at the active centers with molecules of I. The diffusion of hydrogen at constant pressure to the active sites, gas to a solid through liquid, could be the rate-controlling step in the I to II transformation. This could be so until the concentration of I falls below a certain minimum necessary for saturation of the catalyst, when the apparent order increases (Figs. 1 and 2). The incremental addition of I (Fig. 3) proves that maintenance of the concentration of I above this minimum prolongs the apparent zero order of the initial reduction. The difference in initial concentration of I did not significantly change the initial rate.

The apparent zero order of the initial transformation of II to III (up to approximately 80% consumption of I) indicates that the rate is not initially dependent on the concentration of II. This may be explained by a limited, constant number of sites being available to II during the steady state linear rate hydrogenation of preferentially adsorbed I. Thus a constant rate (r_2) of production of III would be expected while I is in excess. It is possible that hydrogen addition to I is 1,6- and 1,6-dihydro-I must desorb and ketonize before readsorption of II on the catalyst.

When II no longer can be displaced by excess I, its rate of conversion to III rapidly increases. The newly attained higher rate (r_3) (Figs. 1, 2) is of apparent zero order, as may be explained by a

catalyst crowded with II and with the rate controlled by hydrogen diffusion. The rate may become progressively dependent on the concentration of II as the crowding of the catalyst diminishes. The ultimate rate dependence of III appearance should be first order on II, as was experimentally shown in run 6.

The increase in rates, r_1 and r_2, with greater catalyst dispersion (run 6 over run 5), is readily understood. With the rate determined by diffusion, the greater the dispersion of sites of action, the greater the expectation of reaction.

The presence of alkali (run 1) increases r_1, decreases r_2 and yields higher II maxima (over run 2) for conditions otherwise comparable. This may be explained by assuming that alkali favors desorption of the 1,6-dihydro-I, the enol form of II. With I still in excess, II loses out in the competition for sites even with increased desorption of the enolized II. Another factor that might be involved is an increase in hydrogen migration to the reaction sites in the presence of alkali, where the presence of hydroxide ion accelerates molecular hydrogen transfer in solution.[3]

Prereduction of the catalyst results in a high r_1/r_2 ratio, the highest maximum in II and the greatest adherence of r_1 to zero order. The primary reason appears to be in the decrease in the magnitude of r_2 so that the hydrogen and I saturated catalyst must provide even fewer contact sites for II than the I saturated catalyst alone.

Comparison of assumed zero-order, diffusion controlled rates, r_1 and r_3, in the three available pairs for the same catalyst dispersion (runs 1, 3 and 4) shows that $r_3/r_1 = 0.58 \pm 0.03$ (Table I). The ratio for a greater catalyst dispersion on carrier deviates from this mean by $+0.12$ (run 6). This ratio may be explained by the relative decrease in available adsorption sites for II over I. The former molecule has less unsaturation and may only undergo change at the more reactive sites which may be estimated as 58% of the total available to I.

Kalamazoo, Michigan

(2) (a) C. N. Hinshelwood, "The Kinetics of Chemical Change," University Press, Oxford, England, 1940, Chapt. VIII; (b) K. S. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1950, Chapt. 6; (c) S. Glasstone, K. S. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, Chap. VII.

(3) W. K. Wilmarth, J. C. Dayton and J. M. Flournoy, This Journal, 75, 4549 (1953).